THE REGIONAL MUNICIPALITY OF PEEL

COMMUNITY WATER FLUORIDATION COMMITTEE

REVISED AGENDA **CWFC - 1/2018**

DATE: **Thursday, April 19, 2018**

TIME: **9:00 AM – 10:30 AM**

LOCATION: **Regional Council Chamber, 5th Floor**
Regional Administrative Headquarters
10 Peel Centre Drive, Suite A
Brampton, Ontario

MEMBERS: **F. Dale; J. Downey; J. Kovac; M. Palleschi; J. Sprovieri**

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1. ELECTION OF CHAIR AND VICE CHAIR

2. DECLARATIONS OF CONFLICTS OF INTEREST

3. APPROVAL OF AGENDA

4. DELEGATIONS

4.1. **Liesa Cianchino, Resident**, Regarding Water Fluoridation in Peel **(Referred from the March 30, 2017 Regional Council Meeting)**

4.2. **Christine Massey, Spokesperson, Fluoride Free Peel**, Regarding Water Fluoridation in Peel **(Referred from the March 30, 2017 Regional Council Meeting)**

4.3. **Dr. Gilles Parent**, Addressing the Ministry of Health and Long-Term Care's Response to Regional Chair Dale's Letter Regarding Regional Water Fluoridation in Ontario (Resolution 2017-68)

5. REPORTS

6. COMMUNICATIONS

6.1. **Tobiah Abramson, Order of Business Coordinator, Office of the City Clerk, The City of Windsor**, E-mail dated March 1, 2017, Responding to a Letter from Regional Chair Dale, Acknowledging Receipt of Resolution 2017-68 (Receipt recommended)

6.2. **Heather Woolsey, Administrative Assistant, Administration and Legislation, City Clerk's Office, City of London**, E-mail dated March 7, 2017, Responding to a Letter from Regional Chair Dale, Acknowledging Receipt of Resolution 2017-68 (Receipt recommended)

6.3. **Nancy J. Bozzato, Town Clerk, Pelham Niagara**, Letter dated March 8, 2017, Responding to a Letter from Regional Chair Dale, Acknowledging Receipt of Resolution 2017-68 (Receipt recommended)

6.4. **Clerk's Office, Municipality of Dutton Dunwich**, Council Resolution dated March 8, 2017, Supporting the Region of Peel's Resolution 2017-68 (Receipt recommended)

6.5. **Kathleen Wynne, Premier of Ontario**, Letter dated March 9, 2017, Responding to a Letter from Regional Chair Dale, Acknowledging Receipt of Resolution 2017-68 and Deferring Consideration to the Minister of Health and Long-Term Care (Receipt recommended)

6.6. **Dan Thibeault, Clerk Treasurer and Chief Administrative Officer, Municipality of Charlton and Dack**, Resolution dated March 13, 2017, Supporting the Region of Peel's Resolution 2017-68 (Receipt recommended)

6.7. **Amber McDonald, Deputy Clerk, Township of Georgian Bay**, Letter dated March 14, 2017, Acknowledging Receipt of a Letter from Chair Dale, With Respect to Resolution 2017-68 (Receipt recommended)

6.8. **Guylaine Coulombe, Chief Administrative Officer and Clerk, Municipality of Mattice Val Côté**, Resolution dated March 20, 2017, Supporting the Region of Peel's Resolution 2017-68 (Receipt recommended)

6.9. **Agatha Armstrong, Deputy Clerk, Corporation of the Town of LaSalle**, Letter dated March 21, 2017, Providing a Copy of a Letter Sent to Kathleen Wynne, Premier of Ontario, Indicating Support of Region of Peel Resolution 2017-68 (Receipt recommended)

6.10. **Alison Collard, Clerk, The Corporation of Champlain Township**, Letter dated March 21, 2017, Supporting the Region of Peel's Resolution 2017-68 (Receipt recommended)

6.11. **Therese Hall, Administrative Assistant, Town of Englehart**, Letter dated March 22, 2017, Supporting the Region of Peel's Resolution 2017-185 Regarding Alternative Approaches to Water Fluoridation to the Current Community Water Fluoridation (Receipt recommended)

6.12. **Krista Royal, Deputy Clerk, Town of The Blue Mountains**, Resolution dated March 27, 2017, Acknowledging Receipt of a Letter from Chair Dale, With Respect to Resolution 2017-68 (Receipt recommended)

6.13. **Liesa Cianchino, Resident**, E-mail dated March 29, 2017, Inquiring if the Region of Peel has Received a Response to Resolution 2017-68 from the Ministry of Health and Long-Term Care (Receipt recommended)

6.14. **John Sprovieri, Regional Councillor, City of Brampton**, E-mail dated March 31, 2017, Providing Information on the Biological Effects of Fluoride (Receipt recommended)

6.15. **Liesa Cianchino, Resident,** E-mail dated March 31, 2017, Requesting a Copy of Regional Chair Dale's Letter to the Minister of Health and Long-Term Care and Responses Received from the Ministry (Receipt recommended)

6.16. **Bonnie Nistico-Dunk, City Clerk, City of St. Catherines**, Letter dated March 31, 2017, Responding to a Letter from Regional Chair Dale, Acknowledging Receipt of Resolution 2017-68 (Receipt recommended)

6.17. **John Sprovieri, Regional Councillor, City of Brampton**, E-mail dated March 31, 2017, Providing Information and Studies Related to the Effects of Fluoride in Relation to Dementia/Alzheimer's (Receipt recommended)

6.18. **John Sprovieri, Regional Councillor, City of Brampton**, E-mail dated March 31, 2017, Providing the 1957 Supreme Court Ruling that Fluoride is a Medication (Receipt recommended)

6.19. **Dr. Lawrence Loh, Acting Medical Officer of Health, Region of Peel**, Email dated April 4, 2017, Responding to an Email from Councillor Tovey Regarding the Environmental Protection Agency's Response to the Challenges to Community Water Fluoridation Asserted by Paul Connett (Receipt recommended)

6.20. **Christine Massey, Spokesperson, Fluoride Free Peel**, E-mail dated April 4, 2017, Providing Information Regarding the Jurisdiction of the Ministry of Environment and Climate Change Over Large Municipal Drinking Water Systems (Receipt recommended)

6.21. **Christine Massey, Spokesperson, Fluoride Free Peel**, E-mail dated April 7, 2017, Responding to Information Contained in the Region of Peel Oral Health Report (Receipt recommended)

6.22. **Robert Deschene, Chief Administrative Officer, Clerk, and Treasurer, Township of Nairn and Hyman**, Letter dated April 13, 2017, Responding to a Letter from Regional Chair Dale, Advocating to the Provincial Government to Clarify and Assume a Legislative Role in Community Water Fluoridation (Resolution 2017-185) (Receipt recommended)

6.23. **Christine Massey, Spokesperson, Fluoride Free Peel**, Email dated April 28, 2017, Providing Comments to Dr. Loh's Response to Ms. Massey's Formal Complaint (Receipt recommended)

6.24. **John Sprovieri, Regional Councillor, City of Brampton**, Email dated April 28, 2017, Providing a List of Issues to be Considered by the Community Water Fluoridation Committee (Receipt recommended)

6.25. **Victoria Bull, Deputy Clerk, The Corporation of the Township of Minden Hills**, Resolution dated May 25, 2017, Supporting the Region of Peel's Resolution 2017-68 (Receipt recommended)

6.26. **Jim Tovey, Regional Councillor, City of Mississauga**, Email dated July 4, 2017, Requesting the Inclusion of a Study Related to Water Fluoridation on the Community Water Fluoridation Committee Agenda (Receipt recommended)

6.27. **Christine Massey, Spokesperson, Fluoride Free Peel**, Email dated July 5, 2017, Responding to Kathryn Lockyer's E-mail dated July 5, 2017, Requesting Clarification on How and What Items will be Referred to the Community Water Fluoridation Committee (Receipt recommended)

6.28. **Olha Dobush, Director, Chronic Disease and Injury Prevention, Region of Peel**, Email dated July 17, 2017, Providing Councillor Sprovieri with Examples of Studies Demonstrating the Effectiveness and Safety of Community Water Fluoridation (Receipt recommended)

6.29. **Christine Massey, Spokesperson, Fluoride Free Peel**, Email dated August 8, 2017, Providing Information from the Fluoride Action Network Regarding Australia's Fluoridation Review (Receipt recommended)

6.30. **Christine Massey, Spokesperson, Fluoride Free Peel**, Email dated August 21, 2017, Providing a Report Regarding Fluoride and Cataract Blindness (Receipt recommended)

6.31. **Christine Massey, Spokesperson, Fluoride Free Peel**, Email dated September 12, 2017, Providing Information from a Former Chief Dental Officer at the US Public Health Service (Receipt recommended)

6.32. **Merilyn Haines, Chair, Fluoride Action Network, Australia**, Email dated September 13, 2017, Regarding Flawed Review of Water Fluoridation from the 2017 National Health and Medical Research Council (Receipt recommended)

6.33. **Christine Massey, Spokesperson, Fluoride Free Peel**, Email dated September 22, 2017, Providing Information on Studies Regarding Fluoride Exposure in Utero Linked to Lower IQ in Kids (Receipt recommended)

6.34. **Christine Massey, Spokesperson, Fluoride Free Peel**, Email dated October 11, 2017, Providing a News Release Regarding Tooth Decay Rates in Calgary (Receipt recommended)

6.35. **Christine Massey, Spokesperson, Fluoride Free Peel**, Email dated January 26, 2018, Regarding the Region of Peel Budget Related to Hydrofluorisilicic Acid in Drinking Water (Receipt recommended)

6.36. **Christine Massey, Spokesperson, Fluoride Free Peel**, E-mail dated February 22, 2018, Providing an Update Regarding Fluoride Effects on Pineal Glands (Receipt recommended)

6.37. **Christine Massey, Spokesperson, Fluoride Free Peel**, Email dated February 8, 2018, Regarding Article in "Nature", an Academic Journal, Regarding "Impact of Drinking Water Fluoride on Human Thyroid Hormones: A Case-Control Study" (Receipt recommended)

6.38. **Gurpreet Singh Dhillon, City Councillor, City of Brampton**, Providing Comments Regarding Water Fluoridation as Referred from the November 16, 2017 Regional Council Budget Meeting (Receipt recommended)

6.39. **John Sprovieri, Regional Councillor, City of Brampton,** Email dated February 27, 2018, Regarding the Minister of Health and Long-Term Care's Resignation (Receipt recommended)

6.40. **John Sprovieri, Regional Councillor, City of Brampton**, E-mail dated March 2, 2018, Regarding a Blog Posted by Siskinds Environmental Law Related to the *Safe Water Drinking* Act and the Standard of Care (Receipt recommended)

6.41. **John Sprovieri, Regional Councillor, City of Brampton, E-mail dated March 10**, 2018, Responding to an E-mail from Christine Massey, Regarding the Medical Officer of Health Declining Fluoridation Debate in Parry Sound (Receipt recommended)

6.42. **Dr. Raymond Ray, Retired Biochemist and Nuclear Physicist**, E-mail dated March 12, 2018 Regarding Concerns Associated with Water Fluoridation (Receipt recommended)

6.43. **Roselle Martino, Assistant Deputy Minister, Population and Public Health Division, Ministry of Health and Long-Term Care**, Letter dated March 23, 2018, Providing a Response to Regional Chair Dale's Letter Regarding Regional Water Fluoridation in Ontario (Resolution 2017-68) (Receipt recommended)

6.44. **Christine Massey, Spokesperson, Fluoride Free Peel**, E-mail dated April 2, 2018, Regarding Fluoride Intake for Children (Receipt recommended)

6.45. **Christine Massey, Spokesperson, Fluoride Free Peel**, E-mail dated April 4, 2018, Regarding Fluoride Exposure in Utero (Receipt recommended)

6.46. **Karen Ras, Regional Councillor, City of Mississauga**, E-mail dated April 5, 2018, Providing Her Resignation from the Community Water Fluoridation Committee (Receipt recommended)

6.47. **John Sprovieri, Regional Councillor, City of Brampton**, E-mail dated April 6, 2018, Submitting a Hyperlink to a Video from Simon Fraser University Regarding the Impact of Toxins on the Developing Brain (Receipt recommended)

6.48. **Annette Groves, Regional Councillor, Town of Caledon**, E-mail dated April 10, 2018, Providing Her Resignation from the Community Water Fluoridation Committee (Receipt recommended)

7. IN CAMERA MATTERS

8. OTHER BUSINESS

9. NEXT MEETING

10. ADJOURNMENT

Region of Peel
working with you

4.1-1

Request for Delegation

FOR OFFICE USE ONLY

MEETING DATE YYYY/MM/DD	MEETING NAME
2018/04/19	**CWFC**

Attention: Regional Clerk
Regional Municipality of Peel
10 Peel Centre Drive, Suite A
Brampton, ON L6T 4B9
Phone: 905-791-7800 ext. 4582
E-mail: council@peelregion.ca

DATE SUBMITTED YYYY/MM/DD
Referred from March 30, 2017

NAME OF INDIVIDUAL(S)
Liesa Cianchino

POSITION(S)/TITLE(S)
Resident

NAME OF ORGANIZATION(S)

E-MAIL	TELEPHONE NUMBER	EXTENSION

REASON(S) FOR DELEGATION REQUEST (SUBJECT MATTER TO BE DISCUSSED)
Regarding Water Fluoridation in Peel

A formal presentation will accompany my delegation ☐ Yes ☐ No

Presentation format: ☐ PowerPoint File (.ppt) ☐ Adobe File or equivalent (.pdf)
☐ Picture File (.jpg) ☐ Video File (.avi,.mpg) ☐ Other

Additional printed information/materials will be distributed with my delegation : ☐ Yes ☐ No ☐ Attached

Note:
Delegates are requested to provide an electronic copy of all background material / presentations to the Clerk's Division at **least seven (7) business days prior** to the meeting date so that it can be included with the agenda package. **In accordance with Procedure By-law 9-2018 delegates appearing before Regional Council or Committee are requested to limit their remarks to 5 minutes and 10 minutes respectively (approximately 5/10 slides).**

Delegates should make every effort to ensure their presentation material is prepared in an accessible format.

Once the above information is received in the Clerk's Division, you will be contacted by Legislative Services staff to confirm your placement on the appropriate agenda. Thank you.

Notice with Respect to the Collection of Personal Information
(Municipal Freedom of Information and Protection of Privacy Act)

Personal information contained on this form is authorized under Section 5.4 of the Region of Peel Procedure By-law 9-2018, for the purpose of contacting individuals and/or organizations requesting an opportunity to appear as a delegation before Regional Council or a Committee of Council. The Delegation Request Form will be published in its entirety with the public agenda. The Procedure By-law is a requirement of Section 238(2) of the *Municipal Act, 2001*, as amended. Please note that all meetings are open to the public except where permitted to be closed to the public under legislated authority. All Regional Council meetings are audio broadcast via the internet and will be posted and available for viewing subsequent to those meetings. Questions about collection may be directed to the Manager of Legislative Services, 10 Peel Centre Drive, Suite A, 5th floor, Brampton, ON L6T 4B9, (905) 791-7800 ext. 4462.

Region of Peel
working with you

4.2-1

Request for Delegation

FOR OFFICE USE ONLY

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2018/04/19	**CWFC**

DATE SUBMITTED YYYY/MM/DD
Referred from March 30, 2017

Attention: Regional Clerk
Regional Municipality of Peel
10 Peel Centre Drive, Suite A
Brampton, ON L6T 4B9
Phone: 905-791-7800 ext. 4582
E-mail: council@peelregion.ca

NAME OF INDIVIDUAL(S)
Christine Massey

POSITION(S)/TITLE(S)
Spokesperson

NAME OF ORGANIZATION(S)
Fluoride Free Peel

E-MAIL	TELEPHONE NUMBER	EXTENSION

REASON(S) FOR DELEGATION REQUEST (SUBJECT MATTER TO BE DISCUSSED)
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Region of Peel
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Request for Delegation

FOR OFFICE USE ONLY

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2018/04/19	CWFC

DATE SUBMITTED YYYY/MM/DD
2018/04/17

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Regional Municipality of Peel
10 Peel Centre Drive, Suite A
Brampton, ON L6T 4B9
Phone: 905-791-7800 ext. 4582
E-mail: council@peelregion.ca

NAME OF INDIVIDUAL(S)

Dr. Gilles Parent

POSITION(S)/TITLE(S)

NAME OF ORGANIZATION(S)

E-MAIL	TELEPHONE NUMBER	EXTENSION

REASON(S) FOR DELEGATION REQUEST (SUBJECT MATTER TO BE DISCUSSED)
Invitation from Liesa Cianchino, Chair, Concerned Residents of Peel to End Fluoridation, on behalf of the many concerned residents of Peel to address the long awaited (14 months) Ministry's letter of response to Chair Frank Dale's letter dated February 22, 2017 regarding Resolution number 2017-68

A formal presentation will accompany my delegation ☑ Yes ☐ No

Presentation format: ☐ PowerPoint File (.ppt) ☐ Adobe File or equivalent (.pdf)
☐ Picture File (.jpg) ☐ Video File (.avi,.mpg) ☐ Other

Additional printed information/materials will be distributed with my delegation : ☐ Yes ☑ No ☐ Attached

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FLUORIDATION CHEMICALS ARE 4.3-2

UNREGULATED

UNTESTED

UNAPPROVED

INEFFECTIVE

DRUGS

By

Gilles Parent, ND.A.

Co-Author of «Fluoridation: Autopsy of a Scientific Error»

APRIL 19th, 2018

Pierre-Jean Morin, Ph.D.
Me John Remington Graham
Gilles Parent, n.d.

Fluoridation

Autopsy of a Scientific Error

BERGER

2012 PEEL RESOLUTION

February 12, 2012 Passed a Resolution calling Health Canada to do at least:

1. **1 long-term toxicology study to determine the health effects in humans**
2. **at least 1 properly conducted controlled clinical trial to determine effectiveness**

Objective:

to reassure the citizens of Peel that the use of fluorosilicates added to drinking water for the purpose of treating a disease is safe.

2017 PEEL RESOLUTION

February 22, 2017 Passed a Resolution calling Ministry of Health and Long Term Care to do at least:

1. **To undertake appropriate and comprehensive toxicity testing necessary to reassure the public that the use of HFSA in water fluoridation treatments is safe;**
2. **Take legislative responsibility for the regulation and administration of HFSA in water fluoridation treatments across the province relieving local governments from what is a provincial responsibility.**

MINISTRY OF HEALTH'S RESPONSE LETTER TO PEEL REGION

«March, 23, 2018

Public health Ontario has review NSF/ANSI 60 on behalf of the ministry. NSF/ANSI 60 establishes requirements to be protective of human health for products and their impurities that may be added directly during water treatment, storage and distribution.»

...

MINISTRY OF HEALTH'S RESPONSE LETTER TO PEEL REGION

«The established safeguard noted above continue to ensure the safety of fluoridate drinking water in Ontario. The ministry will also continue to monitor and review new research.

The ministry urges all municipalities to protect their communities from avoidable health issues by maintaining fluoride in their drinking water, to promote the health of all residents.»

Sincerely,

Roselle Martino
Assistant Deputy Minister
Population and Public Health Division

MINISTRY OF HEALTH'S RESPONSE LETTER TO PEEL REGION

Ms Roselle Martino, assistant Deputy Minister is misleading the Committee :

1. The Ministry hasn't supplied the toxicological review as requested by Peel Region **to prove safety of HFSA**, so without it, **it cannot be claimed SAFE**;
2. The Ministry implies that NSF/ANSI 60 establishes requirements to be protective of human health for fluoridation chemicals **WHICH THEY DO NOT** (see NSF disclaimers);
3. The Ministry implies that NSF/ANSI 60 has the jurisdiction and the competence to guarantee the efficiency of HFSA **WHICH IT DOES NOT**;
4. The Ministry implies that it is legal and ethical to administer to a population a water treatment chemical to mitigate and prevent a disease **WHICH IT IS NOT.**

MINISTRY OF HEALTH'S RESPONSE LETTER TO PEEL REGION

5. The Ministry assumes that fluoridation would supply to each citizen an exact and proper amount of fluoride when using tap water as a vehicle for the administration of the fluoride without considering the huge variability of daily intake of water and fluoride from all other sources. It make fluoridation of water an absurd vehicle of distribution of a drug as a daily dose cannot be controlled.

6. The Ministry assumes erroneously that concentration is equivalent to dose while such a concept is obviously invalid.

7. The Ministry assumes that it knows the exact daily dose of fluoride needed to prevent dental decay without causing any harm to anyone, including the most vulnerable subjects in the society; babies, children, the infirm, the elderly and those that drink a lot of water.

8. The Ministry assumes that it knows what no health authority in the world knows, the exact effective and safe dose of fluoride; that is either 1, 2, 3, 4, 5, 6 or 7 mg daily. **There aren't any scientific consensus on the exact effective and safe dose.**

MINISTRY OF HEALTH'S RESPONSE LETTER TO PEEL REGION

9. The Ministry assumes that it knows what **no health authority** in the world knows, the **exact effective and safe dose** of fluoride that would take in account the weight of the subject expressed in mg/kg/day; is it 0.01, 0.02, 0.03, 0,04, 0.05, 0.06, 0,07, 0.08, 0.09 mg/kg/day.

10. **Without knowing what the exact appropriate intake of fluoride that would be safe for the most vulnerable and that would be effective to prevent decay if such a dose would be proven safe and effective, the Ministry is putting the entire population at risk of side effects, including dental fluorosis that is already reported at an epidemic levels.**

NSF/ANSI 60

TRADE REGULATORY ORGANIZATIONS

- NO LEGAL JURISDICTION ON PRODUCTS USED FOR TREATING OR PREVENTING A DISEASE.
- NO COMPETENCY IN EVALUATING THE EFFECTIVENESS OF A SUBSTANCE USED FOR A THERAPEUTIC PURPOSE.
- NO COMPETENCY IN EVALUATING THE SAFETY OF A SUBSTANCE USED FOR A THERAPEUTIC PURPOSE.

NSF DOCUMENTS

NSF International Standard/
American National Standard
for Drinking Water Additives —

Drinking water treatment chemicals — Health effects

NSF DOCUMENT DISCLAIMERS

Disclaimers[1]

NSF Standards provide basic criteria to promote and protect public health. Provisions for safety have not been included in this Standard because governmental agencies or other national standards-setting organizations provide safety requirements.

NO CANADIAN OR AMERICAN GOVERNMENTAL AGENCY HAS EVER PROVIDED SAFETY TOXICOLOGY STUDIES

FOOD AND DRUG ACT DEFINITIONS

“drug”

“drug” includes any substance or mixture of substances manufactured, sold or represented for use in

(*a*) the diagnosis, treatment, **mitigation or prevention of a disease, disorder or abnormal physical state**, or its symptoms, in human beings or animals,

(*b*) restoring, **correcting or modifying organic functions** in human beings or animals

FOOD AND DRUG ACT DEFINITIONS

FOOD

Prohibited sales of food

4. (1) No person shall sell an article of food that

(*a*) **has in or on it any poisonous or harmful substance**;

(*b*) **is unfit for human consumption;**

(*c*) consists in whole or in part of any filthy, putrid, disgusting, rotten, decomposed or diseased animal or vegetable substance;

(*d*) is adulterated; or

(*e*) **was manufactured, prepared, preserved, packaged or stored under unsanitary conditions**.

FOOD AND DRUG ACT DEFINITIONS

“food”

“food” includes any article manufactured, sold or represented for use as food or drink for human beings, chewing gum, and any ingredient that may be mixed with food for any purpose whatever;

(WATER IS A FOOD BY DEFINITION)

FOOD AND DRUG ACT DEFINITIONS

“Unsanitary conditions”

“unsanitary conditions” means such conditions or circumstances as might contaminate with dirt or filth, or render injurious to health, a food, drug or cosmetic**.**

FOOD AND DRUG ACT DEFINITIONS

Unsanitary manufacture, etc., of food

7. No person shall manufacture, prepare, preserve, package or store for sale any food under unsanitary conditions.

FOOD AND DRUG ACT DEFINITIONS

Deception, etc., regarding food

5. (1) No person shall label, package, treat, process, sell or advertise any food in a manner that **is false, misleading or deceptive** or is likely to create an erroneous impression regarding its character, value, quantity, composition, merit or safety.

LEGAL CLASSIFICATION OF FLUORIDATION CHEMICALS

1. TOXIC AND DANGEROUS SUBSTANCES?
2. DRUGS?
3. NATURAL HEALTH PRODUCTS?
4. MINERAL NUTRIENTS FOR FOOD FORTIFICATION?
5. FOOD ADDITIVES?
6. WATER TREATEMENT CHEMICALS?

CLAIMED PURPOSE DEFINES THE LEGAL NATURE OF A PRODUCT AND ITS APPLICATIONS OF LAWS PERTINENT TO IT

WHY FLUORIDATION ?

1. Claimed to prevent dental cavities?

OR

2. To make drinking water safe/potable?

Products making SPECIFIC HEALTH CLAIMS e.g. Preventing Cavities

ARE DEFINED AS EITHER :

1. **DRUGS**

OR

2. **NATURAL HEALTH PRODUCTS**

THEY MUST THEN COMPLY WITH STRICT REGULATIONS

Supreme Court of Canada 1957[1]

Fluoridation

- **is a "compulsory preventive medication",**
- **is “not to promote the ordinary use of water as a physical requisite for the body”**
- **has a “special health purpose”.**

Ruling never contested by the

Canadian Government.

1- Metropolitan Toronto v. Forest Hill (Village), [1957] S.C.R. 569
http://csc.lexum.umontreal.ca/en/1957/1957scr0-569/1957scr0-569.html

ARE THEY CONTROLLED AND APPROVED BY HEALTH CANADA AS DRUGS OR NATURAL HEALTH PRODUCTS?

NO...

Petition #299, Answer #1 by Health Canada to the the Auditor General of Canada, available from:http://www.oag-bvg.gc.ca/internet/English/pet_lp_e_938.html

ARE THESE FLUORIDATION CHEMICALS APPROVED BY HEALTH CANADA AS MINERAL NUTRIENTS FOR FOOD FORTIFICATION?

NO...

Petition #299, Answer #1 by Health Canada to the the Auditor General of Canada, available from:http://www.oag-bvg.gc.ca/internet/English/pet_lp_e_938.html

FLUORIDATION CHEMICALS ARE NOT PREPARED WITHIN «GOOD MANUFACTURING PRACTICES» («GMP»)

Any drug, natural health product, nutrient for food fortification or food should be prepared in sanitary conditions required to satisfy the Food and Drug Act related to the **«Good Manufacturing Practices» («GMP»)**

DOES HEALTH CANADA EXERT ANY REGULATION ON FLUORIDATION CHEMICALS?

NO...

Petition #299, Answer #1 by Health Canada to the the Auditor General of Canada, available from:http://www.oag-bvg.gc.ca/internet/English/pet_lp_e_938.html

BAG FROM THE WATER TREATMENT PLANT OF THE CITY BÉCANCOUR


SHALL NOT BE USE AS FOOD
FLUOROSILICIC ACID 40% SOLUTION
GROSS WEIGHT:1312KGS
NET WEIGHT:1250KGS
LOT NO.:2010DXJL-07
BATCH:10100701
USED ONLY FOR INDUSTRIAL PURPOSES
SHALL NOT BE USED FOR FOOD

THEN, WHAT ARE FLUORIDATION CHEMICALS?

Fluoridation chemicals are unprocessed scrubber liquor of the phosphate industry smoke stack emissions or manufactured from fluoroapatite

If these emissions are released in the atmosphere, they are air pollutants

If these emissions are released in the river, they are water pollutants

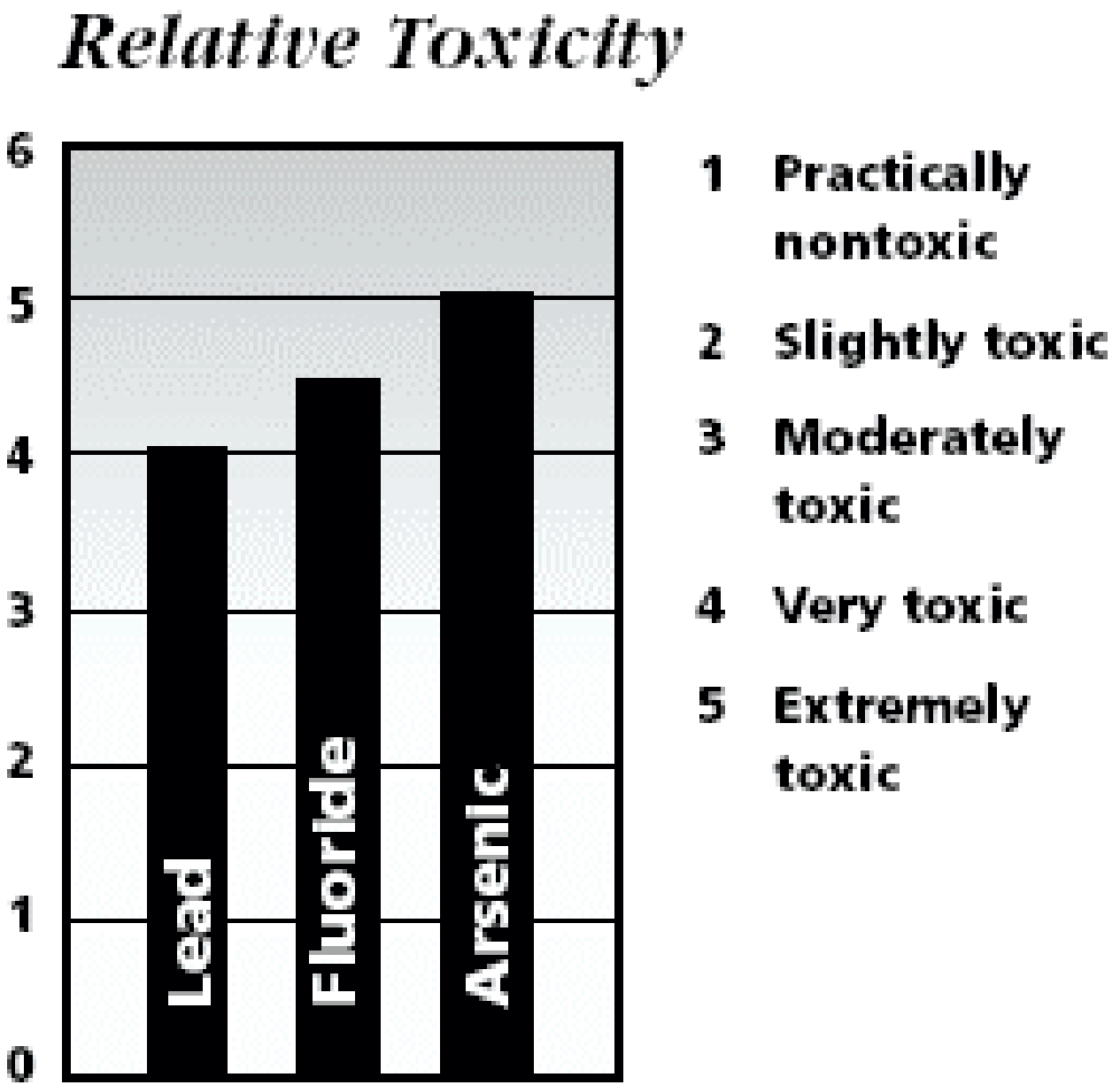
When these same chemicals are added to the municipal water and somehow, they become a beneficial nutrient good for your teeth and your overall health…

Fluoridation chemicals are usually recycled toxic waste

It comes with a small quantity of arsenic, lead, chromium, mercury, and nucleotides.

Fluoride Toxicity

SOURCE: base on lethal (LD 50) de Robert E.Gosselin and al, 1984. Clinical Toxicology of Commercial Products 5th ed., Williams and Wilkins, Baltimore.



Untested, uncontrolled, unregulated chemical waste taken directly from the industry and dripped into your drinking water

Not of pharmaceutical grade nor food grade but industrial grade fluoride.

Are Fluoridation Products “Natural”?

NO...

They are MAN-MADE

ARE THEY WATER TREATMENT CHEMICALS?

HEALTH CANADA,

THE MINISTRY OF HEALTH AND

PUBLIC HEALTH AUTHORITIES

CLAIM THEY ARE.

ARE THEY REALLY WATER TREATMENT CHEMICALS?

NO...

Their aim is not to treat the water to make it safe and drinkable.

Their aim is to prevent dental cavities.

ARE FLUORIDATION CHEMICALS COMPLIANT WITH STANDARD 60 OF THE NATIONAL SANITATION FOUNDATION (NSF)?

NO...

They have a NSF certificate but do not meet all the requirements of NSF Standard 60.

The main essential requirement for the NSF Standard 60 is chronic toxicological tests that demonstrate safety of the HFSA.

«Chronic» means «long term»

Are there any Chronic Toxicology Tests available for HFSA?

NO...

NSF Fact Sheet states that toxicological testing is required,
but the NIEHS 2001 Review, US EPA and Safety Data Sheets state they DO NOT EXIST.

Sodium Fluorosilicate
Material Safety Data Sheet

11. Toxicological Information
11.1 Acute toxicity:
Inhalation: No data available.
Oral: LD50, rat, 125mg/kg (Sodium hexafluorosilicate)
Dermal: No data available.
Irritation: No data available.
Sensitization: No data available.
Comments: No data available.
11.2 Chronic toxicity: No data available.
11.3 Carcinogenic Designation: None

http://www.fluoridealert.org/pesticides/msds/sodium.fluorosilicate.solvay.pdf

- **Letters from the US Congressional Hearings**
- **US EPA**
- **National Institute of Environmental Health Sciences 2001 Review**
- **HEALTH CANADA**
- **ONTARIO MINISTRY OF HEALTH**
- **NSF**

state that fluoridation products do NOT have TOXICOLOGICAL STUDIES

Therefore...

They have not been proven safe...

IF FLUORIDATION CHEMICALS DO NOT HAVE LONG TERM TOXICOLOGICAL STUDIES, THEN

SAFETY

CANNOT BE DEMONSTRATED

They are not proven... safe...

Therefore...

They do not satisfy NSF Standard 60...

Therefore...

THE CERTIFICATION COULD BE CONSIDERED AS INVALID?

They are not compliant with Quebec and Ontario law (Ontario Safe Drinking Water Act)

Finally, what are fluoridation chemicals?

1. IF NOT DRUGS?
2. IF NOT NATURAL HEALTH PRODUCTS?
3. IF NOT MINERAL NUTRIENTS FOR FOOD FORTIFICATION?
4. IF NOT FOOD ADDITIVES?
5. IF NOT WATER TREATMENT CHEMICALS?
6. THEY MUST BE HAZARDOUS WASTES?

FLUORIDATION CHEMICALS SATISFY ALL CRITERIA FOR HAZARDOUS AND TOXIC WASTES

- Règlement sur les matières dangereuses c. Q-2, r.32, Loi sur la qualité de l'environnement (L.R.Q., c. Q-2, a. 31, 46, 70.19, 109.1 et 124.1)
- Export and Import of Hazardous Waste and Hazardous Recyclable Material Regulations DORS/2005-149 (FEDERAL)

THE LEGAL CLASSIFICATION OF FLUORIDATION CHEMICALS AS HARZADOUS AND TOXIC SUBSTANCES ARE DETERMINED IN LAWS

13 laws et regulations

- Loi sur les produits dangereux L.R.C. (1985), ch. H-3
- Liste des substances toxiques – Annexe 1
- Liste des substances d'intérêts prioritaire LSIP1.
- Loi canadienne sur la protection de l'environnement -LCPE (1999) CH. 33
- Loi de 1992 sur le transport des marchandises dangereuses (1992, ch. 34)
- Règlement sur le transport des marchandises dangereuses
- Règlement sur l'exportation et l'importation de déchets dangereux et de matières recyclables dangereuses (REIDDMRD)
- Règlement sur les mouvements interprovinciaux des déchets dangereux
- Loi interdisant la vente, l'importation et la publicité de produits dangereux
- Règlement sur les produits chimiques et contenants de consommation (2001)
- Règlement sur les matières dangereuses c. Q-2, r.32
- Loi sur le contrôle des renseignements relatifs aux matières dangereuses
- Convention de Bâle sur le contrôle des mouvements transfrontiers de déchets dangereux et de leur élimination

LES FLUORURES, LA FLUORATION ET LA QUALITE DE L'ENVIRONNEMENT

Rapport préparé pour

LE MINISTRE DE L'ENVIRONNEMENT

par le

COMITE AVISEUR

SUR LA FLUORATION DES EAUX DE CONSOMMATION

Ministère de l'Environnement

Gouvernement du Québec

Sainte-Foy

Novembre 1979

TOXIC SUBSTANCES CAN FIT ONLY TWO CATEGORIES

1. TOXIC WASTES OR SUBSTANCES

2. DRUGS

HEALTH CANADA HAS NOT APPROVED ANY FLUORIDATION CHEMICALS AS DRUGS.

IT IS ILLEGAL TO ADMINISTER AN APPROVED OR UNAPPROVED DRUG WITHOUT A MEDICAL LICENCE, AND WITHOUT INFORMED CONSENT TO ANY RESIDENT.

ADMINISTERING ANY DRUG, APPROVED OR UNAPPROVED, TO RESIDENTS WITHOUT CONSENT CONTRAVENES ARTICLE 7 OF THE CANADIAN CHARTER OF RIGHTS AND FREEDOMS

Drugs Should Not Be Put Into Drinking Water Because:

1. No one can control how much of any drug is consumed daily by each individual.
2. Citizens are deprived of Informed Choice:
   - Information regarding risks and benefits
   - Choice to refuse or accept drug
   - No trained professional to assess medical need and adverse effects

MUNICIPALITIES SHOULD NOT USE THE PUBLIC WATER SUPPLY AS A VEHICLE TO ADMINISTER A MEDICATION TO THE POPULATION

Fluoridation chemicals

NOT Regulated = NOT Safe

Don’t we deserve
to be
protected by
Government regulation?

Who determines safety and efficacy of fluoridation chemicals ?

NO ONE!

NO Government Agency in Canada regulates fluoridation chemicals.

WHICH HEALTH AUTHORITIES CLAIM ACCOUNTABILITY FOR FLUORIDATION?

NONE...

NO ACCOUNTABILITY

It is not logical to accept the advice of those who accept no responsibility for these chemicals:

- **Health Canada**
- **Ontario Ministry of Health**
- **Ontario Ministry of Environment**
- **Ontario Ministry of Health Promotion**
- **Ontario Dental Association**
- **And over 90 organisations who endorse fluoridation**

Finally, who's Accountable?

Municipalities are legally responsible:

- **You, the councillors, are the final decision makers**
- **for choosing fluoridation chemicals**
- **for adding fluoridation chemicals**

Pleading ignorance of the law is not an excuse

False Assumptions

- **Tax payers incorrectly assume** that these products are compliant with Canadian laws,
- **Tax payers incorrectly assume** that these products have been assessed for safety,
- **Tax payers incorrectly assume** that the product reduces cavities when swallowed,
- **Taxpayers incorrectly assume** that the Health Canada panel evaluating these products had the necessary expertise,
- **Taxpayers incorrectly assume** that the Health Canada panel reviewed all available research – not just the research that supports the policy.

3 methods for Removing Fluoride

1. **Reverse Osmosis** – water wasteful, expensive to purchase and maintain.

2. **Distillation** – expensive to purchase, removes beneficial minerals, energy user

3. **Stop fluoridating** – simple and free

Which is easier?

Which is cheaper?

Which is logical?

MINISTRY OF HEALTH'S RESPONSE LETTER TO PEEL REGION

THE MINISTRY'S RESPONSE DOES NOT ANSWER THE REGIONS RESOLUTION

REQUESTING TO ASSURE THE RESIDENTS OF THE SAFETY AND EFFICACY OF HFSA

FOR THE SOLE PURPOSE OF PREVENTING DENTAL CAVITIES

TO ALL RESIDENTS OF PEEL

BY USING AN UNAPPROVED DRUG TO MEDICATE THE RESIDENTS

WITHOUT THEIR INFORMED CONSENT

MINISTRY OF HEALTH'S RESPONSE LETTER TO PEEL REGION

AS YOU HAVE NOW LEARNED, THE PROVINCE HAS

NOT PROVIDED THE ANSWERS TO YOU

IN ORDER FOR REGIONAL COUNCIL

TO REPORT BACK TO THE CONCERNED RESIDENTS OF PEEL

WHO HAVE BEEN ASKING FOR

PROOF OF SAFETY AND EFFICACY SINCE 2011

NO EVIDENCE OF SAFETY AND EFFICACY (NOT ENDORSEMENTS)

MEANS

YOU CANNOT CLAIM SAFETY AND EFFICACY

THEREFORE, THE INFORMATION YOU ARE RELYING ON FROM

PUBLIC OFFICIALS IS INVALID AS CLAIMS FOR

SAFETY AND EFFICACY OF HFSA

MUST BE BACKED UP BY REQUIRED TOXICOLIGAL STUDIES

WHICH I HAVE CONFIRMED FOR YOU TODAY

DO NOT EXIST!

MINISTRY OF HEALTH'S RESPONSE LETTER TO PEEL REGION

THEREFORE, IT IS INCUMBENT UPON YOU, AS THE

ULTIMATE DECISION MAKERS,

TO PROTECT THE HEALTH AND WELL BEING OF THE RESIDENTS

YOU WERE ELECTED TO SERVE AND PROTECT.

PLEASE CEASE AND DISMISS THIS

UNREGULATED, UNTESTED, UNETHICAL, UNAPPROVED AND INEFFECTIVE PRACTICE

WITHOUT FURTHER DELAY!

ALL RESIDENTS OF PEEL HAVE THE RIGHT TO SAFE DRINKING WATER

WHICH IS A FUNDAMENTAL HUMAN RIGHT

PLEASE JOIN THE 95% OF THE WORLD THAT DOES NOT FLUORIDATE

REDIRECT $500,000.00 SPENT ON THE INEFFECTIVE FLUORIDATION

INTO PUBLIC HEALTH DENTAL PROGRAMS OF PREVENTION

WE HAVE PROVEN THAT FLUORIDATION CHEMICALS ARE

UNREGULATED
UNTESTED
UNAPPROVED
INEFFECTIVE
DRUGS

THE PRECAUTIONARY PRINCIPAL SHOULD BE APPLIED

From: Abramson, Toby [mailto:tabramson@citywindsor.ca]
Sent: March 1, 2017 9:45 AM
To: ZZG-RegionalClerk
Subject: RE: Motion of the Community Water Fluoridation Committee of the Region of Peel

Thank you for your email regarding the attached resolution.

Windsor City Council does not entertain requests from persons, organizations, associations and other municipal governments to endorse resolutions in accordance with its Procedure By-law.

I note that your resolution has been forwarded to the appropriate Provincial Association for consideration.

Yours very truly,

Tobiah Abramson | Order of Business Coordinator (A)

THE CITY OF WINDSOR
ONTARIO, CANADA

Office of the City Clerk
350 City Hall Sq. W | Room 203 | Windsor, ON | N9A 6S1
(519)-255-6100 ext. 6388
www.citywindsor.ca

From: ZZG-RegionalClerk [mailto:zzg-regionalclerk@peelregion.ca]
Sent: Wednesday, March 01, 2017 9:27 AM
Subject: Motion of the Community Water Fluoridation Committee of the Region of Peel

Good morning

Your attention is drawn to the attached letters. The resolution contained in the letters was approved by the Council of the Region of Peel on February 9, 2017.

If you have any inquiries about the information contained please contact Curtiss Law at curtiss.law@peelregion.ca.

Thank you

Summer MacGregor
Legislative Assistant
Clerk's Division, Legislative Services
10 Peel Centre Drive, Suite A
Brampton, ON L6T 4B9
Phone: (905) 791-7800 ext. 4465
Email: Summer.macgregor@peelregion.ca

~No trees were harmed in the making of this e-mail~

REFERRAL TO _____
RECOMMENDED
DIRECTION REQUIRED _____
RECEIPT RECOMMENDED ✓ _____

From: Woolsey, Heather [mailto:hwoolsey@London.ca]
Sent: March 7, 2017 4:13 PM
To: ZZG-RegionalClerk
Subject: FW: Motion of the Community Water Fluoridation Committee of the Region of Peel

Summer MacGregor
Legislative Assistant
Clerk's Division, Legislative Services

Thank you for your email submitting a resolution to with Water Fluoridation.

The London City Council has a policy with respect to resolutions from other municipalities directing the City Clerk to acknowledge such resolutions with the advice that the London City Council does not take action on resolutions received from other municipalities, but rather prefers to make its position on given subjects known through the appropriate municipal association or if it deems it necessary to do so, directly to the concerned Minister(s) of the Senior Government(s) involved.

Sincerely,

Heather Woolsey
Administrative Assistant ll, Administration & Legislation
City Clerk's Office
City of London

P.O. Box 5035, London, Ontario N6A 4L9
P: 519.661.2500 x 4599 | Fax: 519.661.4892
hwoolsey@london.ca | www.london.ca

From: ZZG-RegionalClerk [mailto:zzg-regionalclerk@peelregion.ca]
Sent: Wednesday, March 01, 2017 9:31 AM
Subject: Motion of the Community Water Fluoridation Committee of the Region of Peel

Good morning

Your attention is drawn to the attached letters. The resolution contained in the letters was approved by the Council of the Region of Peel on February 9, 2017.

If you have any inquiries about the information contained please contact Curtiss Law at curtiss.law@peelregion.ca.

Thank you

Summer MacGregor
Legislative Assistant
Clerk's Division, Legislative Services
10 Peel Centre Drive, Suite A
Brampton, ON L6T 4B9
Phone: (905) 791-7800 ext. 4465

REFERRAL TO _____
RECOMMENDED
DIRECTION REQUIRED _____
RECEIPT RECOMMENDED ✓ _____

Pelham
NIAGARA

Vibrant · Creative · Caring

March 8, 2017

Frank Dale
Regional Chair and CEO
The Municipality of Peel
10 Peel Centre Drive, Suite A
Brampton ON L6T 4B9

RECEIVED
March 8, 2017
REGION OF PEEL
OFFICE OF THE REGIONAL CLERK

Dear Mr. Dale:

Regional Peel Resolution – Community Water Fluoridation

At their regular meeting of March 6th, 2017, Council of the Town of Pelham received your correspondence, dated February 22, 2017 and endorsed the following:

BE IT RESOLVED THAT Council receive correspondence from the Regional Council of Peel, dated February 22, 2017 regarding a resolution from the Community Water Fluoridation Committee which was sent to the Premier of Ontario and the Minister of Health and Long Term Care, respecting toxicity testing in water fluoridation treatments to ensure public safety, for information.

On behalf of Council, thank you for this important correspondence.

Yours very truly,

(Mrs.) Nancy J. Bozzato, *Dipl.M.M., AMCT*
Town Clerk

/js

REFERRAL TO _____
RECOMMENDED
DIRECTION REQUIRED _____
RECEIPT RECOMMENDED ✓ _____

From the Clerk's Department
Administrative Services

COUNCIL RESOLUTION

#7

Res: 2017-04-07

Wednesday March 8th, 2017

Moved by: D. McKillop

Seconded by: M. Hentz

RECEIVED
March 8, 2017
REGION OF PEEL
OFFICE OF THE REGIONAL CLERK

THAT the Council of the Municipality of Dutton Dunwich supports Resolution #2017-68 of the Regional Municipality of Peel requesting the Premier of Ontario and the Minister of Health and Long Term Care, whose mandate it is to protect the health of Ontarians to:

i) Undertake appropriate and comprehensive toxicity testing necessary to reassure the public that the use of HFSA in water fluoridation treatments is safe; and

ii) To take legislative responsibility for the regulation and administration of HFSA in water fluoridation treatments across the province, relieving local governments from what is a provincial responsibility.

AND THAT this resolution be forwarded to the Regional Municipality of Peel.

Recorded Vote	Yeas	Nays
I.Fleck	___	___
D. McKillop	___	___
M. Hentz	___	___
B. Purcell	___	___
C. McWilliam - Mayor	___	___

Carried:

C. McWilliam
Mayor

Defeated:

_____
Mayor

REFERRAL TO _____
RECOMMENDED
DIRECTION REQUIRED _____
RECEIPT RECOMMENDED ✓

The Premier of Ontario

Legislative Building, Queen's Park
Toronto, Ontario M7A 1A1

Ontario

La première ministre de l'Ontario

Édifice de l'Assemblée législative, Queen's Park
Toronto (Ontario) M7A 1A1

March 9, 2017

Mr. Frank Dale
Regional Chair and Chief Executive Officer
Regional Municipality of Peel
10 Peel Centre Drive
Suite A
Brampton, Ontario
L6T 4B9

Dear Mr. Dale:

Thank you for your letter providing me with a copy of council's resolution regarding water fluoridation. I appreciate your keeping me informed of council's activities.

As this issue falls under the responsibility of my colleague the Honourable Dr. Eric Hoskins, Minister of Health and Long-Term Care, I have sent him a copy of council's resolution. I trust that the minister will also take council's views into consideration.

Thank you again for the information. Please accept my best wishes.

Sincerely,

Kathleen Wynne
Premier

c: The Honourable Dr. Eric Hoskins

REFERRAL TO _____
RECOMMENDED
DIRECTION REQUIRED _____
RECEIPT RECOMMENDED ✓

(17)

MUNICIPALITY OF CHARLTON AND DACK

Resolution of Council

MOVED BY: Chauncey Corley

MOTION NO: 17-079

SECONDED BY:

DATE: March 13th, 2017

THAT we, the Council for the Municipality of Charlton and Dack support the Regional Municipality of Peel in requesting the Premier and the Minister of Health and Long Term Care undertake appropriate and comprehensive toxicity testing necessary to reassure the public that the use of Hydrofluorosilcic Acid treatments is safe and take legislative responsibility for the regulation and administration of Hydrofluorosilcic Acid in water fluoridation treatments across the Province.

Certified to be a true copy from the Corporation of the Municipality of Charlton and Dack, passed in Council on the 13 day of March, 2017.

Dan Thibeault, Clerk Treasurer CAO
Municipality of Charlton and Dack

RECEIVED
March 13, 2017
REGION OF PEEL
OFFICE OF THE REGIONAL CLERK

REFERRAL TO _____
RECOMMENDED
DIRECTION REQUIRED _____
RECEIPT RECOMMENDED ✓

✓	CARRIED
	DEFEATED
	DEFERRED

Signature of Presiding Officer: M.N. Bond

DIVISION VOTE

Position	Name	Yeas	Nays
Councillor	Chauncey Corley		
Councillor	Jim Huff		
Councillor	Debbie Veerman		
Councillor	Clem Yantha		
Reeve	Merrill Bond		

DECLARATION OF CONFLICT OF INTEREST

_____ _____

declared their interest, abstained from the discussion and did not vote on the question.

Township of Georgian Bay

March 14, 2017

Regional Municipality of Peel
c/o Frank Dale, Regional Char and CEO
10 Peel Centre Drive
Suite A
Brampton, Ontario
L6T 4B9

Dear Mr. Dale:

Re: Regional Fluoridation– Resolution 2017-68

Our office is in receipt of your correspondence, dated February 22, 2017, pertaining to the above-noted matter.

The Township of Georgian Bay's Procedural By-law states that resolutions / requests shall be forwarded to each member of Council for information and shall be placed on an agenda for consideration only at the request of a Council member.

Should a Councillor bring this resolution / request forward at an upcoming meeting, our office will advise you of Council's decision accordingly.

Yours truly,

Amber McDonald
Deputy Clerk (A)
amcdonald@gbtownship.ca

REFERRAL TO _____
RECOMMENDED
DIRECTION REQUIRED _____
RECEIPT RECOMMENDED ✓ _____

Municipalité de
Municipality of
MATTICE-VAL CÔTÉ

Sac postal / P.O. Bag 129, Mattice, Ont. P0L 1T0
(705) 364-6511 – Fax: (705) 364-6431

Meeting no. 17-04 **Resolution no. 17-40** **Date: March 20th, 2017**

Moved by: Richard Lemay **Seconded by: Daniel Grenier**

WHEREAS the Minister of Health and Long Term Care, Dr. Eric Hoskins, supports the benefits of water fluoridation as an important measure to protect the health of Ontarians;

AND WHEREAS Municipal Councillors do not have the detailed familiarity to interpret data regarding the efficacy of Hydrofluorosilicic Acid (HFSA) in water fluoridation treatments and are struggling with a range of conflicting reports and public concern on the matter of fluoridation;

NOW THEREFORE BE IT RESOLVED THAT Council for the Municipality of Mattice - Val Côté hereby supports Resolution 2017-68 made by Council for the Regional Municipality of Peel requesting the Premier of Ontario and the Minister of Health and Long Term Care, whose mandate it is to protect the health of Ontarians, (i) to undertake appropriate and comprehensive toxicity testing necessary to reassure the public that the use of HFSA in water fluoridation treatments is safe and (ii) take legislative responsibility for the regulation and administration of HFSA in water fluoridation treatments across the province, relieving local governments from what is a provincial responsibility, and;

BE IT FURTHER RESOLVED THAT a copy of this resolution be sent to the Regional Municipality of Peel, to MP Carol Hughes and to MPP Gilles Bisson.

Mayor, Michel Brière
President Officer

Carried _X_ Defeated ___ Deferred ___

Recorded Vote
(unanimous unless indicated below)

Name	Yeas	Neas	Abstention
Brière, Michel			
Grenier, Daniel			
Lemay, Richard			
Lemieux, Normand			
Malenfant, Joyce			

Certified by: Guylaine Coulombe, ~~CAO~~/Clerk

REFERRAL TO _____
RECOMMENDED
DIRECTION REQUIRED _____
RECEIPT RECOMMENDED ✓

Corporation of the Town of LaSalle

5950 Malden Road, LaSalle, Ontario, N9H 1S4
Phone: 519-969-7770 Fax: 519-969-4469 www.town.lasalle.on.ca

Agatha Armstrong, Deputy Clerk

March 21, 2017

The Honourable Kathleen Wynne
Premier of Ontario
Legislative Building – Room 281
Queen's Park
Toronto, Ontario
M7A 1A1

Dear Premier Wynne:

RE: Resolution regarding Community Water Fluoridation from the Regional Municipality of Peel

Please be advised that Town of LaSalle Council at its meeting held March 14, 2017 gave consideration to correspondence from the Regional Municipality of Peel regarding community water fluoridation. At this time, Town of LaSalle Council also endorsed and supported this Correspondence through the following resolution:

> ***WHEREAS*** *the Minister of Health and Long Term care is working to establish a health system in Ontario that is based on helping people stay healthy, delivering good care when people need it, and protecting the health system for future generations;*
>
> ***AND WHEREAS****, the Ministry of Health and Long Term Care has changed its focus to work towards better health care for Ontarians, and stewardship has become its mission and mandate;*
>
> ***AND WHEREAS****, this new stewardship role will mean that the Ministry will provide overall direction and leadership for the system, developing legislation, regulations, standards, policies and directives to support the health of Ontarians;*
>
> ***AND WHEREAS****, on January 7, 2016 the Region of Peel received a letter from the Minister of Health and Long Term Care, Dr. Eric Hoskins, supporting the benefits of water fluoridation as an important measure to protect the health of Ontarians;*
>
> ***AND WHEREAS****, the Province of Ontario is responsible for The Safe Drinking Water Act, the purposes of which include (i) recognizing that the people of Ontario are entitled to expect their drinking water be safe and (ii) providing for the protection of human health and the prevention of drinking water health hazards through the control and regulation of drinking water systems and drinking water testing;*

***AND WHEREAS**, Municipal Councillors do not have the detailed familiarity to interpret data regarding the efficacy of Hydrofluorosilicic Acid (FHSA) in water fluoridation treatments and are struggling with a range of conflicting reports and public concern on the matter of fluoridation;*

***THEREFORE BE IT RESOLVED**, that Regional of Peel Council request the Premier of Ontario and the Minister of Health and Long Term Care, whose mandate it is to protect the health of Ontarians, (i) to undertake appropriate and comprehensive toxicity testing necessary to reassure the public that the use of HFSA in water fluoridation treatments is safe; and (ii) take legislative responsibility for the regulation and administration of HFSA in water fluoridation treatments across the province relieving local governments from what is a provincial responsibility;*

***AND FURTHER THAT**, a copy of this resolution be circulated to the Honourable Kathleen Wynne, Premier of Ontario and the Honourable Dr. Eric Hoskins, Minister of Health and Long Term Care.*
Carried.

Thank you for your attention to this matter.

Sincerely,

Agatha Armstrong
Deputy Clerk

Cc: ~~Frank Dale, Regional Chair and CEO, Regional Municipality of Peel~~
Honourable Dr. Eric Hoskins, Minister of Health and Long Term Care

LA CORPORATION DU / THE CORPORATION OF

CANTON DE CHAMPLAIN TOWNSHIP

BUREAU ADMINISTRATIF / ADMINISTRATION OFFICE
948 est, chemin Pleasant Corner Road East
Vankleek Hill, Ontario (KOB 1RO)

613-678-3003
(fax) 613-678-3363

March 21, 2017

Frank Dale
Regional Chair and Chief Executive Officer
The Regional Municipality of Peel
10 Peel Centre Drive, Suite A
Brampton, ON L6T 4B9

RE: Request for Support for Safety of HFSA in Water Fluoridation Treatments

Champlain Township resolved to support Resolution No. 2017-68 of the Regional Municipality of Peel, dated February 9, 2017, requesting that the Government of Ontario (i) to undertake appropriate and comprehensive toxicity testing necessary to reassure the public that the use of HFSA in water fluoridation treatments is safe and (ii) take legislative responsibility for the regulation and administration of HFSA in water fluoridation treatments across the province relieving local governments from what is a provincial responsibility.

A copy of Council's resolution 2017-119 dated March 14, 2017, is attached for your records.

Yours truly,

Alison Collard

Alison Collard
Clerk

RECEIVED
MAR 24 2017
Region of Peel
Clerks Dept.

Attach.

cc: The Honourable Kathleen O. Wynne, Premier
The Honourable Dr. Eric Hoskins, Minister of Health and Long-Term Care
Grant Crack, M.P.P., Glengarry-Prescott-Russell

REFERRAL TO _____
RECOMMENDED
DIRECTION REQUIRED _____
RECEIPT RECOMMENDED ✓

Phone: 705-544-2244

Fax: 705-544-8737

P.O. Box 399
Englehart, Ontario P0J 1H0

March 22, 2017

Municipality of Peel Regional
10 Peel Centre Dr. Suite A
Brampton, ON
L6T 4B9

Re: Motion No: COU1-17-03-04

Please find included a certified copy of a motion that was passed in Council on March 8, 2017 support your resolution requesting the Premier of Ontario and Minister of Health and Long Term Care to undertake water toxicity testing across the province.

Therese Hall
Administrative Assistant
Town of Englehart

REFERRAL TO _____
RECOMMENDED
DIRECTION REQUIRED _____
RECEIPT RECOMMENDED ✓ _____

Email: englehrt@ntl.sympatico.ca

Website: www.englehart.ca

THE CORPORATION OF THE TOWN OF ENGLEHART

NO.: COU1-17-03- 04

MOVED BY: _____

SECONDED BY: _____

DATE: March 8, 2017

Be it resolved that the Council of the Town of Englehart support the attached resolution of the Municipality of Peel Regional requesting the Premier of Ontario and the Minister of Health and Long Term Care to undertake toxicity testing necessary to reassure the public that the use of HFSA in water fluoridation treatments is safe and to take responsibility for the administration of HFSA in water fluoridation treatments across the province;

And further, that a copy of this resolution be forwarded to the Municipality of Peel Regional.

CARRIED ☑ DEFEATED ☐

SIGNATURE: _____

DIVISION VOTE

	F	A		F	A
Councillor D. Metson	☐	☐	Councillor J. Emrick	☐	☐
Councillor P. Brassard	☐	☐	Councillor J. deLeeuw	☐	☐
Councillor T. Wilson	☐	☐	Councillor P. Burey	☐	☐
Mayor N. Wallace	☐	☐	Total	☐	☐

DECLARATION OF CONFLICT OF INTEREST

_____ _____

Disclosed his/her/their interest, abstained from discussion and did not vote on the question.

Certified to be a true copy of the original document _____ Clerk

Town of The Blue Mountains

32 Mill Street, P.O. Box 310, Thornbury, ON N0H 2P0

Tel: (519) 599-3131 • Fax: (519) 599-7723
Toll Free: 1-888-BLU-MTNS (1-888-258-6867)
info@thebluemountains.ca • www.thebluemountains.ca

RECEIVED
March 27, 2017
REGION OF PEEL
OFFICE OF THE REGIONAL CLERK

March 27, 2017

Moved by: Michael Martin **Seconded by:** John McGee

THAT Council of the Town of The Blue Mountains acknowledges receipt of the correspondence from Regional Municipality of Peel the February 9, 2017 Motion of the Community Water Fluoridation Committee regarding Regional Fluoridation, CARRIED.

CERTIFIED TO BE A TRUE COPY

Krista Royal, Deputy Clerk

REFERRAL TO _____
RECOMMENDED
DIRECTION REQUIRED _____
RECEIPT RECOMMENDED ✓

From: Liesa Cianchino [redacted]
Sent: March 29, 2017 4:42 PM
To: Law, Curtiss
Cc: Lockyer, Kathryn
Subject: Request to check for response letter from Minister Hoskins to Chair Frank Dale re: Letter to Province dated May 28th, 2016

Hi Curtiss,

I contacted Regional Chair Frank Dale's office and left a message for Victoria to get back to me. I did not leave her a message with the details of my request.

Sorry to add to your workload. Could you or someone else please find out if the Region received a response to Chair Dale's letter to Minister Dr. Eric Hoskins, dated May 28th, 2016 regarding an update to the provincial policy of water fluoridation. I did try to go through many agendas and was unable to locate it.

If the Region has received a reply, please forward me a digital copy of Chair Dale's letter (I have the copy from the Agenda - I need it as a separate document) and a copy of the response letter if the Region received a response from Dr. Hoskins.

I have attached a copy of the agenda which contains the letter from Chair Dale. It is Item 5.6. Hope this helps.

Thank you for your continued assistance.

Liesa

REFERRAL TO _____
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DIRECTION REQUIRED _____
RECEIPT RECOMMENDED ✓_____

From: Sprovieri, John Councillor <John.Sprovieri@brampton.ca>
Sent: Friday, March 31, 2017 4:12 PM
To: Saha, Sudip
Cc: Loh, Lawrence; Sprovieri, John

Subject: FW: Alzheimer's.

Hello Dr. Saha and Loh,

F.Y.I.

John Sprovieri

Regional Councillor for wards 9 & 10

City of Brampton

(905) 874-2610

«Drinking water contains multiple forms of aluminum, including aluminum–fluoride complexes, which are readily absorbed in the GI tract and cross the blood–brain barrier.[32,68,69] It is the aluminum–fluoride complex form that has the greatest potential for biological impact, where toxicity stems from mimicking gamma-phosphate, altering enzyme activity and activating guanine nucleotide-binding proteins (G-proteins), which are integral to endocrine and nervous system functions.[60,70–78] Al–fluoride complexes have been shown to be markedly more toxic than fluoride alone regarding deposition of aluminum in the brain and kidney and cerebrovascular and neuronal integrity.[32]»

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From: Liesa Cianchino
Sent: March 31, 2017 3:48 PM
To: Stefaniak, Victoria
Subject: Re: Request to check for response letter from Minister Hoskins to Chair Frank Dale re: Letter to Province dated May 28th, 2016

Good afternoon Victoria,

Thank you for returning my call yesterday.

I just called you back and left you a message indicating that I would send you an email with with my request.

Please provide me with an electronic copy of Chair Dale's letter to Minister Dr. Eric Hoskins, dated May 28th, 2016 regarding an update to the provincial policy of water fluoridation.

Also, can you please tell me if Chair Dale received a response letter from Dr. Hoskins and if so, please provide me a copy of the letter.

Thank you for your assistance.

Kind Regards,
Liesa Cianchino

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CITY OF ST. CATHARINES

Legal and Clerks Services

Office of the City Clerk
PO Box 3012, 50 Church Street
St. Catharines, ON L2R 7C2

Phone: 905.688.5600
Fax: 905.682.3631
TTY: 905.688.4TTY (4889)

March 31, 2017

Regional Municipality of Peel
Attn: Frank Dale
10 Peel Centre Dr., Suite A
Brampton, ON L6T 4B9
Sent via email: zzg-regionalclerk@peelregion.ca

Re: Request for Support of Resolution 2017-68 regarding: Community Water Fluoridation Committee (CWFC-1/2017) – Regional Fluoridation
Our File: 35.11.2

Please be advised that the City of St. Catharines Council, at its Regular Meeting held March 20, 2017, were distributed correspondence which included your motion regarding Resolution 2017-68 - Regional Fluoridation.

The Mayor and Members of Council received and filed the correspondence providing no further direction.

Should you have any questions, please do not hesitate to contact the Office of the City Clerk at Extension 1517.

Bonnie Nistico-Dunk
City Clerk

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RECOMMENDED
DIRECTION REQUIRED _____
RECEIPT RECOMMENDED ✓_____

From: Sprovieri, John Councillor [mailto:John.Sprovieri@brampton.ca]
Sent: March 31, 2017 3:24 PM
To: Dobush, Olha; Lockyer, Kathryn
Cc: 'nancy.polsenelli@peelregion.ca'; Loh, Lawrence; Parrish, Carolyn; Palleschi, Michael; Moore, Elaine; Sprovieri, John; Downey, Johanna; Groves, Annette; Ras, Karen; Tovey, Jim; Dale, Frank
Subject: FW: Alzheimer's.

Hi Katheryn,
Can you place these issue on the Agenda for our next Water Fluoridation Committee Meeting.
John.

Hello Olha,
F.Y.I. Can you have a look at the attached studies to discuss at the next Water Fluoridation Committee meeting.
Also, it is my understanding that Health Canada list Fluoride as a Mineral Nutrient whereas the U.S FDA does not recognize Fluoride as a Mineral Nutrient because no Toxicology studies have been done on Fluoride to prove Its safety at any levels. As you may be aware, according to the Clinical Toxicology of Commercial Products, Lead, Arsenic and Fluoride have similar Toxicity levels. Yet, The EPA and MOE allows 400 times more Fluoride then Arsenic and 265 times more Fluoride then Lead in our drinking water. Can you look into this matter, for discussion at the next Community Water Fluoridation Committee.
It is also my understanding that when HFSA is added to the water supply, the Fluoride Eons that are released from the HFSA bind to the heavy metals, such as Lead, Arsenic, Mercury, Radium and Aluminum that are exists in HFSA.
From what I have learned, no Toxicology studies have been done to prove that these new Toxic compounds are harmless to Infants that are bottle fed, People suffering from various health conditions and seniors. Can you look into this matter for discussion at our next Water Fluoridation Committee Meeting.

John Sprovieri
Regional Councillor for wards 9 & 10
City of Brampton
(905) 874-2610

Dear John,

Fluoride may bind with aluminium in tap water and aluminum is a common contaminant in fluoridation chemicals. Aluminum fluoride is a disturbing many enzymes, particularly in the brain. The study of Strunecka is very important in this field.

Mullenix, P. J. «A new perspective on metals and other contaminants in fluoridation chemicals.» *Int J Occup Environ Health*. 2014; vol. 20(2): 157–166.

Varner, J.A., Jensen, K.F., Horvath, W., Isaacson, R.L. «Chronic administration of aluminum-fluoride or sodium-fluoride to rats in drinking water: alterations in neuronal and cerebrovascular integrity». *Brain Res*. 1998; vol. 784 (1-2):284–98.

Chabre M. «Aluminofluoride and beryllofluoride complexes: new phosphate analogs in enzymology». *Trends Biochem Sci*. 1990;15(1):6–10.

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DIRECTION REQUIRED _____
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Li L, Fleming N. Aluminum fluoride inhibits phospholipase D activation by a GTP-binding protein-independent mechanism. *FEBS Lett*. 1999; vol. 458(3):419-23.

Strunecka A, Strunecky O, Patocka J. «Fluoride plus aluminum: useful tools in laboratory investigations, but messengers of false information.» *Physiol Res*. 2002; vol. 51(6):557–64.

Strunecka, A., Patocka, J., Blaylock, R. L., Chinoy, N.J. «Fluoride Interactions: From Molecules to Disease». *Current Signal Transduction Therapy;* 2007; Vol.2 (3): 190-213.

Health Canada has never done toxicological tests on fluoride as a supplement, it has been accepted as with the grandfather rules, being there before Health Canada ruling for drugs.

Hello Councillor,

As discussed please find the information below:

In Finland between 0.1 and 3.0 mg/L

Concentration of fluoride in groundwater in the EU is generally low, but there can be large variation in the levels in natural drinking water between and within countries.

Thank-you,

Hello Councillor,

From multiple sources I received the same information that Finland does not add fluoride artificially to their water anymore only one town allowed it from 1959-1992. However, some fluoride does occur naturally through ground water.

Website: http://www.slweb.org/europe.html
Information: Finland

"We do not favor or recommend fluoridation of drinking water. There are better ways of providing the fluoride our teeth need." *(Paavo Poteri, Acting Managing Director, Helsinki Water, Finland, February 7, 2000). www.fluoridation.com/c-finland.htm*

"Artificial fluoridation of drinking water supplies has been practiced in Finland only in one town, Kuopio, situated in eastern Finland and with a population of about 80,000 people (1.6% of the Finnish population). Fluoridation started in 1959 and finished in 1992 as a result of the resistance of local population. The most usual grounds for the resistance presented in this context were an individual's right to drinking water without additional chemicals used for the medication of limited population groups. A concept of "force-feeding" was also mentioned.

Drinking water fluoridation is not prohibited in Finland but no municipalities have turned out to be willing to practice it. Water suppliers, naturally, have always been against dosing of fluoride chemicals into water." *(Leena Hiisvirta, M.Sc., Chief Engineer, Ministry of Social Affairs and Health, Finland, January 12, 1996.) www.fluoridealert.org/finland.jpeg*

Website: https://en.wikipedia.org/wiki/Fluoridation_by_country
Information: Finland
Only one community (with 70,000 people) was ever fluoridated, Kuopio.[48] Kuopio stopped fluoridation in 1992.[66] In regions with rapakivi bedrock (small, but densely populated regions), 22% of well waters and 55% of drilled well waters exceed the legal limit of 1.5 mg/l; generally, surface and well waters have 0.5-2.0 mg/l fluoride in affected regions.[67]

Website: http://ec.europa.eu/health/scientific_committees/opinions_layman/fluoridation/en/l-2/1.htm
Information:
Concentration of **fluoride** in groundwater in the EU is generally low, but there can be large variation in the levels in natural drinking water between and within countries. In Ireland, for example, levels vary between 0.01 parts per million (ppm), or mg/L and 5.8 ppm, in Finland between 0.1 and 3.0 mg/L and in Germany between 0.1 and 1.1 mg/L.

Thank-you,

From: Sprovieri, John Councillor
Sent: 2017/03/30 1:13 PM
To: Cheema, Reetu (Navreet) <Reetu.Cheema@brampton.ca>
Cc: Sprovieri, John Councillor <John.Sprovieri@brampton.ca>
Subject: Re:

Hi Navreet,
Can you check if Finland is Fluoridated or has high levels of Naturally occurring fluoride.
John.

Sent from my BlackBerry 10 smartphone on the Rogers network.

From: Cheema, Reetu (Navreet)
Sent: Thursday, March 30, 2017 12:17 PM
To: Sprovieri, John Councillor
Subject: RE:

Hello Councillor,

I was able to find data on the death rate of ALZHEIMERS/DEMENTIA per 100 000 people. Please see the information below, the Countries are in order of rank for highest death rate to lowest.

ALZHEIMERS/DEMENTIA
Death Rate Per 100,000
Age Standardized

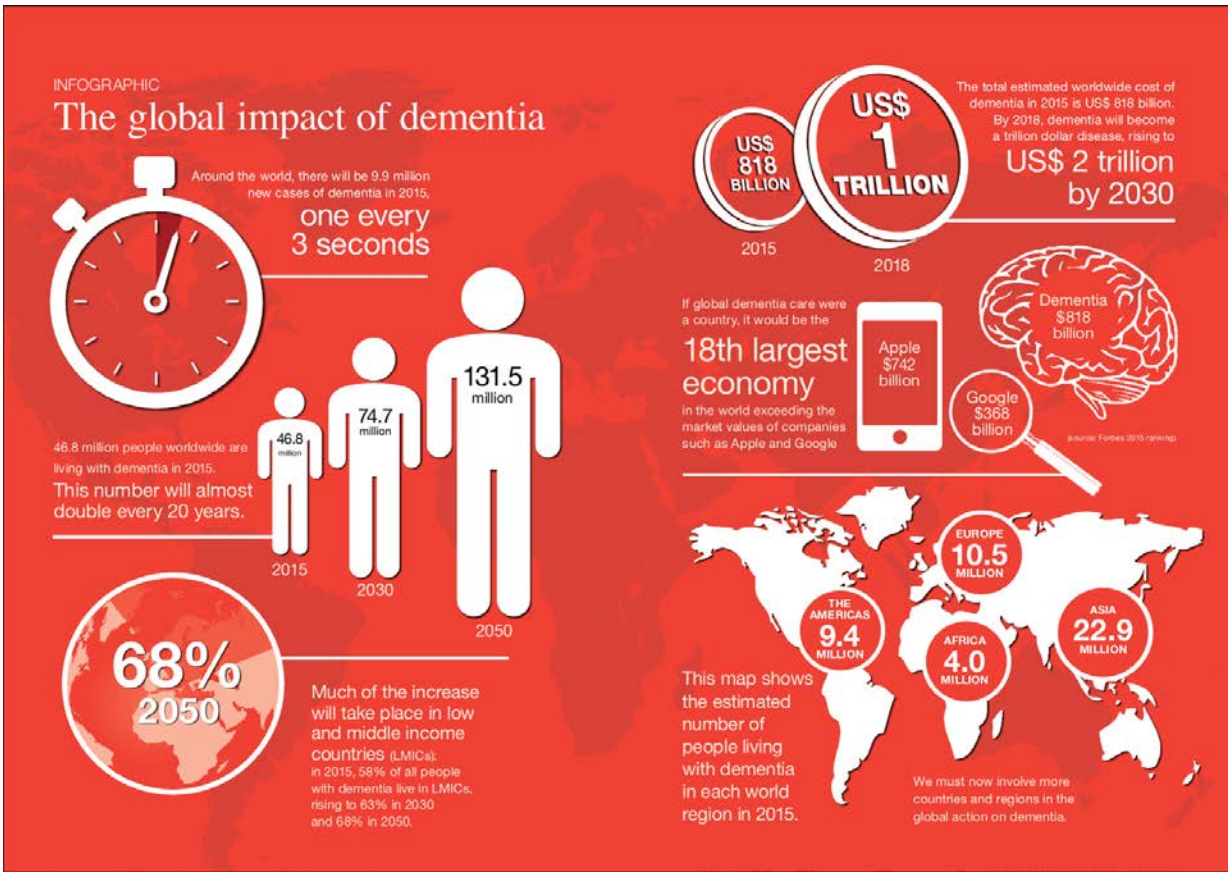
WEBSITE	http://www.worldlifeexpectancy.com/cause-of-death/alzheimers-dementia/by-country/	
RANK	**COUNTRY**	**RATE**
1	**Finland**	53.77
2	**United States**	45.58
3	**Canada**	35.5
4	**Iceland**	34.08
5	**Sweden**	32.41
6	**Switzerland**	32.25
7	**Norway**	30.24
8	**Denmark**	29.53
9	**Netherlands**	29.32
10	**Belgium**	27.23
11	**Spain**	26.9
12	**Australia**	25.91
13	**France**	25.62
14	**United Kingdom**	24.35
15	**Cuba**	22.38
16	**Chile**	21.03
17	**Uruguay**	20.74
18	**Israel**	19.9
19	**New Zealand**	19.02
20	**Ireland**	17.7
21	**Italy**	16.96
22	**Hungary**	15.23
23	**Malta**	14.92
24	**Luxembourg**	14.17
25	**Germany**	13.39
26	**Brazil**	12.56
27	**South Korea**	12.32
28	**Cyprus**	10.4
29	**Costa Rica**	9.98
30	**Iran**	7.75
31	**South Africa**	7.67
32	**Austria**	7.41
33	**Serbia**	7.39
34	**Trinidad/Tob.**	7.25

35	**Bahamas**	6.79
36	**Maldives**	6.71
37	**Portugal**	6.61
38	**Latvia**	6.46
39	**Czech Republic**	6.45
40	**Argentina**	6.44
41	**Qatar**	6.43
42	**Solomon Isl.**	6.42
43	**Croatia**	5.83
44	**Swaziland**	5.45
45	**Arab Emirates**	5.39
46	**Fiji**	5.34
47	**Haiti**	5.21
48	**Equ. Guinea**	5.15
49	**Cape Verde**	5.07
50	**Lesotho**	4.9
51	**Jamaica**	4.83
52	**Botswana**	4.75
53	**China**	4.71
54	**Barbados**	4.48
55	**Iraq**	4.41
56	**Lithuania**	4.33
57	**Cameroon**	4.26
58	**Japan**	4.23
59	**Djibouti**	4.23
60	**Gabon**	4.2
61	**Estonia**	4.05
62	**Guyana**	4.02
63	**Senegal**	3.93
64	**Jordan**	3.9
65	**Mali**	3.88
66	**Namibia**	3.84
67	**Romania**	3.82
68	**Moldova**	3.73
69	**Bahrain**	3.72
70	**Panama**	3.69
71	**Ghana**	3.56
72	**Mexico**	3.48

73	**Sierra Leone**	3.47
74	**Mauritania**	3.43
75	**Tanzania**	3.38
76	**Sri Lanka**	3.36
77	**Poland**	3.36
78	**Benin**	3.31
79	**Mozambique**	3.3
80	**Belize**	3.3
81	**Nigeria**	3.29
82	**Montenegro**	3.27
83	**Angola**	3.24
84	**Gambia**	3.23
85	**Uganda**	3.17
86	**New Guinea**	3.09
87	**Slovakia**	3.04
88	**Guinea-Bissau**	3
89	**Burkina Faso**	2.95
90	**Cote d Ivoire**	2.95
91	**Chad**	2.94
92	**Morocco**	2.85
93	**Comoros**	2.82
94	**Guinea**	2.77
95	**Kenya**	2.76
96	**Greece**	2.74
97	**Zimbabwe**	2.7
98	**Viet Nam**	2.66
99	**Belarus**	2.65
100	**Kazakhstan**	2.64
101	**Rwanda**	2.63
102	**Niger**	2.57
103	**Togo**	2.54
104	**Dominican Rep.**	2.53
105	**South Sudan**	2.53
106	**Malawi**	2.5
107	**Ecuador**	2.46
108	**Brunei**	2.46
109	**Congo**	2.45
110	**Albania**	2.44

111	**Sudan**	2.4
112	**Oman**	2.38
113	**Mauritius**	2.33
114	**Algeria**	2.28
115	**Liberia**	2.26
116	**Libya**	2.24
117	**North Korea**	2.2
118	**Venezuela**	2.2
119	**Zambia**	2.19
120	**Russia**	2.17
121	**Burundi**	2.12
122	**Eritrea**	1.98
123	**Central Africa**	1.92
124	**DR Congo**	1.87
125	**Somalia**	1.84
126	**Pakistan**	1.78
127	**Bolivia**	1.77
128	**Tunisia**	1.77
129	**Bhutan**	1.7
130	**Syria**	1.66
131	**Turkey**	1.65
132	**Nicaragua**	1.63
133	**Egypt**	1.59
134	**Madagascar**	1.58
135	**Bosnia/Herzeg**	1.53
136	**Lebanon**	1.5
137	**Ethiopia**	1.48
138	**Nepal**	1.36
139	**Guatemala**	1.31
140	**Ukraine**	1.28
141	**Paraguay**	1.27
142	**Colombia**	1.24
143	**Bangladesh**	1.22
144	**Saudi Arabia**	1.21
145	**Philippines**	1.2
146	**Indonesia**	1.19
147	**Slovenia**	1.14
148	**Honduras**	1.12

149	**Armenia**	1.11
150	**Peru**	1.03
151	**Thailand**	0.98
152	**El Salvador**	0.93
153	**Yemen**	0.92
154	**Myanmar**	0.85
155	**Bulgaria**	0.84
156	**Turkmenistan**	0.77
157	**Malaysia**	0.74
158	**Macedonia**	0.73
159	**Laos**	0.71
160	**Mongolia**	0.71
161	**Timor-Leste**	0.7
162	**Afghanistan**	0.65
163	**Kuwait**	0.6
164	**Azerbaijan**	0.47
165	**India**	0.46
166	**Cambodia**	0.46
167	**Tajikistan**	0.42
168	**Kyrgyzstan**	0.38
169	**Uzbekistan**	0.37
170	**Georgia**	0.25
171	**Singapore**	0.19
172	**Suriname**	0



From: Sprovieri, John Councillor
Sent: 2017/03/30 11:10 AM
To: Cheema, Reetu (Navreet) <Reetu.Cheema@brampton.ca>
Cc: Sprovieri, John Councillor <John.Sprovieri@brampton.ca>
Subject:

Hi Navreet,
Can you see if there is data on the levels of dementia in European countries, Canada, U.S. Britain, India, Australia and China.
John.

Sent from my BlackBerry 10 smartphone on the Rogers network.

Current Signal Transduction Therapy, 2007, *2*, 000-000

Fluoride Interactions: From Molecules to Disease

Anna Strunecka[1,*], Jiri Patocka[2], Russell L. Blaylock[3] and Niloufer J. Chinoy[4,†]

[1]*Department of Physiology and Developmental Physiology, Faculty of Science, Charles University in Prague, Czech Republic,* [2]*Department of Radiology and Toxicology, Faculty of Health and Social Studies, University of South Bohemia, Ceske Budejovice, Czech Republic,* [3]*Department of Biology, Belhaven College, Jackson, Mississipi, USA,* [4]*Department of Zoology, University School of Sciences, Gujarat University, Ahmedabad, India*

Abstract: Fluoride has long been known to influence the activity of various enzymes *in vitro*. Later it has been demonstrated that many effects primarily attributed to fluoride are caused by synergistic action of fluoride plus aluminum. Aluminofluoride complexes have been widely used as analogues of phosphate groups to study phosphoryl transfer reactions and heterotrimeric G proteins involvement. A number of reports on their use have appeared, with far-reaching consequences for our understanding of fundamental biological processes. Fluoride plus aluminum send false messages, which are amplified by processes of signal transduction. Many investigations of the long-term administration of fluoride to laboratory animals have demonstrated that fluoride and aluminofluoride complexes can elicit impairment of homeostasis, growth, development, cognition, and behavior. Ameliorative effects of calcium, vitamins C, D, and E have been reported. Numerous epidemiological, ecological, and clinical studies have shown the effects of fluoride on humans. Millions of people live in endemic fluorosis areas. A review of fluoride interactions from molecules to disease is necessary for a sound scientific assessment of health risks, which may be linked to the chronic intake of small doses of fluoride and aluminum from environmental and artificial sources.

FINAL

Key Words: Fluoride, aluminofluoride complexes, G proteins, animal modeling, human exposure, neurotoxicity.

INTRODUCTION

The use of fluoride in laboratory investigations helped in the discovery of glycolytic and Krebs-cycle pathways. The finding by Rall and Sutherland in 1958 that adenylyl cyclase (AC) is activated by fluoride started the era of new discoveries on signal transduction processess [1-4]. During the last two decades, there are numerous references of laboratory studies involving fluoride alone or in combination with aluminum ions (Al^{3+}), mostly investigating its role as a general pharmacological activator of G protein-coupled systems. The effects of fluoride have been studied in many cells/tissues *in vitro* and whole organisms *in vivo*. The expanding research provides evidence that fluoride affects life processes from fertilization to ageing, from gene transcription to cognition with powerful efficacy [5, 6]. In addition to the interpretation of laboratory investigations using isolated cells/tissues or animal models, many epidemiological, ecological, and clinical studies have shown the effects of fluoride on domestic animals and humans.

Dean´s reports formed the foundation of the concept that the ingestion of fluoride will harden the surface of teeth and make them less susceptible to dental caries [7, 8]. The artificial fluoridation of drinking water as a way of preventing dental caries has been in practice for over 50 years in several countries. The past 50 years have seen a dramatic increase in the volume of man-made industrial fluoride compounds released into the environment. Fluoridation of drinking water as well as the use of aluminum sulfate as a flocculating agent in water treatment plants, in addition to the wide use of fluoride and Al^{3+} in medicine, industry, and agriculture, started the era of supplementation of living environment with these ions as never before in the history of human race [9, 10]. Dental fluorosis as the sign of fluoride overload is endemic in at least 25 countries across the globe. Millions of people live in endemic fluorosis area. WHO recently estimated that 2.7 million people have skeletal fluorosis in China, over 6 millions suffer this crippling bone disease in India. Carlsson concerns about what increased fluoride levels would do to the developing brain of newborn infants [11] have gained renewed significance in light of recent findings concerning fluoride and Al^{3+} potential neurotoxicity.

The objective of our article is to provide a comprehensive review of fluoride and aluminofluoride complexes interactions with some components and processes of signal transduction. Such knowledge could help to increase scientific understanding of health risks linked to the chronic but cumulative intake of small doses of fluoride plus Al^{3+} from environmental and artificial sources.

*Address correspondence to this author at the Department of Physiology and Developmental Physiology, Faculty of Science, Charles University in Prague, Vinicna 7, 128 00 Prague 2, Czech Republic; Tel: +420 221951769; Fax: +420 221951761; E-mail: strun@natur.cuni.cz

MECHANISMS OF FLUORIDE ACTION

The highly electronegative fluoride ion with the same size and the same valence orbital as oxygen became the useful laboratory tool in our understanding of the biochemical and biophysical mechanisms of enzyme catalysis underlying biological processes as metabolism and signal transduction. Of particular interest is the ability of fluoride to induce free radical generation and lipid peroxidation in the brain.

1. The Effects of Fluoride on Metabolic Enzymes and Energy Metabolism

The most important enzyme of carbohydrate metabolism inhibited by fluoride is enolase, which changes 2-phosphoglycerate to phosphoenolpyruvate and is intimately related to anaerobic production of energy in glycolysis [12]. The inhibitory effect of fluoride on enolase activity was later identified to be through competition with magnesium (Mg^{2+}) [13]. The competition with Mg^{2+} seems to be also a mechanism of fluoride inhibition of the group of inorganic pyrophosphatases, which catalyze one of the oldest and most common reactions in cells [14, 15]. Fluoride interacts first with the Mg^{2+} on the enzyme in a readily reversible reaction causing a 90% decrease of the catalytic activity. Thereafter, a slow isomerization of the enzyme substrate complex takes place, resulting in a complete loss of activity [16].

Lunardi *et al*. [17] reported that the inhibition of mitochondrial F-ATPase by fluoride requires the presence of Al^{3+}. Prior incubation with the Al^{3+} chelator deferoxamine markedly slowed inactivation, whereas adding 1 μM $AlCl_3$ speeded it. Missianen *et al*. [18] studied the fluoride effect on the Ca^{2+}-Mg^{2+}-ATPase of the endoplasmic reticulum and provided evidence that the time course of inhibition and the concentrations of fluoride and Al^{+} required for this inhibition differ for enzymes from different tissues. The mechanism of fluoride inhibition of P-type cation-transport ATPases has been suggested by the action of aluminofluoride complexes (AlFx), which act as phosphate analogues [17-19].

The experimental evidence indicates that the effects of fluoride on some metabolic enzymes might be attributed to the action of fluoride alone. For example, fluoride has been often used as the inhibitor of various tyrosine and serine/threonine protein phosphatases. Nevertheless, in many cases the biological activity of fluoride is realized by synergistic action of fluoride plus Al^{3+} [20-22]. Ta-

1574-3624/07 $50.00+.00

bles **1** and **2** summarize the observed effects of fluoride on various enzymes with indication of the requirements for Al^{3+}.

2. AlFx Intervention into Phosphoryl-Transfer Reactions

The average stoichiometry of AlFx depends on the fluoride concentration and the pH of the solution [14, 84, 85]. For most of the physiological and biochemical studies involving the putative AlFx, the fluoride source is usually NaF and the Al^{3+} source is $AlCl_3$. Moreover, Al^{3+} is a frequent contaminant of commercial chemicals and it can be picked up from the glass surface, depending on the substance stored in the glass container [86]. The phenomenological observations seemed to verify that pH determines the complexation state of AlFx [20, 87]. The theoretical calculation of the Al^{3+}-fluoride predominance is demonstrated on Fig. (**1**). However, the exact structure and the proportions of species such as AlF_3 and tetrafluoroaluminate anion (AlF_4^{1-}) able to simulate PO_4^{3-} group in many biochemical reactions are still disputed [22, 88]. Al^{3+} forms stronger complexes with fluoride than with the other halides. Out of 60 metal species, Al^{3+} is surpassed only by Sc^{3+} in forming the stronger bond to fluorine [89]. AlF_3 is the most thermodynamically stable compound of fluorine and Al^{3+}.

The ability of these complexes to simulate phosphate groups in many biochemical reactions has been documented by numerous studies. AlFx can bind to proteins by hydrogen bonds to the fluorine atom just as with oxygen atoms of a phosphate ion. Analogies between phosphate group and AlFx consist in atomic and molecular similarities. The fluorine atom has the same size and the same valence orbital as oxygen. Aluminum is close to phosphorus; their valence electrons are in the same shell. An Al-F bond is the same length as a P-O bond in phosphate, i.e.1.5 to 1.6 Å. Like phosphorus, aluminum has possible coordination numbers of 1 - 6, due to the possible hybridization of its outer shell 3p electrons with the 3d

Table 1. Inhibitory Effects of Fluoride on Enzymatic Activities. Al Dependency: Yes Means that Al^{3+} is Required, not Required (NR) Means that it has been Examined, not studied (NS) Means that the Presence of Al^{3+} Contamination is not Excluded

ENZYME	SOURCE	NaF	Al^{3+}	REFERENCES
acid phosphatase	ram semen osteoblasts osteoclasts bone marrow, kidney	20-200 µM mM mM <0.5 mM	NS NR Yes NS	[23] [24] [25] [26, 27]
aconitase	liver	mM	NS	[28]
adenylyl cyclase	liver fibroblasts	up to 10 mM 5 mM	Yes Yes	[29] [30]
AChE	red blood cell brain	0.01-10 mM 5-50 mM	Yes NS	[6] [31]
arginase	liver, kidney	>4 mM	NS	[32]
BuChe	blood plasma	50 µM	NS	[33]
enolase	red blood cell hepatocytes embryonic cells oral bacteria	1-50mM 3 mM 1mM, 50µM 16-54 µM	NR NR NS NS	[13, 34] [35] [36] [37]
F-ATPase	mitochondria	mM	Yes	[17]
glucose-6-phosphatase	liver	µM	Yes	[38]
glycogen synthase	hepatocytes	2-15 mM	Yes	[39]
IMPase	fibroblasts brain	mM 20 mM	Yes NR	[40] [41]
lactate dehydrogenase	ram semen fetal osteoblast bone marrow	20-200 µM 6 – 60 µM <0.5 mM	NS NS NS	[23] [42] [26]
lipase	pankreas, liver	10 mM	NS	[12]
L-Ca^{2+}channels	heart	10 mM	NR	[43]
Na^{+}/K^{+} ATPase	plasma membrane kidney	1-10 mM 1-10 mM 5mM	NR Yes NS	[44] [18] [45]
PKC	retina	mM	Yes	[46]
PLD	liver, brain, lymphocyte	mM	Yes	[47]
protein phosphatase	liver bone	10 – 50 mM µM	NR NR	[48] [49]
pyrophosphatase	yeast	5 mM	NR	[16]
pyruvate kinase	red blood cell	10-50 mM	NS	[50]
succinate dehydrogenase	heart, liver, kidney	mM	NS	[51, 52]
urease	animal	mM	NS	[12]

Table 2. Stimulatory Effects of Fluoride on Enzymatic Activities. Al Dependency: Yes Means that Al^{3+} is Required, not required (NR) Means that it has been Examined, not Studied (NS) Means that the Presence of Al^{3+} Contamination is not Excluded

ENZYME	SOURCE	NaF	Al^{3+}	REFERENCES
adenylyl cyclase	heart, liver, brain	10 mM	NS	[2]
	lymphoma cell	10 mM	Yes	[53]
	smooth muscle	10 mM	Yes	[48]
	heart	1-10 mM	Yes	[54, 55]
	turkey RBC	10 mM	Yes	[56]
	brain	10 mM	Yes	[57]
	kidney	10 mM	Yes	[58]
alkaline phosphatase	bone cells	10-100 μM	Yes	[59, 60]
aspartate transaminase	ram semen	20-200 μM NaF	NS	[23]
Ca^{2+}-ATPase	heart, muscle SR	1-10 mM	NR	[61]
c PIPsynthase	liver	10mM	NS	[62]
cytidylate cyclase	rat brain	mM	Yes	[63]
ERK	bone	1 – 10 mM	Yes	[64]
glu S-transferase	ram semen	20-200 μM	NS	[23]
$K^+[ACh]_M$ channel	heart	>1 mM	Yes	[65]
K^+ATP channel	heart	mM	Yes	[66]
lactate dehydrogenase	hepatocytes	1-30 mM	NS	[67]
	ram semen	20-200 μM NaF	NS	[23]
L-type Ca^{2+} channel	rabbit femoral artery	10 mM	NR	[48]
MAP kinases	lung	5-7.5 mM	Yes	[68]
glycogen phosphorylase	hepatocytes	1-50 mM	augments	[29, 69]
PI 3-kinase	human HepG2 cells and HeLa cells	30 mM	Yes	[70]
PKC	lung	5-7.5 mM	Yes	[68]
	macrophages	mM	NR	[71]
PLA2	platelets	5 - 10mM	Yes	[72]
	macrophages	5 – 10 mM	Yes	[73]
			NR	[71]
	endothelial cells	5 – 20 mM	Yes	[74]
PLC	hepatocytes	1-50 mM	Yes	[56, 75]
	RBC	1 mM	Yes	[76]
	rabbit femoral artery	10 mM	Yes	[48]
	astrocytes	AlFx intracellulary	Yes	[77]
PLD	platelets	5-10 mM	Yes	[78]
	lymphocytes	10-40 mM	NS	[79]
	rat atria	10 mM	Yes	[80]
	canine cer. cortex	AlFx only	Yes	[81]
tyrosine kinase	osteoblasts	1 – 10 mM	Yes	[82]
		50-200 μM	NS	[83]
		10 – 100 μM	Yes	[59]

orbital. However, an important functional difference between a phosphate group and the structurally analogous AlFx exists [20]. In phosphate, oxygen is covalently bound to the phosphorus and does not exchange with oxygen from solvent, while in the AlFx the bonding between the electropositive Al^{3+} and the highly electronegative fluorine is more ionic in character, allowing fluorine in the bound complex to exchange freely with fluoride ions in solution. While the reaction of a bound phosphate with orthophosphate is endergonic and slow, the corresponding reaction with AlFx is rapid and spontaneous.

3. Fluoride Effects on G Proteins

The finding that adenylyl cyclase (AC) is activated by fluoride made no sense in molecular terms at the time [1, 2]. The breakthrough for explanation of the fluoride effects on G proteins led to the observation that Al^{3+} is a requirement for activation of the regulatory component of AC by fluoride [53]. Of 28 other metal tested, only beryllium could substitute for Al^{3+}.

The liver membranes, multi-receptor fat cell system, and the light-activated rhodopsin system provided the first insight that AC is both inhibited and stimulated by two independent processes involving GTP and fluoride [90-92]. In a detailed study of the light-activated rhodopsin system it was suggested that hydrolysis of GTP is a very rapid process, whereas the rate limiting step is the release of inorganic phosphate from its binding sites on transducin, the G protein responsible for activation of phosphodiesterase (PDE) in rod outer segments. Thus arose the nomenclature now popularly

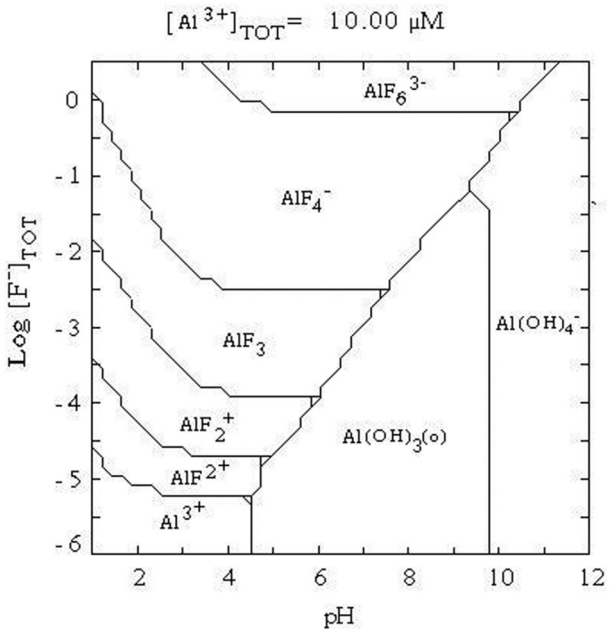


Fig (1). Dependency of the complexation state of AlFx on pH and fluoride concentration for Al^{3+} 10 µM.

known as G_t, G_s, and G_i classes [93]. Beginning with transducin it emerged that G proteins are constructed of three types of subunits, an α-subunit uniquely capable of binding and degrading GTP and a tightly knit complex of β- and γ-subunits. This discovery, eventually established for all G proteins coupled to receptors [3], opened up a new chapter in signal transduction, which, in recent years, has helped to explain the pleiotropic actions of hormones.

Fluoride Plus Al^{3+}: the Tools in the Discovery of the Role of G Proteins

Gilman and co-workers [3, 53] found that the target of the AC activation by fluoride was a heterotrimeric G protein and suggested that the active stimulatory agent was AlF_3. The demonstration that fluoride activation of transducin correlated with the stoichiometric binding of one Al^{3+} to transducin-GDP [19] also led to the suggestion that it is AlFx, which interacts directly with the β-phosphate of GDP. As the heterotrimeric G proteins are activated when they go from the GDP-bound to the GTP-bound state, Chabre [20] suggested that AlFx mimics the role of the γ-phosphate only if the β-phosphate is present and remains unsubstituted on its oxygen. The effect is more readily seen with G proteins because GDP is always tightly bound in the nucleotide site of the protein.

Structures of G_t and G_i have been solved in their GTP-, GDP- and AlFx-liganded states [93]. Gα-subunit is composed of essentially two distinct domains, a Ras-like GTPase domain and a predominantly helical domain that is unique to the Gα-subunit. The bound guanine nucleotide is held at the interface of these domains. In the GTP-bound state, the switch regions are held in place by contacts to the terminal γ-phosphate of the nucleotide, whereas these regions appear to be less ordered in crystals of the GDP-liganded G proteins. The determination of the three-dimensional structures of heterotrimeric G proteins bound to GDP and AlFx [94, 95] confirmed that AlFx is located in the γ-phosphate-binding site of these proteins. The studies of the crystal structures of nucleotide binding proteins complexed with fluoride and Al^{3+} indicate that factors other than pH, such as the location of positively charged amino acid of the active site of the phosphoryl-transferring enzyme may cause deviation from the strict pH dependence of AlF_3 versus AlF_4^{1-} in biological systems [22].

AlFx as Pentavalent Transition State Mimic

The assumption that AlFx acts through its tetrahedral phosphate-like complex was supported by the analogy with beryllium because all beryllium complexes are strictly tetrahedral and cannot take on the pentavalent conformation adopted by phosphate in transition states [20]. However, both ATPase and GTPase pathway must go through a pentacoordinated transition state for the γ-phosphate. The later studies of the crystal structures of nucleotide binding proteins brought evidence that AlFx may also act as the phosphoryl transfer transition state analogue with a pentavalent phosphorus [22]. The X-ray crystallography of heterotrimeric G proteins bound to GDP and AlFx [94, 95] brought evidence that AlF_4^{1-} seems to be the active site species. Al^{3+} is bound to four fluoride ligands in a square-planar coordination with two oxygen ligands at the apical position of the resulting octahedron (Fig. **2**). One oxygen ligand is the γ-phosphate oxygen, the leaving group in the transfer reaction, whereas the other is the oxygen from water believed to represent the attacking nucleophile of the hydrolysis reaction. The structure determination both supports the conclusion that AlF_4^{1-} binding mimics the transition state of the reaction. The structures of the two metabolic enzymes nucleoside diphosphate kinase and uridylate monophosphate kinase unexpectedly indicate that AlF_3 is the transition state mimic [87, 96]. The reason for the differences is not clear at present; however, a pentavalent aluminum more closely resembles the real transition state of the phosphoryl transfer reaction.

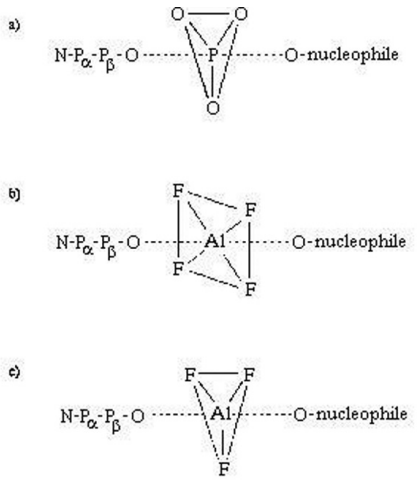


Fig.(2). Conformational changes of the γ-phosphate in a phosphoryl-transfer reaction transition state a) and various species of AlFx: b) AlF_4^{1-}, c) AlF_3. Dotted lines indicate that the degree of bond making and bond breaking determines whether the transition is more dissociative, with a metaphosphate-like intermediate, or associative, with a pentavalent intermediate. Charges have been omitted for clarity. N = guanosine or adenosine.

Fluoride and GTPase Activating Proteins

The GTPase activity of Gα-subunit is regulated by accessory proteins "regulators of G protein signaling" (RGS). The RGS proteins may bind to Gα-subunits accelerating the rate of GTP hydrolysis. The results from a growing number of reconstitution studies indicate that RGS proteins act as GTPase activating proteins (GAPs) of Gα-subunits [93]. The intrinsic GTPase activity of the α-subunit determines the lifetime of the active state of the G protein [4]. Biochemical evidence showed that GAPs bind with higher affinity to G·GDP·AlFx complex of Gα-subunits than to the triphosphate state of G protein, indicating that GAP stabilizes the transition state of the GTPase. This was confirmed by the three-dimensional structure of the GAP·G_{i1}·GDP·AlF_4 complex determined by X-ray crystallography, in which GAP contacts the regions of G_iα-subunit involved in GTP hydrolysis [97].

These findings are complemented and highlighted by the determination of the structure of a complex between RasGAP and Ras·GDP in the presence of Al^{3+} and fluoride ions [98]. The proto-oncogene product Ras is a small G protein that is a component of intracellular signaling pathways involved in cell growth and division. It has a very low intrinsic GTPase reaction rate that is stimulated 105-fold by RasGAPs that downregulate the accumulation of Ras·GTP. Ras binds AlFx only in the presence of RasGAP, and an efficient GTPase site is only created by the addition of stoichiometric amounts of RasGAP [22]. It shows that, in this case AlF_3 forms a pentagonal bipyramid, with the fluorides forming the trigonal base with two apical oxygen ligands. The authors suggest that RasGAP stabilizes the transition state by neutralizing developing charges on the γ-phosphate during phosphoryl transfer.

Subsequently, similar studies demonstrated that several classes of small G proteins can interact with their respective GAPs in the presence of AlFx. Vincent *et al*. [99] reported the ability of fluoride to promote a high-affinity complex between the Ras-related RhoA GTPase and the p190 RhoGAP. Surprisingly, they found that formation of this high affinity complex does not require either Al^{3+} or guanine nucleotide. The possibility of Al^{3+} contamination was examined by the addition of the chelating agents, EGTA and deferoxamine, which can bind Al^{3+}. The chelators did not detectably affect the observed NaF-dependent RhoA-p190 complex. These authors therefore suggested a distinct mechanism of transition state stabilization of small G proteins by fluoride that is not consistent with the phosphate analogue model. However, AlFx can stabilize complexes formed between Ras and RhoA and their corresponding GAPs [100]. AlFx can convert a small G protein Arf1- GDPcomplex into an active conformation *in vitro* and *in vivo*.

4. The Excitotoxic Process

High fluoride levels cause accumulation of large amounts of free radicals and peroxides by inhibiting superoxide dismutase and glutathione peroxidase activities [101]. It mainly causes denaturation of proteins and peroxidation of membrane lipids with increased permeability of cell membrane. Fluoride and AlFx are both known to generate reactive oxygen and nitrogen species (ROS and RNS) and lipid peroxidation (LPO) products [102-105], which have been shown to enhance excitotoxic damage.

There is compelling evidence that excitotoxicity plays a major, if not central, role in a number of neurodegenerative diseases as well as environmental toxicities. Glutamate and aspartate constitute the major excitatory neurotransmitters in the central nervous system (CNS). At low concentrations for brief periods of time, glutamate acts as a neurotransmitter and can even have neurotrophic effects. Yet, higher concentrations over a longer period of time are associated with a series of reactions that can lead to synaptic disruption, dendritic retraction or cell death via necrosis and/or apoptosis. Synaptic loss and dentritic retraction are the earliest reactions and can occur at doses of glutamate below those needed to produce neuron death. Intense, or prolonged interactions of glutamate, or other excitatory molecules, with the glutamate receptors can initiate a series of other destructive reactions that include ROS and/or RNS (especially peroxynitrite), LPO products, the proinflammatory ecosanoid pathways, immune hyperactivity and depressed mitochondrial energy production.

Glutamate receptors are divided into ionotropic (ion-gated) and metabotropic receptors. The inotropic receptors consist of NMDA, AMPA and kainate receptors, each with a specific gating mechanism, distribution and physiological activity. Yet, all three are modulated through direct phosphorylation by both serine/threonine and tyrosine kinases. These ionic receptors have been further characterized by a number of subunits through cloning techniques to include specific patterns of these subunits. For example, NMDA is composed of NR1 and one or more of the NR2A-D subunits. AMPA is composed of GluR1-4 and kainate is encoded by GluR5-7 subunits. These subunits greatly increase the specificity and diversity of reactions possible. In addition to the ionic receptors there are three classes of metabotropic glutamate receptors with eight subtypes thus far identified. These receptors are seven-α-helix receptors connected to G proteins. In the excitatory synapse the metabotropic receptors are arranged along the periphery of the post-synaptic density, with the ionic receptors within the core [106]. Gegelashvili and co-workers [107] demonstrated that metabotropic receptors play a modulatory role on the glutamate transport system. The AlFx complex can activate these receptors since they are operated by G protein systems.

There is an intimate interaction between the metabotropic receptors and NMDA and AMPA receptors, allowing rapid modulation of the excitatory unit. Recent studies indicate that group I and II metabotropic receptors can enhance excitotoxicity through their regulatory effects on the NMDA receptor [108]. Within the post-synaptic density there also exist actin, tubulin, scaffolding proteins and an array of regulatory molecules such as protein kinase A (PKA), protein kinase C (PKC) and protein phosphatase-1. These help direct the information intracellularly and amplify and sharpen the signal.

Because glutamate is excitotoxic when existing in the extracellular space, a glutamate gradient ratio of intracellular to extracellular concentration of 1000 to 1 exist in nervous tissue. This gradient is maintained by a sodium-coupled, high affinity transport system on both the membranes of nerve terminals and fine astrocytic processes. Cloning techniques have identified five glutamate transporters [109]. The interactions between various types and subtypes of glutamate receptors, second messenger molecules, eicosanoid metabolites, ROS, RNS, and phosphorylating enzymes makes control of these protective systems extremely complex. Brain protection by the glutamate transport system has been shown to be vulnerable to a number of toxicities, including free radicals, cytokines, arachidonic acid (AA), proinflammatory eicosanoids and Al^{3+} [110]. When overactivated, glutamate ionic receptors trigger a series of intracellular events that include PKC activation with phosphorylation of PLA_2, which in turn catalyzes the release of AA from the plasma membrane [111]. This triggers the proinflammatory eicosanoid pathways, leading to microglial activation, inflammation, cytokine release and oxidative stress.

By opening the Ca^{2+} pore through activation of the NMDA receptor, the rising cytosolic Ca^{2+} level ($[Ca^{2+}]_i$) activates inducible nitric oxide (NO) synthetase, leading to accumulating concentrations of NO. In conjunction with the elevation of superoxide generated by eicosanoid activation and other radical activators, we see a reaction between superoxide and NO that produces the very destructive peroxynitrite radical. Peroxynitrite has been shown to damage mitochondrial energy-producing enzymes, mDNA and mitochondrial membranes, leading to low cellular energy levels [111]. With severe damage to the mitochondria, cytochrome c is released into the cytosol, which activates caspase 3, leading to apoptosis. Peroxynitrite, along with the hydroxyl radical, have also been shown to inhibit the glutamate transport proteins, thereby further increasing extracellular levels of glutamate [110, 112]. This viscous cycle leads to increasing synaptic and dendritic damage and eventual neuronal death. Toxicity of Al^{3+}, fluoride and AlFx have all been shown to be connected to these various processes. Further interactions of fluoride and AlFx have recently been reviewed [101].

THE EFFECTS OF FLUORIDE AND ALFx ON VARIOUS CELLS/TISSUES *IN VITRO*

The use of fluoride in medicine opened the need to study the effect of fluoride on various biological processes. The effects of fluoride *in vitro* have been thus studied in most of the cells/tissues

of animal or human organisms. Fluoride activation in the presence of trace amount of Al^{3+} has been often used as evidence for involvement of a heterotrimeric G protein in a system [5, 22]. Many of these studies also provide evidence that fluoride influences various functions and biochemical reactions of many cells and tissues of the animal kingdom. On the other hand they provide evidence about the pharmacological efficacy of fluoride and a small molecule, which is AlFx.

1. Photoreceptor Cells

The retinal transducin cascade represents the most accessible G protein system to study. The cGMP PDE plays a central role in visual excitation in vertebrate rod photoreceptor cells. Absorption of a photon by the photopigment rhodopsin leads to activation of the PDE which, in turn, catalyzes the hydrolysis of cGMP, causing closure of cGMP-gated cation channels and hyperpolarization of the cell membrane [113]. Bigay *et al*. [19] demonstrated that AlFx activate stoichiometric amounts of transducin in the micromolar range. This activation requires the presence of GDP in the nucleotide site of transducin α-subunit. Purified α-subunit activates purified cGMP PDE in the absence of photoactivated rhodopsin and in the presence of fluoride plus Al^{3+}. It has been reported that transducin serves as a high affinity substrate for PKC in its native form in intact rod membranes. Sagi *et al*. [46] reported that AlFx inhibited PKC mediated phosphorylation of purified transducin α-subunit.

2. Hepatocytes and Liver

Hepatocytes maintain responsiveness to hormones and serve as model cells equipped with very complex biochemical pathways. The stimulation of glycolysis by vasopressin, angiotensin II, and α_1-adrenergic agonists is mediated in the liver through the increase of the $[Ca^{2+}]_i$ [29, 69, 75]. It has been demonstrated that the phosphoinositide (PPI) signaling pathway [114, 115] is activated and involved in these events.

Blackmore with coworkers [39, 75] demonstrated in their studies that the treatment of isolated hepatocytes with NaF produced the efflux of Ca^{2+}, rise in $[Ca^{2+}]_i$, the decrease in phosphatidylinositol 4,5-bisphosphate (PIP_2) content, the increase in inositol 1,4,5-trisphosphate ($Ins(1,4,5)P_3$) and diacylglycerol (DAG). The lowering of cAMP induced by AlFx was mediated by the G_i. $AlCl_3$ potentiated the effects of low doses of NaF (2-15 mM) and deferoxamine abolished this potentiation. Fluoride in the presence of Al^{3+} thus mimicked the action of Ca^{2+}-mobilizing hormones glucagon and vasopressin in hepatocytes. Vasopressin-stimulated $Ins(1,4,5)P_3$ formation was evident in the presence of GTP or GTP(S) in a purified rat liver plasma membrane preparation. The effects of submaximal doses of AlFx were potentiated by submaximal doses of glucagon, vasopressin, angiotensin II, and α_1-adrenergic agonists. The conclusion was made that AlFx mimics the effects of Ca^{2+} mobilizing hormones by activating the G protein, which couples the hormone receptor to PLC.

Fluoride has been used as the laboratory tool for the study of prostaglandylinositol cyclic phosphate (cPIP), which is endogenous cAMP antagonist [62]. NaF activates the plasma membrane-bound enzyme cPIP synthase, which combines prostaglandin (PG) E and inositol phosphate to cPIP. Preincubation of liver plasma membranes with the tyrosine kinase src kinase causes a 2-fold increase of cPIP synthase activity. The authors conclude that inactivation of the enzyme is connected with protein tyrosine defosforylation. The cPIP degrading activities have been found in all rat tissues tested, but are highest in the liver and lowest in the brain [116]. Inhibition of PG synthesis by the drug indomethacin suppresses the synthesis of cPIP in rat liver and leads to a metabolic state comparable to diabetes type 2 [117]. These authors also observed the stimulation of cAMP synthesis by fluoride in indomethacin-treated rats. Fluoride in the presence of Al^{3+} thus affects the liver as an organ involved in glycogenolysis, fatty acid oxidation, and lipolysis.

3. Cells of Blood and Immune System

The investigators in the first three decades of the last century tried to solve the simple question whether fluoride stimulates clotting of blood, attributing fluoride effect to a retardation of glycolysis [12]. Multiple external signals and signaling systems that are involved in the function of various blood elements were described during the past three decades [118].

Platelets

The majority of platelet physiological agonists stimulate the breakdown of PIP_2, the generation of $Ins(1,4,5)P_3$ plus DAG, and mobilization of $[Ca^{2+}]_i$ from the dense tubular system [119]. Following the increased $[Ca^{2+}]_i$ induced by $Ins(1,4,5)P_3$, the Ca^{2+}-dependent PLA_2 releases AA from membrane phospholipids and thromboxane (TX) synthesis is activated. Activation of platelets is connected with shape changes. Rendu *et al*. [78] observed that incubation of platelets with NaF (5-10 mM) induced only slight morphological changes. Addition of 10 μM $AlCl_3$ resulted in aggregation. One minute after addition of $AlCl_3$, most of the granules were concentrated in the center of the cell, but some were extruding their contents by direct exocytosis. According to authors, this observation suggests that the active species for platelet activation was AlF_4^{1-}.

Padfield *et al*. [120] examined the effect of AlFx on G protein control secretion from α- and dense-core granules in human platelets. As shown for permeabilized platelets, Ca^{2+} alone stimulated a concentration-dependent increase in 5-hydroxytryptamine (dense-core-granule marker) and platelet-derived growth factor (α-granule marker) release. Neither GTP(S) nor AlFx appeared to have a significant effect on Ca^{2+}-dependent release from α- and dense-core granules. GTP(S) stimulated Ca^{2+}-independent release from both α- and dense-core granules. In contrast, AlFx had no effect on Ca^{2+}-independent release from either α- or dense-core granules. Padfield with co-workers based their interpretation on the presumption that GTP(S) can activate both heterotrimeric and small G proteins in platelets, whereas AlFx activates only heterotrimeric G proteins and suggested that the secretion is regulated by a small G protein in the human platelets.

Red Blood Cells (RBC)

RBC provided the model for the discovery of fluoride inhibition of enolase *in vitro*. A significant reduction in the content of ATP and ADP and an increase in the content of AMP in RBC was also found in rats after 4 weeks of exposure to 4 or 16 ppm NaF [121].

Avian RBC have contributed enormously to our understanding of β-adrenergic regulation of AC via the G_s protein and understanding the mode of activation of PLC by a G protein [56, 122]. $G_{q/11}$α-subunit has been purified, sequenced and cloned from turkey RBC [123]. This protein has the capacity to activate PLC in an AlFx-dependent manner. Reconstitution of [^{3}H]inositol-labeled turkey RBC membranes with G protein β/γ-subunits resulted in inhibition of AlFx-stimulated PLC activity and in AlFx-stimulated AC activity [124].

Plasma membrane of human RBC is not equipped with receptor molecules. The question of why human RBC maintain a high turnover rate of PPI remains unanswered. Surprisingly, the presence of G proteins and PLC was reported [118]. However, no physiological agonist evoking PLC activation has been found. Fluoride in the presence of Al^{3+} seems to be one of the rare stimuli, which is able to activate PLC, to induce PPI hydrolysis and, in parallel, to evoke shape changes of human RBC [76]. AlFx increased the level of $Ins(1,4,5)P_3$ and released Ca^{2+} from the RBC plasma membrane. Shape changes and disorganization of the tubulin structure were observed. It has been reported that AlFx may impair the polymeri-

sation-depolymerisation cycle of tubulin coupled to the hydrolysis of bound GTP into GDP [20]. AlFx can bind to tubulin molecules in GDP-β phosphate and thus mimic the GDP+P intermediate state. Their binding affinity is three fold higher than that of phosphate.

Neutrophils

Rapid and dynamic changes of the actin network are of vital importance for the motility of human neutrophils. AlFx, in combination with GDP, stimulates actin assembly in electropermeabilized neutrophils and could be totally abolished by GDP(S) [125, 126]. This effect parallels an increase in $[Ca^{2+}]_i$, indicating that PLC is activated. The binding of ligands to chemoattractant receptors in human neutrophils resulted in a rapid association of these receptors with a cytoskeletal fraction and a specific activation and release of $G_{i2}\alpha$-subunits from this fraction. Sarndahl *et al*. [127] observed that GTP(S) or AlFx not only caused a release of $G_{i2}\alpha$-subunits from the cytoskeleton but also an association of chemoattractant receptors with the cytoskeleton. Adhesion and chemoattractant receptors are known to trigger activation of the small G protein Ras in human neutrophils, but the signaling mechanism that activates Ras has only been partially elucidated [128].

Lymphocytes

Lymphocytes with their central role in immunity attract a great deal of laboratory investigations. The binding of antigen to the multicomponental T cell receptor activates several signal transduction pathways. Activation of PLC represents one of them. T cell receptor activation has been shown to cause an increase in tyrosine phosphorylation [129]. Regulation of the development of thymocytes into mature T cells within the thymus is now known to involve antigen-induced deletion, by apoptosis, of potentially autoreactive thymocytes. Stimulation of immature thymocytes or of mature T cells through their T cell receptor complex activates PLC. The treatment of thymic lobes cells with fluoride in the presence of Al^{3+} provoked apoptosis of a wider range of thymocyte subtypes and such stimulation also provoked an accumulation of inositol phosphates (InsPs). The responses to AlFx were not prevented by inhibitors of tyrosine kinases, suggesting that unidentified G proteins, which couple to PLC activation may also be capable of initiating apoptosis by a route independent of the T cell receptor. AlFx stimulated PLC activity and PPI turnover was observed in resting T cells of autoimmune-prone mice, mature $L3T4^+$ and Ly^{2+} double-negative T cells from normal thymus, and from enlarged lymph nodes of autoimmune-prone mice [130]. Increased $[Ca^{2+}]_i$ induced by AlFx has been observed in cloned helper T lymphocytes.

AlFx mimicked CD2-, CD3-, and CD43- mediated Ca^{2+} responses in T lymphocytes derived from human peripheral blood and in leukemic T cell line [131, 132]. Later studies revealed that NaF augments the human lymphocyte response from human blood to a mitogen (phytohemagglutinin, PHA) or a specific morbilli antigen [133]. The cytokine interferon-γ released from activated human T lymphocytes and/or NK cells, was significantly increased when whole blood cells were simultaneously incubated with fluoride. The authors suggest that the ability to influence interferon-γ release during an immune response could be one of the primary means by which the fluoride ion influences the immune system.

AlFx enhanced eicosanoid synthesis in macrophages [73]. NaF led to *in situ* activation of PLC, PKC, and PLA_2. NaF was shown to reduce intracellular ATP levels, to suppress agonist-induced protein tyrosine phosphorylation, and ROS formation. Addition of $AlCl_3$ or deferoxamine had little or no effect on NaF-mediated enzyme activation. Goldman *et al*. [71] therefore suggested that at least some of the pleiotropic effects of fluoride in intact macrophages might not be mediated by G protein activation but rather by depletion of ATP.

4. Heart

Fluoride and AlFx stimulate AC activity in the heart [2, 54, 55]. Hrbasova *et al*. [55] reported that the stimulation of AC activity was 6 times higher after the addition of 10 mM NaF + 500 μM $AlCl_3$ than the stimulation by GTP and 4.4 times higher than the stimulation by isoproterenol in the right ventricle. It seems, that $G_s\alpha$-subunit is involved in mediating fluoride stimulation of cardiac AC. In rat atria the rate of fluoride-induced PLD activation (and mass production of DAG) was maintained for at least 60 min [80]. Experimental evidence suggests that the myocardial PLD-PA phosphohydrolase-signaling pathway may regulate Ca^{2+} movements and contractile performance of the heart. Williams *et al*. [134] suggested that the increased production of DAG by PA phosphohydrolase might lead to impairment of Ca^{2+} homeostasis associated with cardiomyopathy.

Yatani *et al*. [65] studied a mechanism of fluoride activation of G protein-gated muscarinic atrial K^+ channels. They applied KF to the cytoplasmic face of inside-out membrane patches excised from guinea pig atria. Fluoride activated single K^+[ACh] channel currents in both a concentration- and a Mg^{2+}-dependent manner, while deferoxamine inhibited this activation. At low concentrations of KF (<1 mM), micromolar Al^{3+} potentiated KF stimulation. When ATP closed cardiac ATP-sensitive K^+ channels, activators of endogenous G proteins, GTP, GTP(S), or AlFx stimulated channels [66]. Fluoride (1-75 mM) also increased the activity of the L-type Ca^{2+}channel dose-dependently [135]. Fluoride had no effect on the Ca^{2+} channel activity when the myocytes were pretreated with a potent inhibitor of protein kinases, indicating that fluoride increased the Ca^{2+}channel activity via modulation of the phosphorylation state of the channel protein.

5. Kidney Cells

Fluoride has been considered to be a nephrotoxic substance. The effects of fluoride plus Al^{3+} on the kidney have been studied *in vitro* using glomerular mesangial cells, proximal tubular cells, and the collecting tubule cells of rat kidney. The transepithelial movement of fluids, electrolytes, and larger molecules is achieved by the activity of specialized transporting proteins, including enzymes, receptors, and channels, that are located on either the apical, basal, or lateral plasma membrane domains of kidney epithelial cells [136, 137]. Fluoride and Al^{3+} in kidney tubular cells were found to affect ion transporting processes, stimulate AC, inhibit amiloride-sensitive Na^+/H^+ exchange regulated by cAMP-dependent protein kinase, enhance epidermal growth factor-stimulated PG production, and mimic vasopressin and bradykinin induced Ca^{2+} mobilization. Acid phosphatases were suggested as the potential cellular targets of fluoride action in the renal tissue [27]. A 9.3 fold peak increase in the AC activity was observed in the basolateral membranes incubated with fluoride plus Al^{3+} [58]. Exposure of intact cells of the rat inner medullary collecting tubule to fluoride enhanced both basal and epidermal growth factor-stimulated PG production in the presence of Al^{3+} [138]. After 24 h of exposure, 5mM fluoride decreased cell number (-23%), total protein content (-30%) and increased LDH release (+236%) in human and rabbit collecting duct cells and Henle's loop. The Na^+/K^+ ATPase activity was inhibited (-58%) [45].

6. Lung Endothelial Cells

Lung inflammatory response has been observed as the symptom of fluorine intoxication. Lung endothelial cells (EC) play an important role in the inflammatory process by releasing cytokines in a complex cell to cell network. Interleukins (IL) are important mediators of this cell signaling. Exposure to fluorides can induce inflammatory reactions, cell cycle arrest, and apoptosis in different experimental systems. NaF has been reported to induce a strong IL-8 response in human lung EC via mechanism that seems to involve the activation of G proteins [68]. NaF induced sustained increase in PKC activity. In contrast, the PKC activator TPA induced a relatively strong, but transient effect and augmented the NaF-induced PKC activity. Inhibition of the mitogen-activated protein

kinase (MAPK) p38 partially reduced the IL-8 response to NaF. The NaF-induced IL-8 response was weakly augmented by forskolin and the G_i inhibitor pertussis toxin. These data suggest that NaF-induced increase of IL-8 in human lung EC involves PKC- and MAPK p38-linked pathways.

The inhibition of proliferation by NaF in the human lung EC line was observed [139]. NaF induced apoptosis with a maximum at 5-7.5 mM after 20 hours of exposure. The number of cells with plasma membrane damage increased moderately up to 5 mM, but markedly at 7.5 mM. Deferoxamine almost completely prevented the NaF-induced responses, which may suggest a role for G protein activation. NaF induced a weak but sustained increase in PKC activity. Using various pharmacological tools these authors concluded that activation of MAPK p38 and c-jun-NH_2-terminal kinase (JNK) are involved in the NaF-induced apoptosis. The tyrosine kinase inhibitor genistein also markedly reduced the NaF-induced apoptosis, whereas the phosphatidylinositol 3-kinase (PI 3-K) inhibitor wortmannin augmented the response.

7. Brain

Fluoride, AlFx and Al^{3+} are all known to interfere with a number of glycolytic enzymes, including enolase, phosphofructokinase, aconitase, pyruvate dehydrogenase and ATPase. Al^{3+} has been shown to inhibit pyruvate dehydrogenase with a resulting decline in acetyl-CoA. This results in a significant suppression of cellular energy production [140]. NaF has been shown to inhibit glycolytic enzymes *in vitro*, with a loss of mitochondrial membrane potential, caspase 3 and 9 elevation, DNA fragmentation and eventual apoptosis [141]. A number of studies have shown that when neuronal cellular energy production and/or Mg^{2+} are deficient, no matter the cause, excitoxicity is greatly enhanced - so much so that even physiological levels of glutamate or other excitatory amino acids can produce excitotoxicity [142]. There is compelling evidence that excitotoxicity plays a major, if not central, role in a number of neurodegenerative diseases. It is known that elevation of ROS, RNS, and LPO products act as nonspecific activators of glutamate triggered excitotoxicity in the brain. Likewise, both fluoride and AlFx are known to increase brain oxidative and nitrative stress and LPO. Because of the intimate link between elevations in brain ROS and RNS and LPO products and excitotoxicity, we can be confident that the latter process most likely plays a critical role in fluoride neurotoxicity.

The family of cell-surface receptors that require coupling to G proteins is vast and diverse in the brain [143, 144]. PPI was shown to turn over rapidly in the brain and participate in many processes of neurotransmission. Fluoride salts in the presence of Al^{3+} have been often used to stimulate PPI hydrolysis in laboratory experiments *in vitro*. The ability of AlFx to mimic the effects of Ca^{2+}-mobilizing hormones suggests the coupling of hormone receptors to PPI breakdown through G proteins [145].

Impaired Glutamate Reuptake

Direct toxicity of fluoride or AlFx to the major glutamate transport proteins, GLAST and GLT-1 has not been shown, mainly because no one has looked at the possibility. The brain contains five sodium-coupled, high affinity glutamate transport proteins [146]. It is known that PKC plays a vital role in the availability of glutamate transport molecules [147] as well as those for serotonin [148], GABA [149], norepinephrine [150], and dopamine [151]. Because fluoride is known to stimulate activity of PKC, one would expect elevations in fluoride to improve glutamate clearing by the glutamate transport proteins. Yet, fluoride and AlFx are both associated with significant induction of ROS and LPO products that are known to inhibit glutamate transport proteins as discussed above. In addition, both induce the release of AA from cell membranes, and AA is a rather potent inhibitor of glutamate transporters as well [152]. In addition, PKC is known to play a role in microglial activation and glutamate release [153], as well as a central role in glutamate toxicity [154]. Blocking PKC significantly reduced excitotoxic damage *in vitro*.

It has also been shown that PI 3-K plays a modulatory role in glutamate transporter activity as well. Davis *et al*. [155] demonstrated that PI 3-K inhibitor wortmanin inhibited glutamate uptake in a glioma cell line by 35%, indicating less than complete control. This represents another phosphorylation reaction that could be influenced by AlFx. PI 3-K is upstream to PIP_2, which forms Ins(1,4,5)P_3 and DAG, regulators of intracellular Ca^{2+} and PKC activation, respectively. Guillet *et al*. [156] found PKA, PKC and PI 3-K to all to be involved in glutamate uptake. In addition, direct phosphorylation of GLAST-1 has been shown to inhibit its activity [157].

Hypomagnesmia

Zeevalk and Nicklas [158] found that the potency of glutamate excitotoxicity was enhanced two to five-fold in the absence of Mg^{2+} and that it reduce the minimal concentration of agonist needed from 25 μM to 5 μM and 300 μM for NMDA and 300 μM to 10 μM for glutamate. As we have seen, fluoride and AlFx stimulate PKC activity. One study found that activation of PKC enhanced excitotoxicity and appeared to do so, at least in part, by interfering with Mg^{2+} blockade of the NMDA receptor [159]. It has also been shown that Na^+/K^+ ATPases are necessary for maintaining the voltage-dependent Mg^{2+} block of NMDA receptors [160]. Previous studies indicated that AlFx (most likely as AlF_4^{1-}) inhibited the activity of Na^+/K^+ ATPase and that they do so by way of G protein-coupled receptors [161]. Taken together this would strongly suggest that AlFx could interfere with neuronal protection from NMDA receptor overactivity (excitotoxicity), especially in the face of low Mg^{2+} or neuronal energy levels.

Microglial Cells

The microglial cells are the resident immune cells in the CNS. Under resting conditions microglia are quiescent but are easily activated by a number of insults, including trauma, infections, heavy metals, systemic immune activation, ß-amyloid (Aß), rotenone, stress, oxidized LDL-cholesterol, hypoxia/ischemia and hypoglycemia. While transient, mild to moderate activation can be neuroprotective, chronic activation, especially at high levels, is known to trigger neurodegeneration, especially under certain conditions. Astrocytes regulate intersynaptic communication between neighboring synapses and, probably, overall volume transmission in the brain [162]. When activated, microglia down-regulate surface karatan sulfate proteoglycans and assume ameboid characteristics. Microglia contain a number of surface receptors such as IL-8 and glutamate receptors, and when activated can secrete a large number of molecules including various ILs, TNF-α, chemokines, TGF-ß, matrix metalloproteinases, metalloprotease-disintegrin ADAM8 and elastase. Most importantly, when activated microglia secrete considerable amounts of glutamate, which can reach excitotoxic levels.

Fluoride has been used as an enzymatic inhibitor or as the activator of G proteins in laboratory investigations of astrocytes functioning. Astrocytes respond to extracellularly applied ATP, which causes release of Ca^{2+} from an intracellular Ins(1,4,5)P_3-sensitive pools. Increases in PPI hydrolysis and $[Ca^{2+}]_i$ were elicited by intracellular application of GTP(S) and AlFx in astrocytes from the dorsal spinal cord [77, 163]. AlFx also stimulated the tyrosine phosphorylation of a 42 kDa protein (p42) and activation of p42 MAP kinase in primary cultures of mouse embryo astrocytes [164].

Since no one has examined the possibility of direct microglial activation by fluoride or the AlFx, we must examine other ways they could activate microglia. Fluoride and AlFx are both known to generate ROS and RNS and LPO products [104, 105]. ROS and LPO activate microglia, thus linking both AlFx and fluoride to chronic brain inflammation. Al^{3+} itself is known as an immune

adjuvant and it is suspected that Al^{3+} within the brain, especially that complexed with amyloid plaque may activate resident microglia through this mechanism [165, 166].

Cytokine Enhancement of Excitotoxicity

While cytokines are known to play a role in neuroprotection, when chronically elevated or existing within the brain in high concentrations they can be quite neurotoxic. A number of studies have shown enhanced excitotoxicity in the face of elevated inflammatory cytokines [167-169]. ILs and TNF-α have been found to be strongly upregulated during diseases such as Alzheimer's disease (AD), stroke or Parkinson's syndrome [170]. There is considerable cross-talk between cytokines, so that IL-ß and TNF-α, when existing in higher concentrations within the brain, activate neurodegenerative processes, especially in the presence of elevated levels of glutamate [171]. IL-1 has also been shown to mediate the effects on protein τ hyperphosphorylation by microglia through p38-MAPK activation [172]. As stated previously, PKC plays an important role in microglia activation. The entry point for this activation appears to be MAPK. In addition, ERK and JNK were also activated. Once activated by Al^{3+}, fluoride or other triggers, microglia secrete large concentrations of IL-1ß and TNF-α, which can then recruit more microglial activation in a vicious cycle that ultimately leads to neurodegeneration. This is suspected to be one of the mechanisms responsible for AD pathology [173]. Likewise, excitotoxins can activate microglia and stimulate release of inflammatory cytokines and additional glutamate.

Aß has been shown to activate all three MAPK pathways on microglia, thereby resulting in microglial activation and secretion of neurotoxic elements, including glutamate [174]. Further evidence of this interaction between cytokines and excitotoxins comes from the work by Sass *et al*. [175] who demonstrated that Al^{3+} treated astrocytes when mixed with neurons caused no degeneration of these cells unless glutamate was added to the culture. It was later that the reason for this effect was elucidated, that is cytokine enhancement of excitotoxicity. It is accepted that IL-1 is neurotoxic, whereas TNF-α can be either neuroprotective or neurotoxic depending on the presence of excess glutamate in a dose and duration-dependent manner. The anti-inflammatory cytokines, IL-10 and TGF-ß appear to be mostly neuroprotective, whereas IL-6 is neuroprotective unless glutamate release has been triggered [176].

Recent studies have shown that fluoride can induce strong IL-8 response in human lung EC by a G-protein activation pathway [68]. Downstream, PKC activation over a prolonged time was observed, which as we have seen in the case of the CNS can activate microglia, resulting in inflammatory cytokine and glutamate release. Again, it is possible that AlFx complex is the operating molecule rather than fluoride alone. An earlier study by Refsnes and coworkers, in which deferoxamine was shown to significantly reduce NaF-induced IL-6 and IL-8 release, strongly indicated that AlFx was indeed the operant molecule in these EC [177].

Also of interest is the finding that focal lesions can produce distant inflammatory injury and that anterograde degeneration was associated with a somewhat later expression of cytokines, whereas retrograde degeneration was associated with earlier cytokine expression in these damaged areas [178]. These observations, when combined with the well demonstrated ability of Al^{3+}, fluoride and AlFx to induce cytokines expression from microglia and astrocytes and at least secondarily increase glutamate release make a strong case for excitotoxicity as an important, if not central mechanism in fluoride neurotoxicity. Likewise, fluoride, Al^{3+} and the AlFx have been shown to dramatically increase brain ROS, RNS and LPO, which has been shown to enhance excitotoxic damage.

Many of these affected reactions involve intracellular Ca^{2+} regulation. It has also been shown that excessive NMDA receptor activation causes an overload of mitochondrial Ca^{2+} with resulting loss of cellular energy levels [179]. The fact that AlFx produces prolonged activation of InsPs and subsequent $Ins(1,4,5)P_3$ generation, would suggest chronic elevations in $[Ca^{2+}]_i$ with eventual triggering of apoptotic pathways. Nicholls and co-workers [180] found that glutamate elevations in the presence of depressed mitochondrial function resulted in Ca^{2+} dysregulation and an elevation of mitochondrial-generated superoxide. Glutamate excess is also known to increase cellular NO generation, which reacts with the excess superoxide to form the mitochondrial inhibitor peroxynitrite. Also of importance is the observation of Mercocci *et al*. [181] as to the extreme sensitivity of mitochondrial DNA to oxidative stress. The combination of excitotoxicity, oxidative stress, LPO, Ca^{2+} dysregulation and mitochondrial dysfunction greatly increases neuron and glial sensitivity to damage. Toxicity of Al^{3+}, fluoride and AlFx have all been shown to be connected to these various process [101].

The Effects of Fluoride on PPI Signaling Pathways in the Brain

In experiments with brain cortex membranes NaF mimicked the action of GTP(S) in stimulating PPI turnover and generation of InsPs [182, 183]. This effect was highly synergistic with that of $AlCl_3$, supporting the concept that AlFx is the active stimulatory species. Coincubation of submaximal concentration of GTP(S) with AlFx did not result in an additive stimulation of PPI hydrolysis. Paradoxically, $AlCl_3$-induced PPI hydrolysis was potentiated by coincubation with both GDP(S) and phorbolester. Shafer *et al*. [184] compared the effect of 5-30 mM NaF and various concentrations of $AlCl_3$ on muscarinic, adrenergic, and metabotropic receptor-stimulated PPI hydrolysis in cortical and hippocampal slices from rat brain. In agreement with many others, these authors found that NaF stimulates InsPs accumulation as well as the cholinergic agonist carbachol, the adrenergic agonist norepinephrine, and the glutaminergic agonist quisqualate. The higher concentrations of $AlCl_3$ (0.5 mM) inhibited InsPs accumulation stimulated by agonists and that stimulated by NaF.

Tiger *et al*. [41] studied actions of fluoride upon the PPI pathway in the rat brain miniprisms. NaF concentration dependently increased basal PPI breakdown, with a maximum effect being seen at 20 mM. On the other hand, NaF reduced the PPI breakdown responses to stimulation by carbachol, noradrenaline, and serotonin. These authors concluded that fluoride inhibits agonist-stimulated PPI breakdown via actions not only on G proteins but also on PPI-specific PLC substrate availability. The finding that fluoride ions inhibit agonist-stimulated PPI breakdown also on PPI-specific PLC substrate availability was later confirmed [185].

Other Effects

A 2-3-fold stimulation of the basal PLD hydrolytic activity by AlFx in the synaptosomes from canine brain was reported [81, 186]. These results not only indicated that the muscarinic acetylcholine receptor-G protein-regulated PLD is responsible for rapid accumulation of choline and phosphatidic acid (PA) in the brain but also revealed involvement of PLD in a novel, previously unrecognized, signaling pathway in the brain. Kanfer *et al*. [187] used NaF as a PA phosphatase inhibitor to study PLD activity in rat brain cerebral cortical neuronal nuclei. In the absence of NaF the principal product was DAG; whereas in the presence of NaF, the principal product was PA. These authors reported that BeF_2, AlF_3, and PA inhibited the neuronal nuclei PLD activity.

Hypothalamic suprachiasmatic nuclei have been suggested as the site of a biological clock responsible for generation of circadian rhythms. Melatonin receptors are involved in this function [188]. AlFx was used to indicate that the effects of melatonin are mediated by heterotrimeric G protein [189]. AlFx blocked the increase in cAMP stimulation by forskolin, being as effective as melatonin, and increased $[Ca^{2+}]_i$ [190]. The stimulatory effects of AlFx and Ca^{2+} on InsPs accumulation were not additive [191].

When rat hippocampal slices were exposed to 10 mM NaF and 10 μM $AlCl_3$ for a brief period of time (12-15 min), spike amplitude fell to very low levels. Upon washout, spike amplitude recovered beyond control values and in half of the preparations a prolonged enhancement of spike amplitude occurred. If $AlCl_3$ was omitted from fluoride-containing saline, enhancement of spike amplitude, when observed, was brief [192]. Brief bath application of AlFx in standard saline consistently induced a long lasting potentiation in area CA1 of rat hippocampus [193]. NaF (50 μM) and $AlCl_3$ (12.5 μM) were administered alone or in a combination to cultured hippocampal neurons from fetal rats [194]. Al^{3+} affected the development of the interconnecting fibers. This phenomenon was enhanced when NaF was given together with Al^{3+}.

Chen and Penington [195] tested hypotheses concerning the actions of AlFx in the inhibitory effect of G proteins on Ca^{2+} channel activity of dorsal raphe (DR) neurons. These authors suggested that there can be a competition between the receptor and AlFx stimulated G protein activity and investigated whether the interaction occurs at the level of the G protein, or the interaction of the with Ca^{2+} channels. The main findings of this study were that intracellular AlFx caused approximately a one-third of maximum tonic stimulation of the G protein coupled to Ca^{2+} channels of DR neurons, consistent with a G·GDP-AlFx complex resulting in mimicry of the G·GTP complex. These authors suggested a fairly parsimonious explanation of the sequence of events occurring after agonist application to a DR neuron in the presence of AlFx. They proposed that after several applications of 5-hydroxytryptamine, some G proteins are in the basal state and some are activated by AlFx. In summary, their detailed study brought evidence that AlFx modified the OFF-rate kinetics of G protein activation by agonists. Agonist application temporarily reversed the effects of AlFx, making it a complementary tool to GTP(S) for the study of G protein interactions. The concentration of fluoride used in this study was high (130 mM) in comparison with other laboratory studies. The high excess of fluoride ions could therefore exert many other effects on energy metabolism or protein conformation, including ion channels.

8. Bone Cells

Fluoride becomes the most potent agent inducing uncoupling between bone resorption and formation in favor of formation, thus resulting in an increased bone volume. NaF and AlFx have been shown to be bone cell mitogens [64, 196]. This characteristic of fluoride action on bone together with the observed skeletal fluorosis in human prompted several laboratories to investigate the mechanism, by which fluoride enhances the proliferation and the activity of osteoblastic cells. The high demands for energy are placed on osteoblasts during proliferation, maturation, and production of mineralized matrix. Glycolysis provided ~50% of the energy requirement of mature osteoblasts and is likely to be important for their function [197]. AlFx simultaneously inhibits osteoclastic bone resorption [25, 198].

Osteoblasts

Osteoblasts secrete bone matrix and regulate mineralization process in bone formation. Following the initial observations, that fluoride can directly influence the activity of osteoblastic cells in culture, the effects of fluoride on human osteoblastic cells proliferation were investigated in several laboratories. A first hypothesis for the mechanism by which fluoride enhances cell proliferation has emerged from the observation that osteoblastic acid phosphatase was inhibited in a dose-dependent manner by fluoride. Since fluoride has been known as inhibitor of tyrosin phosphatases, Lau *et al.* [24] suggested that this unique acid phosphatase has tyrosine phosphatase activity in bone-forming cells. In addition to these results, it was shown that fluoride could potentiate the mitogenic action of several growth factors acting through tyrosine kinase membrane receptors.

On the other hand, Caverzasio with co-workers [64] suggested and tested the hypothesis that the mitogenic action of fluoride could involve activation of heterotrimeric G proteins. In their initial studies [82, 199] they noted that the micromolar fluoride concentrations in the presence of traces of Al^{3+} reproducibly enhanced cell proliferation. These observations strongly suggested that AlFx is probably the active fluoride species responsible for the change in bone mineral mass *in vivo*. The sensitivity of the mitogenic effect of AlFx to pertussis toxin suggested a potential role of the G_i protein in mediating this cellular response. Their observations also supported the notion that the change in protein tyrosine phosphorylation, which mediates the proliferative effect of fluoride in bone-forming cells, involves the activation of a tyrosine kinase. With this information, a new mechanism for the enhancement of osteoblastic proliferation by fluoride was proposed.

Two competing models, both of which involve the MAPK mitogenic signal transduction pathways were thus suggested. The first one [49] involves a fluoride inhibition of a unique fluoride-sensitive phosphotyrosine phosphatase in osteoblasts. Such inhibition results in a sustained increase in the tyrosine phosphorylation level of the key signaling proteins of the MAPK pathway, leading to the potentiation of the osteoblastic proliferation initiated by growth factors. A benefit of this model is that it accounts for all the unique properties of the osteogenic action of fluoride. These include the low effective fluoride dose, the requirement of tyrosin kinase-activating growth factors, the sensitivity to changes in medium phosphate concentration, the preference for undifferentiated osteoblasts, and the involvement of the MAPK. The competing model proposes that fluoride acts in coordination with Al^{3+} to form AlFx [64]. This activates a pertussis toxin-sensitive $G_{i/o}$ protein on osteoblast membrane, leading to an activation of cellular protein tyrosine kinases, which in turn leads to increases in the tyrosine phosphorylation of adaptor molecules, activation of the Ras/Raf/ERK pathway, and enhanced cell proliferation.

There is a controversy in these two hypotheses of whether enhancement of tyrosine phosphorylation induced by fluoride results from inhibition of tyrosine phosphatase(s) or activation of tyrosine kinase(s). However, the mechanism by which heterotrimeric G proteins, in particular G_i and G_q, enhance osteoblastic cell proliferation is not completely understood. The mitogenic action of AlFx shows several different characteristics than that of fluoride [49].

Sun with co-workers [200] established a method for isolating and culturing osteoblasts from the newborn rat calvaria. They found that fluoride at low doses promotes the proliferation and differentiation of osteoblasts, whereas at high doses it can induce DNA damage, arrest the cell cycle in S phase, and induce apoptosis. The inhibition of rat osteoblast growth at 10^{-3} M fluoride has been reported [201-203].

Osteoclasts

Osteoclasts function to support calcium homeostasis and to remodel bone. During bone resorption, osteoclasts generate very high $[Ca^{2+}]_e$ in the resorption space. PLC may mediate Ca^{2+}-induced effects in osteoclasts, because Ca^{2+} increases production of $Ins(1,4,5)P_3$ in GCT23 osteoclast-like cells and chicken osteoclasts [204]. Exposure of osteoclasts to AlFx resulted in a marked concentration-dependent inhibition of bone resorption [25, 198]. This inhibition was associated with a dramatic increase of the secretion of an osteoclast-specific enzyme, tartrate-resistant acid phosphatase. Cholera toxin, a G_s stimulator, similarly abolished bone resorption and enhanced acid phosphatase secretion. In contrast, pertussis toxin, a G_i inhibitor, inhibited bone resorption. It seems that AlFx stimulate both PLC and AC in osteoclasts. The osteoclast activity may be influenced by EC via generation of products including PGs, NO, and endothelin.

9. Commentary to Observations of Fluoride Effects on the Cell Level *In Vitro*

Based on the observed effects on enzymatic activities in intact cells, it seems that fluoride easily permeates across the plasma membrane and reaches cytosolic concentration required for its effects as observed on isolated enzymes, homogenates, and membranes. The phenomenological observations of the effects of AlFx on intact cells also indicate that these complexes are, in many cases, appearing in the system after the addition of fluoride and Al^{3+} into the extracellular solution. The slow equilibration kinetics between various compounds of fluoride and Al^{3+} could give rise to puzzling kinetics that also could cause misinterpretation of results. The critical analysis of reported findings does not allow us, in many cases, to conclude whether the observed effects can be accounted to the action of fluoride alone or to its synergistic effect with Al^{3+}. The added Al^{3+} might also react with some non-protein ligands, such as phosphate, citrate, and buffers. Nevertheless, it seems that AlFx exert their effects at very low concentrations. It cannot be excluded that the excess of free fluoride binds further to protein molecules, changing their conformations, stability, and enzymatic activity. The inhibitory effects of fluoride on energy metabolism followed by depletion of ATP [195] and reduction of PLC substrate synthesis [185] could also contribute to the explanation of mechanisms for the observed effects.

G Proteins

The observation that AlFx can activate heterotrimeric G proteins has been useful for the study of G protein involvement in numerous biological systems, for the elucidation of three-dimensional structures of G proteins and several GTPases, for understanding the mechanism of GTP hydrolysis, and the role of GAPs. AlFx can stabilize complexes formed between small G proteins Ras and RhoA and their corresponding GAPs. Nucleotide exchange and GTP hydrolysis are fundamental to the regulation of all types of G proteins that have been examined to date. G proteins regulate the activities of a structurally diverse group of effectors molecules. These also include enzymes engaged in the synthesis and degradation of intracellular second messengers, as well as ion-selective channels. However, the question of the coordination state of AlFx remains open [88].

PPI Signaling Pathway

The increased breakdown of PIP_2 and the increased production of InsPs have been reported quite often (Table **3**). PLC has been found activated by all classes of cell surface receptors [205].

The regulatory input from G_q-coupled receptors can also control AC activity by Ca^{2+} or PKC-dependent processes. Morris and Malbon [93] explained in their review some paradoxical and unique characteristics of the regulation of the G_q family of heterotrimeric G proteins. Their intrinsic steady-state GTPase activities are much lower than those of members of the other heterotrimeric G protein families but the G_q/PLC- system is activated very rapidly upon addition of an agonist. In this system, receptor-promoted binding of GTP(S) to the G protein and PLC-catalyzed PIP_2 hydrolysis are tightly coupled. When the nonhydrolyzable GTP(S) was replaced by hydrolyzable GTP, PLC activation was much reduced. More detailed studies of the time courses of PIP_2 hydrolysis by PLC-1 in such reconstitution systems suggest that, in the presence of saturating agonist, receptor-G_q complexes can remain stable over multiple GTPase cycles. The binding of AlFx to GDP of G_q might therefore lead to tight coupling of PLC and induce the state of sustained activation.

Physiological Implications

The significant physiological implication brought the observations of additive effect of low fluoride concentrations with an ineffective hormonal agonist resulting in a maximally effective response [39, 64, 69, 74, 138]. On the other hand, NaF reduced the PPI breakdown responses to stimulation by noradrenaline and serotonin. It therefore seems that fluoride might also inhibit agonist-stimulated PPI breakdown via actions on PPI-specific PLC substrate availability [41]. It is evident that interventions of AlFx in a myriad of reactions that involve G proteins have the potential of altering the signaling pathways. The principle of amplification of the initial signal during its conversion into functional response has been a widely accepted tenet in cell physiology. It is evident that AlFx is a molecule giving a false message, which is amplified by processes of signal transduction (Fig. **3**).

Table 3. The Effects of NaF (mM) Plus $AlCl_3$ (μM) on Components of Signaling Pathways

Cells/ Tissue	AC	PLC	InsPs	$[Ca^{2+}]_i$
Hepatocytes	↓↑	↑	↑	↑
Platelets		↑	↑	↑
RBC	↑	↑	↑	↑
Neutrophils		↑		↑
Leucocytes			↑	↑
Fibroblasts	↓	↑	↑	↑
Macrophages		↑		↑
Heart	↑			
Lung cells		↑	↑	
Kidney cells	↑			↑
Neurones	↓↑	↑	↑↓	↑
Astrocytes		↑		↑
Osteoclasts	↑	↑	↑	↑

Protein phosphorylation constitutes one of the major posttranslational mechanisms employed in the physiological regulation of G protein-linked signaling. Phosphoryl-transfer reactions are also involved in processes such as regulation of cell metabolism, energy transduction, cytoskeletal protein assembly, regulation of cell differentiation and growth, aging, and apoptosis. Several authors reported the observation of fluoride-induced apoptosis in various tissues. Fluoride and AlFx can induce cell death by the activation of a cell surface receptor and damaging DNA. Understanding cell type specific regulation of apoptosis allows the design of new selective drugs capable of modulating the cellular response [206]. Considering that all these reactions are fundamental for nearly all biological processes, the common denominator of which is the transfer of a phosphoryl group, we can conclude that fluoride, in the presence of trace amount of Al^{3+}, represents a very useful tool for further investigations.

Previous studies have shown PKC to play a central role in glutamate toxicity [154]. Blocking PKC significantly reduced excitotoxic damage *in vitro*. It is also important to point out that the effect of PKC activation is tissue dependent. While in the CNS it enhances glutamate uptake, in EC of human umbilical veins it inhibits glutamate uptake [207]. If it has the same effect on all vascular EC cells, then AlFx and fluoride could increase atherosclerotic changes via glutamate triggered inflammatory eicosanoid generation, excitotoxicity and an increase in ROS and LPO within vessel walls. This would be especially important in vascular dementia. Glutamate has been shown to dramatically increase LPO products in arterial tissue in adult male mice and to lower all of the major antioxidants in the arterial wall [208]. NaF induced EC barrier dysfunction [209], which was accompanied by the development of actin stress fibers,

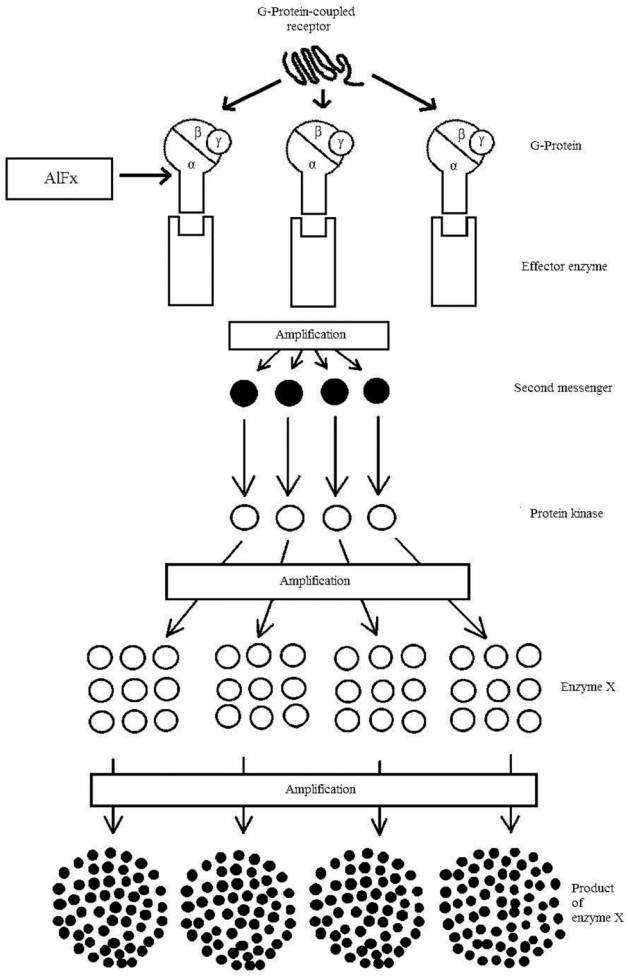


Fig (3). AlFx acts as the messenger of false information. Its message is greatly amplified during the conversion into the functional response of a cell. The second messenger molecule could be cAMP, Ins(1,4,5)P_3, and DAG. Moreover, AlFx can participate as the analogue in the phosphoryl-transfer reactions involved in the signaling cascade.

intercellular gap formation, and significant time-dependent increases in myosin light chain phosphorylation. Stimulation of AA release and PGI2 production by AlFx was observed in cultured EC from rabbit coronary microvessels and cultured pig aortic EC [74, 210].

Refsnes and co-workers demonstrated that NaF powerfully induced IL-6 and IL-8 production and that deferoxamine abolished this response indicating that it was AlFx and not fluoride alone that was responsible for the induction of these cytokines [177]. This implicates a G protein mediated effect. What makes this important is that inflammatory cytokines have been shown to interfere with glutamate transporter protein function. Dysfunctions of glutamate transport play a major role in a number of neurological conditions as well as neurodevelopment. In addition, glutamate transporter proteins have been characterized in a number of tissues outside the CNS, including the placenta, liver, intestine, pancreas, ovary, lung and kidney [211]. These observations, when combined with the well demonstrated ability of Al^{3+}, fluoride and AlFx to induce cytokines expression from microglia and astrocytes and at least secondarily increase glutamate release make a strong case for excitotoxicity as an important, if not central mechanism in fluoride neurotoxicity.

The use of fluoride in laboratory investigations contributed to the discovery of new signaling pathways and their cross talks. Numerous studies of fluoride effects in laboratory investigations from the last decades bring new evidence for our understanding of complicated integrative networks, which regulate the signal transduction processes of the whole organism.

ANIMAL MODELS IN FLUORIDE RESEARCH

The artificial fluoridation of public water supplies at 1-4 ppm in many countries after the Second World War opened the need to study the effects of long-term fluoride intake. A large variety of fluoride concentrations in drinking water was used in animal laboratory studies. For example, rats were fed pure spring water with a natural concentration of 0.2 ppm fluoride or spring water enriched with NaF to a concentration of 0.8, 1.1 or 2.2 ppm fluoride during 180 days exposure [212]. Mullenix *et al*. [213] reported that when rats consumed 75-125 ppm and humans 1-10 ppm fluoride in their respective drinking waters, the result was equivalent ranges of plasma fluoride levels of 0.06-0.64 ppm (2.8-32 $\mu mol.L^{-1}$). The weanling male rat required water fluoride levels of 10 ppm to produce plasma fluoride levels of about 2 $\mu mol.L^{-1}$ [214]. Exposure of rats to 175 ppm resulted in dehydration and the death of 50% of exposed young rat females within 10 days [213]. On the other hand, Ekambaram and Paul [215] studied fluoride effects in adult female Wistar rats after treatment with 500 ppm NaF in drinking water for 60 days. Administration of high doses of fluoride did not produce lethality in this study. Two long-term studies [216, 217] compared the effects of 0.5, 5 or 50 ppm of AlF_3 with comparable levels of NaF in rats. Surprisingly, the highest mortality was observed in the 0.5 ppm AlF_3 group. The administration of NaF alone did not produce a similar mortality rate. The effects of various doses of fluoride are summarized in Table **4**.

1. Systemic Effects of Fluoride

Fluoride when absorbed is rapidly distributed by systemic circulation. Steady-state fluoride concentrations are achieved more rapidly between plasma and well-perfused tissues, such as liver and kidney. The major route for the removal of fluoride from the body is by the kidney [218]. Fluoride in tissues is associated with structural changes and disorders of their function. Laboratory investigations to validate predictive animal models of fluoride or AlFx effects provide evidence that chronic administration of fluoride influence physiological homeostasis in experimental animals. The observed differences might be due to variations in dose, duration of exposure, sensitivity of species, gender, and physiological status of the animals.

The occurrence of hypocalcaemia was reported after fluoride overload of rats and mice [222, 232, 233]. Verma and Sherlin [220] suggested that hypocalcaemia observed in their study might be due to decreased Ca^{2+} absorption from the gut. With a high fluoride intake, insoluble calcium fluoride is formed in the intestine and excreted in faeces increasing the likelihood of low blood Ca^{2+} if there is an insufficient dietary intake. In turn, hypocalcaemia may lead to parathyroid stimulation with a secondary hyperparathyroidism, bone matrix resorption, osteoporosis and osteomalacia [234].

Heard *et al*. [222] reported that the acute fluoride intraperitoneal administration resulted in cardiac dysrhythmias, and cardiovascular collapse in a mouse model. Progressive deterioration of cardiopulmonary function after intravenous infusion of 1.5 mg F^-/kg/h for 3 h (with or without $AlCl_3$) was observed in pigs [225]. At 3 h, mean pulmonary arterial pressure, pulmonary vascular resistance, tracheal pressure, and plasma concentrations of TXB2, 6-ketoPGF1α, and PGF2α were significantly increased to approximately 200, 520, 175, 759, 402, and 336%, respectively, of baseline values. Cardiac irregularities and low blood pressure have been reported in young albino rabbits of both sexes after long-term fluoride administration [229]. The myocardium showed cloudy swellings, sarcoplasmic vacuolization, and small hemorrhages followed by fibrous necrosis.

Table 4. Systemic Effects of Fluoride as Observed Under Various Conditions in Animal Models

Animals	DOSE	EXPOSURE	Systemic Effects	References
RATS	0.5 ppm	52 weeks	cell proliferation, nephritis	[216]
	0.8, 1.1 or 2.2 ppm	180 days	↓Ca^{2+}, Mg^{2+}, Zn^{2+} in adrenals, myocardium, bone ↑Na^{+} in aorta, lung, joint, ECG affected	[212]
	5 and 25 ppm	12 weeks	fluoride accumulation in kidney and liver, increased lipid peroxidation	[218, 219]
	40 mg/ kg of body weight/daily	during pregnancy	dams + F1 generation ↓body weight, ↓serum proteins, hypocalcemia, hypoglycemia, nephrotoxicity	[220, 221]
	175 ppm	10 days	dehydratation, death	[213]
	500 ppm	60 days	↓body weight, ↓serum proteins, hypocalcemia, dental lesions, impaired motor activity	[215]
MICE	57 mg F^{-}/ kg	60 minutes	hypocalcemia, cardiac dysrythmias, cardiovascullar collapse, death	[222]
	10 - 30 mg NaF/kg/day	30 days	hypocalcemia, decrease in fertility, altered sperm structure	[223]
	226 ppm	20 days	↓body weight, renal damage	[224]
PIGS	1.5 mg F/kg/h i.v. infusion	1-3 h	deterioration of cardiopulmonary function	[225]
	100 - 400 mg F/ kg/day	50 days	lassitude, anorexia, sluggishness, lesions in liver, kidney, and thyroid	[226, 227]
RABBITS	5-50 mg NaF/kg/day	105 days	cardiac irregularities, myocardial damage, degenerative and inflammatory changes in the liver, pulmonary damage, functional sterility	[228, 229]
SHEEPS	13.8 ppm	12-24 weeks	↓body weight ,↓serum proteins, dental lesions	[230]
	chronic fluorosis area	long-term	P-Q interval prolonged, sinus bradycardia, decreased heart beats	[231]

The degree of myocardial damage seemed to be directly proportional to the dosage of fluoride.

Degenerative and inflammatory changes were also observed in the liver of the exposed animals [228]. Histopathological examination revealed increasing degrees of hepatocellular necrosis, hyperplasia, extensive vacuolization in hepatocytes, and centrilobular necrosis in the liver. Experimental fluorosis in rabbits produced pathological lesions in the trachea, pulmonary damage, hypertrophy and hyperplasia in skeletal muscle, and structural alterations in the lens. Pathological lesions in liver, kidney, and thyroid were observed in young pigs exposed to fluoride for 50 days, along with lassitude, anorexia, and sluggishness [226, 227].

Several authors observed that fluoride causes various histological structure changes of the kidney, resulting in impairment of renal function and metabolism. A large number of kidney cells, taken from a group of young pigs after 50 days of fluoride administration, were undergoing or had finished a program of cell death, thus resulting in kidney lesions [226, 227]. These results therefore provide valuable insight on the effects of chronic fluorosis on kidney deterioration.

Isaacson *et al*. [216] compared the effects of 0.5 ppm of AlF_3 with a comparable level of NaF after 52 weeks. No differences were found between the body weights of rats in the different treatment groups although more rats died in the AlF_3 group than in the control group. A progressive decline in the appearance of the AlF_3 animals was noted throughout the experiment, with the hair becoming sparse and the yellowing which occurs with age. The skin became dry, flaky and of a copper color. The kidneys of the AlF_3 group had higher Al^{3+} levels compared to both the control and NaF groups, while liver Al^{3+} levels did not differ between groups. Pathological changes were found in the kidneys of animals in both the AlF_3 and NaF groups. The kidneys from rats drinking the NaF-treated water exhibited glomerular hypercellularity and mesangial proliferation together with patchy focal nephritis. Al^{3+}-containing deposits were found in the kidney blood vessels, and the renal Al^{3+} content was doubled when the rats drank the AlF_3 water. More monocyte infiltration was present in the kidneys of the AlF_3 group compared to the controls. No morphological abnormalities were observed in the liver. Since the administration of NaF alone did not produce a similar mortality rate, this effect does not appear to be directly related to fluoride intake. Both the AlF_3 and NaF groups had increased brain Al^{3+} levels relative to controls. The Al^{3+} level in the NaF group was double that of controls and the Al^{3+} level of the AlF_3 group was even greater.

Fluoride administered at 226 ppm to female mice in drinking water caused thyroid impairment, retarded growth, altered liver, kidney, and bone weights [224]. The plasma level of T_3 and T_4 were lowered by 58%. At the same time, the plasma TSH level were increased 3.15-fold. Hypothyroidism induced by fluoride also affected haematopoiesis. Ge *et al*. [235] suggested that fluoride may directly damage cells and induce rupture of DNA strands and thereby cause dysfunction of the thyroid gland. These authors demonstrated that fluoride can directly induce structural changes and dysfunctions of the thyroid gland of rats. Also, fluoride disturbes the synthesis and secretion of thyroid hormone, interferes with the activity of enzymes that catalyze the conversion of thyroxine (T_4) into the active thyroid hormone triiodothyronine (T_3) and inactive metabolites, thereby leading to perturbations of circulating thyroid hormone levels. DNA strands in thyroid gland cell were adversely affected when rats were exposed to high fluoride, low iodine, and their interactive combination from the age of one month to 20 months. These findings demonstrate that excessive intake and accumulation of fluoride in the body is a serious risk factor for the development of thyroid dysfunction, especially when iodine deficiency also exists.

2. Effects of Fluoride on Embryonic and Fetal Development

Several contradictions have been raised regarding transfer of fluoride through placental barrier. Ream *et al*. [236] reported that the amount of fluoride crossing the placenta is insufficient to produce morphological changes in bones of weanling rats born to dams given 150 ppm of fluoride. On the other hand, various reports have suggested that fluoride crosses the placenta in a number of species including rats, guinea pigs, rabbits, and Holstein cows [237-241].

Collins *et al*. [242, 243] investigated effects of oral administration of 10, 25, 100, 175, and 250 ppm NaF daily throughout gestation in rats and throughout three generations. Decreased fluid con-

sumption observed at 175 and 250 ppm was attributed to decreased palatability and did not affect reproduction. No cumulative effects were observed in three generation. Mating, fertility and survival indices were not affected. The number of corpora lutea, implants, viable fetuses and fetal morphological developments were similar in all groups. NaF up to 250 ppm did not affect reproduction in rats in this study. Oral administration of NaF (20, 40 or 80 mg. kg^{-1} /body weight/day) from day 6 to 19 of gestation in rats significantly lowered body weight gain and feed consumption [244]. No external malformations were observed in any of NaF-treated dams. Increased numbers of resorptions/dead fetuses were observed in 40 and 80 mg NaF-treated rats. Visceral abnormalities such as subcutaneous hemorrhage were also observed.

In another experiment, rats and rabbits were exposed to NaF in drinking water for 10 and 14 days of pregnancy, respectively. The NOAEL for maternal toxicity was 150 ppm for rats and 200 ppm for rabbits based on decreased water consumption and a reduction in maternal body weight gain. No convincing reproductive effects were seen even at the maximum tested concentrations providing doses of 27 mg. kg^{-1} /body weights for rats and 29 mg. kg^{-1} /body weights for rabbits [245]. Trabelsi *et al*. [246] examined the effect of administration of 500 ppm to pregnant and lactating mice from the 15th day of pregnancy to the 14th day after delivery. Compared to a control group, the NaF-treated pups, at age 14days, showed a 35% decrease in body weight, a 75% decrease in plasma free T_4, and reductions in the cerebellar and cerebral protein concentrations by 27% and 17%, respectively. Serum sodium, potassium, and protein concentration increased significantly in the serum of NaF-treated P-generation females and F1-generation rats [221].

Fluoride content in fetal skeleton and teeth increases with the age of the fetus and with the fluoride concentration in the drinking water consumed by the mother. Fluoride is deposited in mineralizing new bone more readily than in existing bone. Bone in which fluoride ions are incorporated is more resistant to bone remodeling and thus lead to a more brittle skeleton as it ages [247]. An increase in incidence of skeletal abnormalities, such as presence of 14 ribs, wavy ribs, dumbbell shaped 6^{th} sternebrae, and incomplete skull ossification, were observed in fetuses after oral administration of various doses of NaF from day 6 to 19 of gestation in rats [244]. A significant increase was seen in rats in average number of fetuses with three or more skeletal variation in the 250 ppm (25.1 mg/kg body weight) group [238, 243]. Ossification of the hyoid bone of F2 fetuses was significantly decreased. Fluoride has been reported to decrease the bone quality of femoral shaft and neck in 30 and 60 mg $F^-.L^{-1}$ treated young growing rats 6 weeks of age [248].

The potent teratogenicity of fluoride was demonstrated *in vitro* on embryo limb bud cells of both rat (13-day) and mouse (12-day), which were subjected to culture for 5 days [42]. Fluoride inhibited cell differentiation (ID_{50} 6.8 $\mu g.ml^{-1}$ for rat, 7.3 $\mu g.ml^{-1}$ for mouse) and proliferation (ID_{50} 44.1 $\mu g.ml^{-1}$ for rat, 63.6 $\mu g.ml^{-1}$ for mouse). The ability of NaF to induce changes in the development was also studied in frog *Xenopus* embryo for NaF concentrations ranging from 0 to 200 ppm. The minimum concentration to inhibit growth was found to be 140 ppm [249]. The reduction in the head-tail lengths of tadpoles by NaF, the pigmentation, the eye diameters, and the touch reflex of embryos were observed. Immobility has been linked to defects in the neuromuscular system of tadpoles. Neuromuscular developmental defects and effects on the brain and behavior were also demonstrated in newborn rats when pregnant dams were treated with fluoride in the drinking water [213, 217].

3. Brain and Behavior

During the last decade numerous animal studies have been published, which have raised the level of concern about the impacts of increasing fluoride exposure on the brain. A considerable amount of research has accumulated indicating that fluoride/AlFx can adversely affect the brain in a number of animal species. A decrease in learning abilities and altered behavior, poor motor coordination, loss of neuronal and cerebrovascular integrity, changes in brain membrane lipids and oxidative stress by fluoride alone or in synergy with Al^{3+} in animals drinking fluoridated water have been reported [217, 250-254]. Malondialdehyde, the marker for the extent of LPO, was elevated in the brain of rats treated with 100 ppm fluoride. Also levels of total glutathione, GSH, and ascorbic acid were decreased. Increased oxidative stress could be the mediating factor in the pathogenesis of fluoride toxicity in the brain of the young rats [104, 255].

The observed effects were dependent on the age at exposure to fluoride. The fetal blood-brain barrier is immature and readily permeable to fluoride [256]. Mullenix *et al*. [213] reported the first laboratory study, which demonstrated *in vivo* that the CNS function was vulnerable to fluoride. The accumulations of fluoride were found in all the regions of the brain, with the highest levels in the hippocampus, one of the most sensitive area of the brain to neurotoxicity.

Behavioral Changes

The behaviors identified by the computer consisted of five major body position (stand, sit, rear, walk, and lying down) and eight modifiers (groom, head turn, look, smell, sniff, turn, wash face, and blank) were tested in pups and adult animals of both sexes. Experimental dams received subcutaneous injection of 0.13 mg $.kg^{-1}$ NaF to produce peak plasma fluoride levels of 0.15-0.20 ppm (0.79-1 μM) [213]. This level corresponds to the inorganic fluoride level in human blood in areas with 1 ppm of fluoride in drinking water. Beyond the prenatal period, these pups received no other experimental fluoride treatment. Male and female adult rats were given 100 ppm fluoride in drinking water for 6 weeks (to reach the plasma fluoride level comparable with humans). The behavioral changes common to weanling and adult exposures were different from those after prenatal exposure. Whereas the prenatal exposure to NaF via the mother induced many behaviors in the pup such as drug-induced hyperactivity, weanling and adult exposures led to behavior-specific changes more related to cognitive deficits. When fluoride exposure began at 21 days of age, a common pattern among behavior disturbances developed in both sexes. Adult exposure was associated with significant behavioral impact only in females. Adult males did not have significantly elevated fluoride levels in the hippocampus. This study has gained support from other animal studies [251, 253, 257]. While these studies have employed different methods and animals, they are consistent in that fluoride exposure may impact behavior and/or learning. Also the interactive effects of high fluoride concentration and iodine deficiency might affect the functions of the CNS. Such combination has a negative effect on learning-memory of offspring rats [258]. In addition, even mild hypothyroidsm of the mother during gestation has been shown to lead to significant and permanent defects in brain development in the offspring in both experimental animals and humans.

Neuropathological Changes

Some authors suggested that the effects on behavior were consistent with interrupted hippocampal development histology. Prenatal exposure on 17-19 days of gestation in the rat is a period when pyramidal cells of hippocampus are forming and granule cells of the dentate gyrus of hippocampus form at the ages when weanling and adult exposures were administered. Histological changes were found in the cerebellum of the pups after exposure of pregnant and lactating mice from the 15th day of pregnancy to the 14th day after delivery to NaF [246]. The external granular layer was markedly reduced or absent, the Purkinje cell bodies were poorly differentiated and arranged in a single layer at the surface of the internal granular layer. More apoptotic Purkinje cells were observed.

Neuropathological changes were found in brain tissues from albino rabbits after fluoride subcutaneous injections in different doses to rabbits of both sexes for 100 days [259]. Tremors, seizures, and paralysis indicating brain dysfunction were seen. The Purkinje neurons exhibited chromatolysis and acquired a "ballooned" appearance. Nissl substance showed various degrees of decrease and even complete loss. A reduction in unmyelinated nerve fibres, external granular layer of cerebellum and increased neuronal apoptosis have also been reported in rats and mice [246, 260]. All of these changes are seen with excitotoxicity.

Chronic exposure to fluoride (0.5 ppm for 52 weeks) in drinking water of rats compromised neuronal (hippocampal) and cerebrovascular integrity [216, 217]. These studies were undertaken to compare 0.5 ppm of AlF_3, with a comparable level of fluoride administered alone in the form of NaF. The effects of the two treatments on cerebrovascular and neuronal integrity were qualitatively and quantitatively different with the alterations being greater in animals in the AlF_3 group than in the NaF group, and greater in the NaF group than in the controls.

In the hippocampus, more moderately damaged and grossly abnormal cells were present in areas of the right hippocampus of both the AlF_3 and NaF groups than in the control group. The right hippocampus also had higher levels of Al^{3+}-induced fluorescence than the left hippocampus. The reduction of neuronal density in the neocortex of the left hemisphere was more prominent in the AlF_3 group than the NaF and control groups. Cellular abnormalities in the form of chromatin clumping, enhanced protein staining, pyknosis, vacuolation, and the presence of ghost-like cells were also more common in the AlF_3 group in the left hemisphere. Striking parallels were seen between Al^{3+}-induced alterations in cerebrovasculature and those associated with AD and other forms of dementia. The AlF_3 group had more immunoreactivity for Aβ in the lateral posterior thalamic areas of both hemispheres relative to the controls. The NaF group differed from the control for immunoreactivity for Aβ in the right lateral posterior thalamic area with the controls having low reactivity and the NaF group having no or high levels of immunoreactivity. While the small amount of AlF_3 (0.5 ppm) in the drinking water of rats required for neurotoxic effects was seen as surprising, the neurotoxic effects of NaF (1 or 2.1 ppm of fluoride) was seen as even more so. In summary, the chronic administration of AlF_3 and NaF in the drinking water of rats resulted in distinct morphological alterations in the brain, including effects on neurones and the cerebrovasculature. Many of these pathological changes could be due to either secondary or primary excitotoxicity [101].

Further studies are needed to establish the relative importance of a variety of potential mechanisms contributing to the observed effects of fluoride, Al^{3+}, and AlFx in the brain as well as to determine the potential involvement of these agents in neurodegenerative diseases. In addition, studies need to be done on the effects of fluoride and AlFx on microglial activation, glutamate transport proteins and brain extracellular glutamate levels in response to fluoride/AlFx toxicity. It is also known that excitotoxicity induces brain calcification micro-deposits, which could be a nidus for fluoride accumulation in high concentrations. Studies are needed which measure fluoride levels in brain calcifications in humans, such as basal ganglion calcifications.

4. Paradoxical Dose-Response Effects of Fluoride in Animal Studies

The review of laboratory studies on the physiological and biochemical effects of fluoride reveals the existence of paradoxical dose-responses. Some of them show that, under certain circumstances, the inhibitory or stimulatory impact of fluoride can actually be greater at a lower level of intake than at a higher level (hormesis effect) [261]. Messer *et al*. [262] reported that low levels of fluoride in food rendered mice infertile while a high fluoride diet improved their fertility. Mullenix with co-workers [213] found that the six weeks of consuming drinking water with 75 and 100 ppm fluoride produced higher plasma fluoride levels than did 125 ppm in rats. Bohatyrewicz *et al*. [248] recorded higher compressive bone strength after six weeks in rats drinking water with 8 ppm than with 30 or 60 ppm. The hormesis effect of fluoride has been demonstrated during the initial bone-forming stage in rat skull-cap bone [200]. Fluoride at low doses promotes the proliferation and differentiation os calvarial osteoblasts, whereas at high doses affects the cell structure and cell cycle by rendering the cell stagnant in the S phase and inducing apoptosis. While a significant reduction in the content of ATP in RBC was found in rats after 4 weeks of exposure to 4 or 16 ppm NaF, after 8 weeks, the ADP content remained significantly reduced with the smaller dose, while the greater dose was surprisingly associated with a higher energy potential of the cells [121].

The *in vivo* study of brain LPO and antioxidant systems of young rats in chronic fluoride intoxication revealed that an overriding adaptive response appeared to be operating at the higher fluoride intake [104]. Young rats were exposed to 30 ppm or 100 ppm fluoride in their drinking water for 10 weeks after birth. Malondialdehyde as a marker of LPO was elevated in the young rats exposed to 100 ppm but not to 30 ppm dose. On the other hand, levels of total glutathione, reduced glutathione, and ascorbic acid were elevated in the rats exposed to 30 ppm but were lower in the 100 ppm group. The elevation of glutathione S-transferase activity compared to the controls was much greater in the 30 ppm rats (143% higher) than in the 100 ppm group (21% higher). Such reactions are common. In the lower dose, the cells have time to upregulate protective glutathione and glutathione S-transferase levels, but at the higher dose the mechanism is quickly overwhelmed.

An impressive illustration of this fact is seen in the administration of AlF_3 to rats. In both a 45-week study and a confirmatory 52-week study [216, 217] the neuronal, cerebrovascular, and nephritic toxicity of AlF_3 at 0.5 ppm in the drinking water was significantly greater than with higher levels of AlF_3 (5 or 50 ppm). It is unclear why higher levels of AlF_3 produced less impairment, fewer deaths and generally healthier animals than the low levels. The authors suggested the possibility that fluoride, at certain low levels, may exert a protective effect against the Al^{3+} when given at a certain absolute level.

HUMAN EXPOSURE TO FLUORIDE

In 1942, H. Trendley Dean published his famous 21 City study in which he showed that at 1 ppm fluoride there was a marked decrease in tooth decay [7]. The artificial fluoridation of drinking water as a way of preventing dental caries has been a practice for many years in several countries. Recently, we have witnessed that a growing majority of countries do not support water fluoridation. Today, approximately 60-70% of the American people and more than 50% of the population of Australia, Columbia, Ireland, New Zealand, and Singapore are supplied with fluoridated drinking water. However, people now get fluoride from many other sources, such as food and beverages, pesticide and fertilizers, industry, dental treatments, fluorinated drugs, and fluoride air pollution, so total fluoride intake has become an issue of particular concern [9, 10]. The problem of high fluoride in ground water is one of the most important health-related environmental issues in India. Endemic fluorosis occurs in many parts of China, where the major sources are ground water, coal-burning and brick-tea. In central and northern Mexico millions of people are affected by high fluoride content in household-use groundwater [263].

Numerous epidemiological and clinical studies demonstrate the positive correlation between the higher intake of fluoride and various non-specific symptoms, changes in teeth and bone structure, reduction of children intelligence, and psychiatric symptoms in

adults. Most of the ill effects caused by fluoride were first recognized among workers in aluminum factories, where fluoride and Al^{3+} are present in high concentrations [264, 265]. It has become apparent that dental and skeletal fluorosis impact millions of people in fluoridated communities and in countries with regions of high endemic levels of fluoride, like India and China.

1. Fluoride Levels in Human Body Fluids

Under most conditions, fluoride is rapidly and extensively absorbed from the gastrointestinal tract. The rate of gastric absorption is inversely related to the pH of the gastric contents. High concentrations of Ca^{2+} and Al^{3+} can reduce the uptake of fluoride at this stage and the complexes or insoluble fluoride usually exit the body in the feces. Fluoride removal from plasma occurs by calcified tissue uptake and urinary excretion. About 99% of the body burden of fluoride is associated with calcified tissues, and most of it is not exchangeable. In general, the clearance of fluoride from plasma by the skeleton is inversely related to the stage of skeletal development [266]. In a healthy adult, about 50% of the fluoride, which enters plasma, is excreted by the kidney. The estimation of fluoride concentration in human body fluids has been widely performed, since the levels of fluoride in the serum, plasma or urine are important determinants of fluoride effects in the body. However, numerous data are expressed in various units, authors are using various methodologies, and wide variations in fluoride content might exist within various areas and within the same community.

Plasma Fluoride Level

Pak *et al*. [267] suggested the "therapeutic window"of fluoride level in blood to be 5 $\mu mol.L^{-1}$ (95 ppb). Concentrations of fluoride up to 1-2 $\mu mol.L^{-1}$ are not assumed to be overtly cytotoxic. The mean plasma fluoride levels in healthy subjects of 1-3 $\mu mol.L^{-1}$ (19 - 57 ppb) were reported [268, 269] in nonfluoridated areas. Table **5** shows selected examples of the average fluoride concentrations in human blood serum and body fluids. The comparison of fluoride level in serum of children living in areas with low fluoride level (0.30 ppm) in drinking water shows the lowest values for 8-16 year old students from Switzerland [270], while in China the estimated serum level was higher [271, 272]. In the group of 21 children living in areas of Delhi, India, with comparable levels of fluoride in drinking water, the mean value of serum fluoride content was 7.37 $\mu mol.L^{-1}$ (140 ppb). Only 4 children had serum fluoride content 1 $\mu mol.L^{-1}$ (19 ppb), the remaining had elevated levels up to 15.8 $\mu mol.L^{-1}$ (300 ppb) [273].

The US Environmental Protection Agency currently consideres safe levels of fluoride in drinking water ≤ 4 ppm. Children from the high fluoride village in China (2.45 ppm) had serum fluoride level 4.26 $\mu mol.L^{-1}$ (81 ppb) [271, 272], while in children from area in India with 4.37 ppm in drinking water their serum ranged from 1 to 21.6 $\mu mol.L^{-1}$ (19-410 ppb) [273].

Fluoride in Saliva and Urine

Oliveby *et al*. [274] reported the normal concentration of fluoride in saliva about 1 $\mu mol.L^{-1}$. Tóth *et al*. [275] estimated fluoride levels in saliva in a group of 79 subjects of both genders in the age from 19-45 years under experimental design with no fluoride from food chain. The average baseline fluoride concentration in saliva calculated from these published data was 3.13 $\mu mol.L^{-1}$ (59.5 ppb). This increased after four week test period with daily intake of 1 mg of fluoride from fluoridated salt, milk, and tablets to 19, 32, and 30 $\mu mol.L^{-1}$ (360, 610, and 570 ppb), respectively. Salivary fluoride concentrations peak rapidly (1 to 15 min) after ingestion but the return to baseline takes 20 to 60 min.

The concentration of fluoride in urine is higher in comparison with the serum and saliva. It is very difficult to compare the results in various studies since various methods have been used. The values given for fluoride concentration in urine from unpolluted areas in the Europe [270, 275] are lower than that reported from China. Analysis of the literature data of Chinese populations in different geographical regions without fluorosis [276] demonstrate a mean urinary fluoride content of 36.84 $\mu mol.L^{-1}$ (700 ppb) for children and 43.7 $\mu mol.L^{-1}$ (830 ppb) for adults. Surprisingly high urinary fluoride was found in children in Gdańsk, Poland [283]. Fluoride has been determined in urine of 1 240 children, aged 7-14. Their schools are located near a fluoride-bearing phosphate fertilizer waste disposal site or near a phosphate fertilizer plant. The mean fluoride concentration in urine of 992 children from areas with low fluoride in drinking water (0.2-05 ppm) was 919 ppb (210 – 5 240), while in areas with 1-2 ppm the mean concentration 1 800 ppb (500-6 000ppb) was found. Significantly higher urinary fluoride concentrations were found in boys than in girls.

Fluoride Level in Pregnancy

Although promoted now for some years, prenatal systemic administration of fluoride supplements to pregnant women for caries prevention in their offspring has continued to be controversial. The fasting morning urine levels of 31 pregnant women aged 22–34 living in Poznan, Poland, where the level of fluoride in drinking water ranges from 0.4 to 0.8 ppm were 653 ppb for women in their 28th week and 838 ppb in their 33rd week of pregnancy [284]. The difference of fluoride concentrations in urine samples of the study and the control group of non-pregnant women (835–2 221 ppb) may be explained by incorporation of fluoride into fetal hard tissues and, accordingly, decreased elimination in the urine. This fact must be remembered when evaluating fluoride exposure in women who are pregnant. The statistically significant increase in urine fluoride

Table 5. Fluoride Concentration in Human Body Fluids (Areas <1 ppm, Without Fluoride Supplementation)

BODY FLUID	ppb	µmol L^{-1}	REFERENCES
Blood serum			
Europe	13 - 57	0. 68 - 3	[268, 270]
China	41	2.16	[271, 272]
India	19 - 300	1 - 15.8	[273]
Saliva	19 - 59.5	1 - 3.13	[274, 275]
Urine			
Europe	245 - 615	12.89 - 32.6	[270, 275]
China	700 - 830	36.84 - 44.37	[276]
Cord plasma	28	1.42	[277-280]
Amniotic fluid	10 - 17	0.53 - 0.89	[277]
Mother´s milk	5 - 10	0.26 – 0.53	[281, 282]

concentrations observed in the 33rd week of pregnancy suggests that fluoride metabolism is changing with the progress of pregnancy. This fact might be connected with the lower uptake of fluoride in fetal calcified tissues and decreased bone calcification toward the end of pregnancy.

Fluoride has been found in fetal cord blood at various stages of normal pregnancies, from an area with a relatively low water fluoride content (less than 0.5 ppm). Chlubek *et al*. [278] reported that maternal and cord plasma did not differ significantly (33 and 28 ppb, respectively), while Gupta *et al*. [280] found that average fluoride concentration in the cord blood was 60% of that in mother's blood. A significant difference between the cord plasma fluoride levels of the newborns in the untreated group of women (27 ppb) and the fluoride- supplemented groups (58 ppb) was found [279]. Amniotic fluid fluoride levels were significantly higher at term than in midtrimester pregnancy (17 vs 10 ppb). This higher concentration may imply higher fetal urinary excretion of fluoride at term [277].

Mother´s Milk

The very low level of fluoride (5 – 10 ppb) present in mother's milk is probably the evidence that fluoride is not an "essential nutrient" [281, 282] and it is only moderately increased with substantially greater fluoride intake by the mother. Even at the very low normal level, breastfed babies excrete more fluoride than they ingest from the milk. The body usually retains trace minerals that have a genuine physiological role rather tenaciously.

2. Dental and Skeletal Fluorosis

Neither dental fluorosis (DF) nor skeletal fluorosis (SF) are the specific topic of this review. Nevertheless, DF is the first evident sign of increased fluoride intake and several studies bring correlation between the prevalence of DF and other variables studied. Teeth are the first tissue, which shows the excess of fluoride. SF is the end result of the long-term exposure to chronic fluoride intake. The mean urinary fluoride, which can serve as an indicator for identifying endemic fluorosis areas are 84.21 $\mu mol.L^{-1}$ (1. 6 ppm) for adults and 73.68 $\mu mol.L^{-1}$ (1.4 ppm) for children [276]. Levels of 310 $\mu mol.L^{-1}$ (5. 9 ppm) fluoride were found in 80´s in endemic fluorosis areas in China [285].

Dental Fluorosis

The compilation of studies worldwide indicates that somewhere between 13.5% and 48% of children in fluoridated communities has DF [286, 287]. The overall prevalence of DF is higher in endemic areas. In Rajastan, India, 76.9% of examined children exhibited DF [288] and 84 % of resident children were affected with DF in Haryana, India [289]. DF was detected in more than 80% of the population in endemic areas in Mexico [263]. Moderate and severe DF is associated with negative psychological effects on those afflicted.

Skeletal Fluorosis

Fluoride causes paralysis of limbs in advanced SF, which is related to pressure upon the spinal cord by newly formed bone protruding into it and also upon nerves at the point of their exit from the spine. The spinal cord lesions and muscular damage in patients suffering from SF are also the result of direct action of fluoride on ganglion and muscle cells. Crippling SF was found at and above 2.8 ppm fluoride in drinking water in villages in India with a prevalence of 38%. A prevalence of 31% was found in Wamiaho village (China) with 2.45 ppm fluoride in drinking water [271]. In a group of 1998 subjects above 21 years examined in central Rajastan, SF was diagnosed in 47.5% [288]. A positive significant dose-response relationship between the serum fluoride concentration and the prevalence of SF was demonstrated. However, extremely polluted areas exist in China, where the daily fluoride intake might reach 6.57 and 8.54 mg. The prevalence of SF was 44.4% and 95%, respectively [290].

3. Nephrotoxicity

High fluoride concentrations in drinking water in endemic areas are known to cause impaired kidney function involving renal tubular and glomerular dysfunctions [291, 292]. The fluoride excretion is reduced and fluoride accumulates in the body. In people with kidney disease, the distribution of fluoride in the body fluids and tissues can change dramatically, with less fluoride excreted and more incorporated in mineralized tissues and more remaining in the plasma. As a result, people with kidney disease in areas with 1 ppm fluoride have been found to have significantly elevated bone and serum fluoride levels (up to 19 $\mu mol.L^{-1}$ ~360 ppb) [293]. Fluoride intoxication has been described in chronic hemodialysis patients [294, 295]. Arnow *et al*. [296] reported that 12 of 15 patients receiving dialysis treatment in one room became acutely ill, with severe pruritus, multiple nonspecific symptoms, and/or fatal ventricular fibrillation. Death was associated with longer hemodialysis time and increased age compared with other patients who became ill. The source of fluoride was the temporary deionization system used to purify water for hemodialysis. In some regions, the water used for the dialysate also contained a lot of Al^{3+}. Some patients used Al^{3+}-containing medications. Moreover, patients with renal failure cannot remove Al^{3+} from the blood. Elevated Al^{3+} levels have been also implicated as the cause of dialysis encephalopathy or dementia [297, 298]. Although flurane anesthetics may produce plasma fluoride concentrations in excess of 50 $\mu mol.L^{-1}$ (950 ppb), they have not produced the acute nephrotoxic effects [299]. It seems that the human body has efficient homeostatic mechanism to respond to short time peak of fluoride in the blood.

4. Central Nervous System

In light of the published findings, the long-term synergistic action of fluoride and AlFx represents a risk factor for the functioning of the CNS. G protein-coupled receptors have key roles in information processes in the brain. A number of conditions can trigger excitotoxicity and increase excitotoxic sensitivity including hypoxia/ischemia, depressed cellular energy production from any cause, hypomagnesmia, inflammatory cytokines and eicosanoids, free radical and LPO products, trauma, certain heavy metals, viral, bacteria and fungal infections. This means that a large number of people fall within a hypersensitive state to excitotoxicity. Under such conditions, even physiological levels of extracellular glutamate can be neurotoxic.

Fluoride Exposure and IQ Deficits in Children

While we know that fluoride might cross the placenta, we know little of its impact on the human fetal brain. A study by Du [300] revealed adverse effects on the brains of 15 aborted fetuses between the 5-8th months of gestation from an endemic fluorosis area in China compared with those from a non-endemic area. Stereological study of the brains showed that the numerical density of the volume of the neurons and the undifferentiated neuroblasts as well as the nucleus-cytoplasm ratio of the neurons was increased. The mean volume of the neurons was reduced. These results showed that chronic fluoride overload in the course of intrauterine fetal life may produce certain harmful effects on the developing brain of the fetus. This could represent fluoride/AlFx alterations in cerebral glutamate levels, which are known to play a vital role in neuron migration and pruning of synaptic connections and dendrites.

Several studies appeared from China, which indicated a lowering of IQ associated with fluoride exposure [301-303]. Their conclusions have been criticized because of the possibility of unaccounted confounding variables. However, the latest study by Xiang *et al*. [304] controlled for parental economic status and education, as well as exposure to iodide and lead. These authors found that IQ

scoress below 80 were significantly associated with higher serum fluoride level and estimated that children's IQ would be lowered at 1.8 ppm fluoride in drinking water. Such a finding represents little margin of safety considering the potentially serious outcome for infants drinking fluoridated water.

Psychiatric and Mental Disturbances in Adults

A distinct decline in mental activity, poorer memory, inability to coordinate thoughts and reduced ability to write were observed in aluminum smelter workers and persons living near the factory [265, 305, 306]. In light of the published findings, the long-term synergistic action of fluoride plus Al^{3+} represents a hidden but serious and powerful risk factor for the development of AD. Laboratory investigations bring evidence that AlFx may induce and affect all pathological hallmarks of AD [6]. The etiopathology of AD might serve as the example of AlFx long-term action from affecting molecules to the development of this devastating disease. Fluoride alone or in synergistic action with Al^{3+} affects processes of neurotransmission, generation of second messengers, and Ca^{2+} homeostasis. It has been demonstrated that AlFx induces toxic Aß generation, protein τ phosphorylation, and alterations in cytoskeletal protein organization. Amyloid plaques in AD contain Al^{3+} [307]. Many neurodegenerative disorders are generally accepted to stem from pathological changes in the conformation of proteins and thus, are characterized by the accumulation of extracellular and/or intracellular protein aggregates [308]. Moreover, the disturbances of energy metabolism can contribute to the development of neurodegenerative diseases, primarily by enhancing excitotoxic sensitivity and microglial activation. $[Ca^{2+}]_i$ affects many of these processes. Ca^{2+} homeostasis in the cell is also known to deteriorate with aging [309], making the elderly more vulnerable to both excitotoxicity and fluoride/AlFx toxicity.

Suppressed activity of pyruvate dehydrogenase and α-ketoglutarate dehydrogenase complex (KGDHC) was found in a number of neurodegenerative diseases, particularly AD and Parkinson's disease [310]. Inhibition of KGDHC has also been shown to alter intracellular Ca^{2+} regulation, something common in neurodegeneration [311]. Gibson *et al*. [310] found that patients with AD carrying the ε4 allele of apolipoprotein E (ApoE4) demonstrated a stronger correlation between their dementia scores and KGDHC activity than did those with non-ApoE4 genes. While there is no direct evidence that fluoride or AlFx complex can suppress KGDHC activity, it is known to be very sensitive to free radical and LPO suppression [312]. That fluoride and Al^{3+} have been shown in a number of studies, both *in vitro* and *in vivo*, to trigger the formation of ROS and LPO products has been well demonstrated. Mercocci *et al*. [181] found that oxidative mtDNA damage was 10-fold higher in mtDNA than nuclear DNA and 15-fold higher in samples taken from individuals older than 70 years. The study was done in individuals aged 42 to 97 years without neurological disease or injury. The combination of excitotoxicity, oxidative stress, LPO, Ca^{2+} dysregulation and mitochondrial dysfunction greatly increases neuron and glial sensitivity to damage.

5. Endocrine Glands

Understanding the role of G proteins in cell signaling allows us to accept the fact that fluoride entering the human body from the environment, water, and food chains followed by Al^{3+}, can affect the activity of endocrine glands and the processes of hormonal regulation of the human body.

Pineal Gland

Luke [313, 314] reported that fluoride accumulates in the human pineal gland. When Luke had the pineal glands from 11 human corpses analyzed, the fluoride in the apatite crystals averaged about 9,000 ppm and in one case went as high as 21,000 ppm. The pineal gland is considered to be a transducer of photoperiodical information [315, 316]. Production of the both chief pineal hormones serotonin and melatonin is cyclical and influenced by light. Melatonin is responsible for regulating numerous life processes, including development and aging. Mongolian gerbils fed higher doses of fluoride excreted less melatonin metabolite in their urine and took a shorter time to reach puberty. In the light of these findings it is interesting to note that the Newburgh-Kingston fluoridation trial (1945-55) found that the girls in fluoridated Newburgh were menstruating on average 5 months earlier than girls in unfluoridated Kingston [317]. Considering the importance of hormonal production of the pineal gland, this issue warrants further study. It is also known that production of melatonin by the pineal is controlled by a metabotropic glutamate receptor and that excess aspartate or glutamate activity can inhibit melatonin release. Being a G protein type receptor, AlFx could also activate this receptor.

Thyroid

Up until the late 1950's, the doses of fluoride as low as 2.3 - 4.5 mg/day were recommended in Europe to reduce the activity of the thyroid gland of those suffering from hyperthyroidism [318]. The search for a mechanism to explain how fluoride might lower thyroid activity has a very long and elusive history. A promising hypothesis is that fluoride mimics the thyroid-stimulating hormone (TSH) by switching on its associated G protein. However, this is puzzling because this would suggest that fluoride would stimulate thyroid activity, not lower it. A possible explanation has come from Tezelman *et al*. [319] who have suggested that overproduction of cAMP leads to a feedback mechanism resulting in a desensitization of the TSH receptor, thus ultimately leading to reduced activity of the gland. It was shown that normal healthy individuals had thyroid function lowered when consuming water at 2.3 ppm [320]. The thyroid gland appears to be the most sensitive tissue in the body to fluoride burden, which is able to increase the concentration of TSH and decrease the concentration of T_3 and T_4 hormones, thereby producing hypothyroidism [258].

Dysturbance of thyroid hormone production has been found in correlation with lowered IQ in children in China [304]. A decreased level of thyroid hormone T_3 was found in residents of Villa Ahumada, Mexico, where fluoride concentration in drinking water averages 5.3 ppm [321]. The first study, which investigated the production of thyroid hormones and TSH, included 90 children living in fluoride endemic, non-iodine deficient areas of Delhi, India, along with 21 children from non-endemic areas [273]. The received data indicate the association of excess of fluoride intake and thyroid hormone disturbances leading to manifestation of iodine deficiency disorders (IDD). This study clearly documents that the primary cause of IDD may not always be iodine deficiency, but the excess of fluoride might induce it. Susheela suggests that iodine metabolism is being disturbed through the fluoride effect on deiodinases, the three enzymes, which regulate the conversion of T_4 to T_3 in target tissues. Even in some of the children from the control group consuming water < 1 ppm F, fluoride levels in their blood and urine are above current upper limits. This indicates other sources of fluoride, such as food and beverages, dental products, air, etc. In those children disturbances in thyroid hormone levels were observed as well. The role of excess of fluoride in development of IDD has been largely unnoticed at present, despite the fact that millions of children suffer with IDD. Considering the globally increasing problem of IDD that issue needs to be taken into consideration.

Testes

The comparison with healthy males living in areas nonendemic for fluorosis suggest that fluoride toxicity may cause adverse effects in the reproductive system of males living in fluorosis endemic areas [322, 323]. A reduction in the circulating testosterone level of males was found in males with or without the presence of clinical SF. The authors concluded that a fluoride exposure of 3–27 mg/day

induces a subclinical reproductive effect that can be explained by a fluoride-induced toxic effect in both Sertoli cells and gonadotrophs. A significant decrease in fertility in 30 regions spread over 9 U. S. states with 3 ppm fluoride or more in the water was also reported [324]. Most regions showed an association of decreasing total fertility rate with increasing fluoride levels.

AMELIORATION OF FLUORIDE PATHOPHYSIOLOGICAL EFFECTS

Laboratory studies have revealed that withdrawal of fluoride resulted in some recovery. Withdrawal of fluoride during lactation caused significant recovery in serum changes in both P- and F1-generation rats [220, 221]. Complete recovery from fluoride toxicity in reproductive functions in male mice on co-treatment with vitamins E and D alone and in combination was reported [233]. Ameliorative effect of these vitamins in NaF-treated dams could be due to removal of cell damaging free radicals. Recovery was also possible by feeding antioxidants (superoxide dismutase, glutathione, β-carotene, and some herbal extracts) [102]. Liu *et al*. [325] reported that synthetic catalytic scavengers of ROS proved beneficial in mouse brain for reversal of age related learning deficits and oxidative stress in mice.

Vitamins C and E act as antioxidants scavengers of free radicals and peroxides, which accumulate after fluoride exposure. Vitamin E channels the conversion of oxidized glutathione to reduced glutathione, which in turn helps compression of mono- and dehydroascorbic acid to maintain ascorbic acid levels. Oral administration of vitamin C (50 mg/kg body weight/day) and vitamin E (2 mg/0.2 ml olive oil/animal/day) from day 6 to 19 of gestation along with NaF (40 mg/kg body weight) significantly ameliorates NaF-induced total percentage of skeletal and visceral abnormalities. Vitamin E was comparatively less effective than vitamin C [326]. Vitamin D is known to promote intestinal absorption of Ca^{2+} and phosphate. Cotreatment with vitamins C, D, and E ameliorates NaF-induced reduction in serum Ca^{2+} and phosphorus [327]. Ekambaram and Paul [215] reported that calcium carbonate prevents not only fluoride-induced hypocalcemia but also the locomotor behavioral and dental toxicities of fluoride by decreasing bioavailability of fluoride in rats. Toxic effects of fluoride were reversible if its exposure was withdrawn for 2 months. Intraarterial administration of 1.8 mM $CaCl_2.kg^{-1}$ reduced the risk of death by 33% in a mouse lethal model of fluoride poisoning [222].

Poor nutrition is seen to be an important cause of endemic osteomalacia in high fluoride areas. Reversal of fluoride induced cell injury and fluorosis through the elimination of fluoride and consumption of a diet containing essential nutrients and antioxidants have been shown [328]. Increasing dietary proteins, Ca^{2+}, and vitamins may help in its prevention especially in pregnant and nursing women and children [234]. The mitigation of the genotoxic effects of fluoride and Al^{3+} was possible by ascorbic acid [102, 329, 330]. Treatments of vitamins C, D, and Ca^{2+} showed significant improvement in skeletal, clinical, and biochemical parameters in children consuming water containing 4.5 ppm of fluoride.

CLOSING COMMENTARY

Science has already accumulated evidence demonstrating how diverse molecules and biological processes can be affected by fluoride. It is conceivable that exposure of cells/tissues to fluoride could lead to a depletion of ATP, GTP, and PLC substrates. Fluoride intesifies LPO and protein oxidation and reduces the antioxidant potential in the cells. While fluoride in whole organism may not reach concentrations, which were used in the laboratory experiments *in vitro*, there may be instances where fluoride ions reach microenvironments where interference may occur, especially at the active sites of certain enzymes. Later it was demonstrated that AlFx causes many effects primarily attributed to fluoride. The discovery of synergistic action of fluoride plus Al^{3+} expanded our understanding of mechanisms of fluoride effects on living organism. The presence of AlFx has been demonstrated by many studies with crystallized proteins, intact cells, and whole animals.

The widespread use of fluoride as a general activator of heterotrimeric G proteins provided evidence that AlFx is a molecule giving false messages, which are amplified by processes of signal transduction. The phosphate analogue model of AlFx has been extended to many enzymes that bind phosphate groups. Regarding the role of phosphoryl transfer reactions in cell metabolism, we can predict hundreds of reactions, which might be influenced by AlFx. It seems probable that we shall not find any physiological process, which is not potentially influenced by synergistic action of fluoride plus Al^{3+}. The actual phosphorylation level of a given protein is the result of a delicate balance between kinases and phosphatases. Recent studies are highlighting the importance of tyrosine and serine/threonine phosphatases in the regulation of many different cellular processes. Fluoride in high concentrations (up to 100 mM) has been included into various design systems as a putative inhibitor of phosphatases. The potential interactions of fluoride in study design warrant a careful assessment and further investigation. The discoveries of receptor diversity, numerous isoforms of G proteins, and effector molecules broaden enormously the possibilities of interactions of signal transduction events. The use of fluoride in laboratory investigations contributed to the discovery of new signaling pathways and their cross talk. On the other hand, it is evident that fluoride might evoke disturbances of the communication networks.

The explanation of the observed effects in animals and humans is complicated by the chemical interactions of fluoride, Al^{3+}, and AlFx with numerous non-protein and protein ligands in body fluids and inside the cells. Competing reactions and disruptions of homeostasis can produce a hormetic dose-response and elicit unexpected responses. Also the fluoride effects on production of free radicals might have adverse influences on the defence mechanisms. It is therefore difficult to predict the actual effective concentrations of fluoride. It is evident that the definition of a "safe" concentration of fluoride for humans must consider that the dose, at which beneficial effects such as caries reduction are expected, is not far away from that one, which causes chronic, yet sub clinical toxic effects. The severity and the development of symptoms depend on age, nutrition status, kidney function, and many other factors.

Understanding the role of G proteins in cell signaling allow the hypothesis that the synergistic action of fluoride and Al^{3+} in the environment, water, and food chains, might impair many physiological functions of human body. The origins of many human diseases are in the malfunctioning of signaling components. Signaling disorders represent a major cause for the pathological states and many of the recently identified validated target molecules of drug research are signal transduction related macromolecules, mostly kinases [331]. Strunecka and Patocka [6] proposed that fluoride could complex with any pre-existing Al^{3+} within body fluids to produce the AlFx and this could lead to a combination of chronic activation of G protein regulated systems and suppression of other critical enzymes, especially kinases. Clinical, epidemiological, and ecological studies over the whole world bring evidence about potential health risks of chronic human exposure to fluoride and Al^{3+}.

One reason to suspect AlFx as the true culprit in these studies is that both Al^{3+} and fluoride is known to exist in appreciable concentrations in all commercial animal feeds and that Al^{3+} readily complexes with fluorine. The same is true with public drinking water. The water supply industry uses aluminum salts to produce a less turbid drinking water. Pesticides and fertilizers also increase fluoride content of food and processed beverages. The trend toward fluorinating pharmaceuticals increases fluoride exposure via medication. Al^{3+}, the metal of the earth's lithosphere, is everywhere: in water sources, in food chains, and in air in the form of dust particles. Contact of food and beverages with Al^{3+} during processing

and storage can increase food levels of Al^{3+}. With exposure so common, we can no longer afford to ignore potential consequences of fluoride plus Al^{3+} for human health. The awareness of increasing load of fluoride and Al^{3+} as a new ecotoxicological phenomenon could contribute to the qualified assesment of their widespread use.

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ABBREVIATIONS

$[Ca^{2+}]_i$	=	Cytosolic Ca^{2+} level
Aβ	=	β-amyloid
AA	=	Arachidonic acid
AC	=	Adenylyl cyclase
AChE	=	Acetylcholinesterase
AD	=	ALZHEIMER'S disease
AlFx	=	Aluminofluoride complexes
AMPA	=	α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid
ApoE4	=	ε4 allele of apolipoprotein E
ATPase	=	Adenosine triphosphatase
BuChE	=	Butyrylcholinesterase
cAMP	=	Cyclic AMP
cGMP	=	Cyclic GMP
CNS	=	Central nervous system
cPIP	=	Prostaglandylinositol cyclic phosphate
DAG	=	1,2-diacylglycerol
DF	=	Dental fluorosis
DHDG	=	*N*-(3-dodecyloxy-2-hydroxy propyl)-*N,N*-dimethylglycine
EC	=	Endothelial cells
ERK	=	Extracellular signal-regulated kinase
GABA	=	γ-amino butyric acid
GAP	=	GTPase activating protein
GDP	=	Guanosine diphosphate
GLAST	=	Glutamate aspartate transporter
GTP(S)	=	Guanosine-5'-*O*-3-[^{35}S](thio)triphosphate
IDD	=	Iodine deficiency disorders
IL	=	Interleukin
IMPase	=	Inositol monophosphatase
$Ins(1,4,5)P_3$	=	Inositol 1,4,5-trisphosphate
InsPs	=	Inositol phosphates
JNK	=	c-jun-NH_2-terminal kinase
KGDHC	=	α-ketoglutarate dehydrogenase complex
LPO	=	Lipid peroxidation
MAPK	=	Mitogen activated protein kinase
MIP-1α	=	Macrophage inflammatory protein-1α
NMDA	=	*N*-methyl-D-aspartic acid
NO	=	Nitric oxide
PA	=	Phosphatidic acid
PAF	=	Plateled activating factor
PDE	=	Phosphodiesterase
PG	=	Prostaglandin
PI 3-K	=	Phosphatidylinositol 3-kinase
PIP_2	=	Phosphatidylinositol 4,5-bisphosphate
PKC	=	Protein kinase C
PLA_2	=	Phospholipase A_2
PLC	=	Phospholipase C
PLD	=	Phospholipase D
RBC	=	Red blood cells
RNS	=	Reactive nitrogen species
ROS	=	Reactive oxygen species
SF	=	Skeletal fluorosis
T_3	=	Triiodothyronine
T_4	=	Thyroxine
TGF-β	=	Transforming growth factor-β
TNF-α	=	Tumor necrosis factor-α
TSH	=	Thyroid stimulating hormone
TX	=	Thromboxane

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From: Sprovieri, John Councillor [mailto:John.Sprovieri@brampton.ca]
Sent: April 4, 2017 4:22 PM
To: Lockyer, Kathryn
Cc: Sprovieri, John; Polsinelli, Nancy; O'Connor, Patrick; Parrish, Carolyn; Palleschi, Michael; Ras, Karen; Loh, Lawrence; Dale, Frank; Tovey, Jim; Downey, Johanna; Groves, Annette; Moore, Elaine
Subject: FW: Faxes April 4th. FLUORIDATION IS A MEDICATION.

Hi Katheryn,
The attached material supports the 1957 Supreme Court Ruling that Water Fluoridation is a Medication. Can you place the attached material on our next Community Water Fluoridation Committee meeting for discussion.
The aim of the discussion is ''What is the purpose of Water Fluoridation'' and ''Does the Province [The Fluoridation Act] have the Authority to Authorize Municipal Councillors to Force Medicate the Population.
John.

Hi Patrick,
Can you have a look at the attached material so that you can provide an opinion to the committee.
John.

The Supreme Court of Canada has found that the liberty interest protected by s. 7 includes the right to make fundamental personal choices free from state interference. 30 **In the context of medical treatment, the Ontario Court of Appeal has held that the right not to be subject to medical treatment without informed consent is an aspect of the security of the person interest under s. 7. 31 Section 7 thus protects "the right to be free from unwanted medical treatment."** 32 To deprive individuals of the ability to make decisions with respect to their treatment and to force them to submit to medication against their competent wishes infringes the Charter right to security of the person as protected under s. 7 of the Charter. 33.

Health Care Consent Act, 1996 (applies to the Medical Officers if they treat someone, but not Councillors, as far as I can tell): https://www.ontario.ca/laws/statute/96h02

"**health practitioner" means a member of a College** under the Regulated Health Professions Act. 1991 or a member of a category of persons prescribed by the regulations as health practitioners; ("praticien de la sante")

Consent to Treatment

No treatment without consent

10. (1) **A Health practitioner** who proposes a treatment for a person shall not administer the treatment, and shall take reasonable strps to ensure that it is no administered, unless,

(a) He or she is of the opinion that the person is capable with respect to the treatment, and the person has give consent; or

…. Elements of consent

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RECOMMENDED
DIRECTION REQUIRED _____
RECEIPT RECOMMENDED ✓_____

11. (1) the following are the elements required for consent to treatment:

1. The consent must relate to the treatment
2. The consent must be informed
3. The consent must be given voluntarily
4. The consent must not be obtained through misrepresentation or fraud. 1996, c. 2, Sched. A, s. 11 (1).

"Water fluoridation aims to reduce social inequalities in dental health, (10) but few relevant studies exist. The quality of research was even lower than that assessing overall effects of fluoridation."

- "If fluoride is a medicine, evidence on its effects should be subject to the standards of proof expected of drugs, including evidence from randomised trials. If used as a mass preventive measure in well people, the evidence of net benefit should be greater than that needed for drugs to treat illness. (17)...There have been no randomised trials of water fluoridation."

Wilson PM, Sheldon TA. Muddy waters: evidence-based policy making, uncertainty and the "York review" on water fluoridation. Evidence & Policy 2006;2(3):321-331.

- "Evidence relating to reducing inequalities in dental health was both scanty and unreliable."

A recent review in the public health journal called Critical Public Health, (Peckham 2011 Nov15) "Slaying sacred cows: is it time to pull the plug on water fluoridation?" states the following:

- "While traditionally the problem of evidence is characterised as one where policy makers either accept or ignore evidence, a central concern of this article is where poor evidence is promoted by professionals and accepted by policy makers."
- "[a] more balanced reading of the evidence is that water fluoridation has little effect, is a poor delivery mechanism, causes dental fluorosis and may have other long-term harmful health effects. It certainly does not meet Skrabanek's (1994) standard for evidential proof of benefit. Fluoride is effective when applied topically but is potentially harmful when ingested (SCHER 2011)."
- "-the link between evidence and public health interventions should be stronger than that for other forms of medical interventions because public health deals with people who are not 'ill' nor have they approached a health care practitioner asking for medical assistance." (Skrabanek 1994)

The definition of "Drug" in Food and Drugs Act: available from: http://laws-lois.justice.gc.ca/eng/acts/F-27/page-1.html

"includes any substance or mixture of substances manufactured, sold or represented for use in: the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or its symptoms, in human beings and animals".

The Supreme Court of Canada in 1957 (1) ruled that fluoridation was a "compulsory preventive medication", which is "not to promote the ordinary use of water as a physical requisite for the body" but has a "special health purpose". This ruling has never been contested by the Canadian Government.

- **Supreme Court Justice Cartwright stated:** "In pith and substance the by-law relates not to the provision of a water supply but to the compulsory preventative medication of the inhabitants of the area. In my opinion, the words of the statutory provisions on which the appellant relies do not confer upon the council the power to make by-laws in relation to matters of this sort."
- **Supreme Court Justice Rand stated:** "But it is not to promote the ordinary use of water as a physical requisite for the body that fluoridation is proposed. That process has a distinct and different purpose; it is not a means to an end of wholesome water for water's function but to an end of a special health purpose for which water supply is made use of as a means."

6.18-4

Minister of Health / Ministre de la Santé

Ottawa, Canada K1A 0K9

APR 04 2012

Regional Municipality of Peel
Office of the Regional Chair

APR 17 2012

RECEIVED

Mr. Emil Kolb
Regional Chair and Chief Executive Officer
Regional Municipality of Peel
10 Peel Centre Drive
Brampton, Ontario L6T 4B9

Dear Mr. Kolb:

Thank you for your correspondence of February 6, 2012, concerning Peel Regional Council's resolution to request that Health Canada regulate fluorosilicates (i.e., hexafluorosilicic acid and sodium silicofluoride) as drugs under the *Food and Drugs Act*. I regret the delay in responding.

In Canada, responsibility regarding the safety of drinking water generally lies with the provincial and territorial governments. Health Canada worked with the provinces and territories, through the Federal-Provincial-Territorial Committee on Drinking Water, to develop the *Guidelines for Canadian Drinking Water Quality*. The provinces and territories use the Guidelines to establish their own requirements for drinking water quality and have sole responsibility regarding implementation. For that reason, your request that Health Canada regulate municipal drinking water supply treatment chemicals as drugs is an issue that falls outside the jurisdiction of the *Food and Drugs Act*.

With respect to your request regarding a long-term toxicology study, Health Canada recommends that drinking water treatment additives such as fluoridation agents be certified to the appropriate standard, specifically NSF/ANSI Standard 60: Drinking Water Treatment Chemicals - Health Effects. This standard requires a toxicology review of the product to ensure its safety at the maximum use level and to evaluate potential contaminants in the product.

Regarding human clinical evidence of the efficacy of adding fluoride to water supplies, most published scientific studies on the effectiveness of water fluoridation are based on comparisons between communities with minimal fluoride levels in the water supply versus communities with fluoridation, rather than a clinical intervention. The first controlled clinical trial at a community level was conducted in the U.S. and published in 1956; a recent human double-blind placebo-controlled clinical trial on how effectively fluoride is taken up from drinking water was conducted in the U.K. in 2005.

.../2

Canada

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RECEIPT RECOMMENDED ✓

Sprovieri, John Councillor

m: Sprovieri, John Councillor
nt: 2016/06/09 7:28 AM
To: Sprovieri, John Councillor
Subject: FW: New Zealand plans to drown its citizens in toxic fluorides

Does this help, for drugs?
http://www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/fs-fi/reviewfs_examenfd-eng.php

What is considered to be a drug?

Drugs include both prescription and nonprescription pharmaceuticals; biologically-derived products such as vaccines, blood derived products, and products produced through biotechnology; tissues and organs; disinfectants; and radiopharmaceuticals. According to the Food and Drugs Act, "a drug includes any substance or mixture of substances manufactured, sold or represented for use in:

1. *the diagnosis, treatment, mitigation or prevention of a disease, disorder, abnormal physical state, or its symptoms, in human beings or animals;*
2. *restoring, correcting or modifying organic functions in human beings or animals; or*
3. *disinfection in premises in which food is manufactured, prepared or kept."*

tural health products, such as vitamin and mineral supplements and herbal products for which therapeutic claims are made are also considered drugs at the level of the Food and Drugs Act; however, these products are regulated as natural health products under the Natural Health Products Regulations and not as drugs under the Food and Drug Regulations.

Health Canada / Santé Canada

Healthy Environments and Consumer Safety Branch / Direction générale, Santé environnementale et sécurité des consommateurs

Your file / Votre référence

Our file / Notre référence

Water, Air and Climate Change Bureau
Safe Environments Directorate
269 Laurier Avenue West
Address Locator 4905D
Ottawa, Ontario K1A 0K9

SEE PAGE 2+3

December 22, 2011

Ms. Hazel McCallion, Mayor
City of Mississauga
300 City Centre Drive
Mississauga, Ontario L5B 3C1

REFERRAL TO
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DIRECTION REQUIRED
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Dear Mayor McCallion,

This is in response to your letter of December 20, 2011, addressed to Michèle Giddings, in which you seek information regarding fluoride in drinking water. I would like to use this opportunity to also provide some clarification on the information included in your letter.

DENTAL BENEFITS

Fluoride occurs naturally in many source waters in Canada. Fluoridation is the process of adding an inorganic fluoride compound to municipal water supplies to adjust the level of fluoride to its optimal level for dental benefits. The fluoridation of drinking water supplies is a well-accepted measure to protect public health and is strongly supported by scientific evidence. Fluoride has been added to public drinking water supplies around the world for more than half a century, as a public health/dental health measure, and its use is endorsed by over 90 national and international professional health organizations including Health Canada, the Canadian Dental Association, the Canadian Medical Association, the World Health Organization and the Food and Drug Administration of the United States.

HE-C3 -3-

THERAPEUTIC CLAIM.

Finally, in response to your question regarding the regulation of fluoridation products by Health Canada, I would provide the following information: Fluoride, either offered for sale in a final dosage form, used in large concentration and with a drug delivery system (e.g., dental rinse, toothpaste) or labeled for therapeutic use (or making therapeutic claims), would be considered a drug under the *Food and Drugs Act* and regulated under the *Natural Health Product Regulations*. Where minerals are added or where food is fortified with a mineral (e.g., iron in cereals), the food does not become a drug. Fluoride used in drinking water fluoridation is not considered a drug under the *Food and Drugs Act* and cannot be regulated under the *Natural Health Product Regulations*.

IRON NOT TOXIC.

CONCLUSION. - SODIUM FLUORIDE - CLINICAL GRADE IS A MEDICATION.

For specific questions regarding the fluoridation of drinking water in Ontario, I would suggest you contact your provincial representative on the Federal-Provincial-Territorial Committee on Drinking Water, Dr. Satish Deshpande, at the following coordinates:

HYDROFLUOSILIC ACID. A TOXIC CHEMICAL CAN'T REGARDED AS A DRUG.

Mr. Satish Deshpande, Team Leader, Water Standards Section
Standards Development Branch, Ministry of the Environment

Ministry of Health and Long-Term Care

Office of the Minister

10th Floor, Hepburn Block
80 Grosvenor Street
Toronto ON M7A 2C4
Tel. 416 327-4300
Fax 416 326-1571
www.ontario.ca/health

Ministère de la Santé et des Soins de longue durée

Bureau du ministre

Édifice Hepburn, 10e étage
80, rue Grosvenor
Toronto ON M7A 2C4
Tél. 416 327-4300
Téléc. 416 326-1571
www.ontario.ca/sante

Ontario

January 7, 2016

HLTC2976IT-2015-267

Dear Heads of Council,

We are writing to you today to draw your attention to a significant public health issue and to seek your support to address this important issue at the municipal level. There are a growing number of communities across Ontario that are choosing to discontinue fluoridation of their municipal drinking water system in spite of consistent evidence that water fluoridation is a safe and effective method to reduce the risk of oral health problems for Ontarians.

Tooth decay is the single most common chronic disease among Canadian children. The importance of maintaining good oral health should not be taken lightly - it is an important part of being healthy overall. Poor oral health is linked to diabetes, heart disease, respiratory conditions, osteoporosis, rheumatoid arthritis and low birth weight in babies. As such, water fluoridation is, and must be recognized, as a very important measure to protect the health of Ontarians.

The benefits of water fluoridation are well documented. More than 90 national and international professional health organizations, including Health Canada, the Canadian Public Health Association, the Public Health Agency of Canada, the Canadian Dental Association, the Canadian Medical Association, the U.S. Centers for Disease Control and Prevention (CDC) and the World Health Organization, have endorsed the use of fluoride at recommended levels to prevent tooth decay. In fact, the use of fluoride in drinking water has been called one of the greatest public health achievements of the 20th century by the CDC. According to expert research, fluoridated drinking water reduces the number of cavities in children's teeth, which contributes to their healthy development. Reductions of tooth decay have also been observed in adults and seniors who reside in communities with fluoridated water.

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RECOMMENDED
DIRECTION REQUIRED _____
RECEIPT RECOMMENDED ✓ _____

.../2

Water fluoridation helps to reduce the cost of dental care. The Ontario Dental Association has stated that the cost of providing dental care if waiting until tooth decay occurs is much higher than the cost of preventing it. The CDC estimates that for every $1 invested in community water fluoridation, $38 is saved in dental treatment. Removing fluoride from drinking water will place those least able to afford or access dental treatment at a much higher risk for oral health problems. The health benefits of drinking water fluoridation extend to all residents in a community, regardless of age, socioeconomic status, education or employment.

Municipal leaders should consider carefully the range of factors and implications of removing fluoridation from municipal drinking water systems. We urge all of you to support fluoridation of drinking water in your communities so that everyone can enjoy the long-term health benefits.

Yours sincerely,

Dr. Eric Hoskins
Minister

David C. Williams, MD, MHSc, FRCPC
Acting Chief Medical Officer of Health

c. Roselle Martino, Assistant Deputy Minister, Population and Public Health Division

Sprovieri, John Councillor

m: Sprovieri, John Councillor
..nt: 2016/06/09 7:28 AM
To: Sprovieri, John Councillor
Subject: FW: New Zealand plans to drown its citizens in toxic fluorides

Does this help, for drugs?
http://www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/fs-fi/reviewfs_examenfd-eng.php

What is considered to be a drug?

Drugs include both prescription and nonprescription pharmaceuticals; biologically-derived products such as vaccines, blood derived products, and products produced through biotechnology; tissues and organs; disinfectants; and radiopharmaceuticals. According to the Food and Drugs Act, "a drug includes any substance or mixture of substances manufactured, sold or represented for use in:

1. *the diagnosis, treatment, mitigation or prevention of a disease, disorder, abnormal physical state, or its symptoms, in human beings or animals;*
2. *restoring, correcting or modifying organic functions in human beings or animals; or*
3. *disinfection in premises in which food is manufactured, prepared or kept."*

...tural health products, such as vitamin and mineral supplements and herbal products for which therapeutic claims are made are also considered drugs at the level of the Food and Drugs Act; however, these products are regulated as natural health products under the Natural Health Products Regulations and not as drugs under the Food and Drug Regulations.

National Research Council 2006 Review: Fluoride in Drinking Water

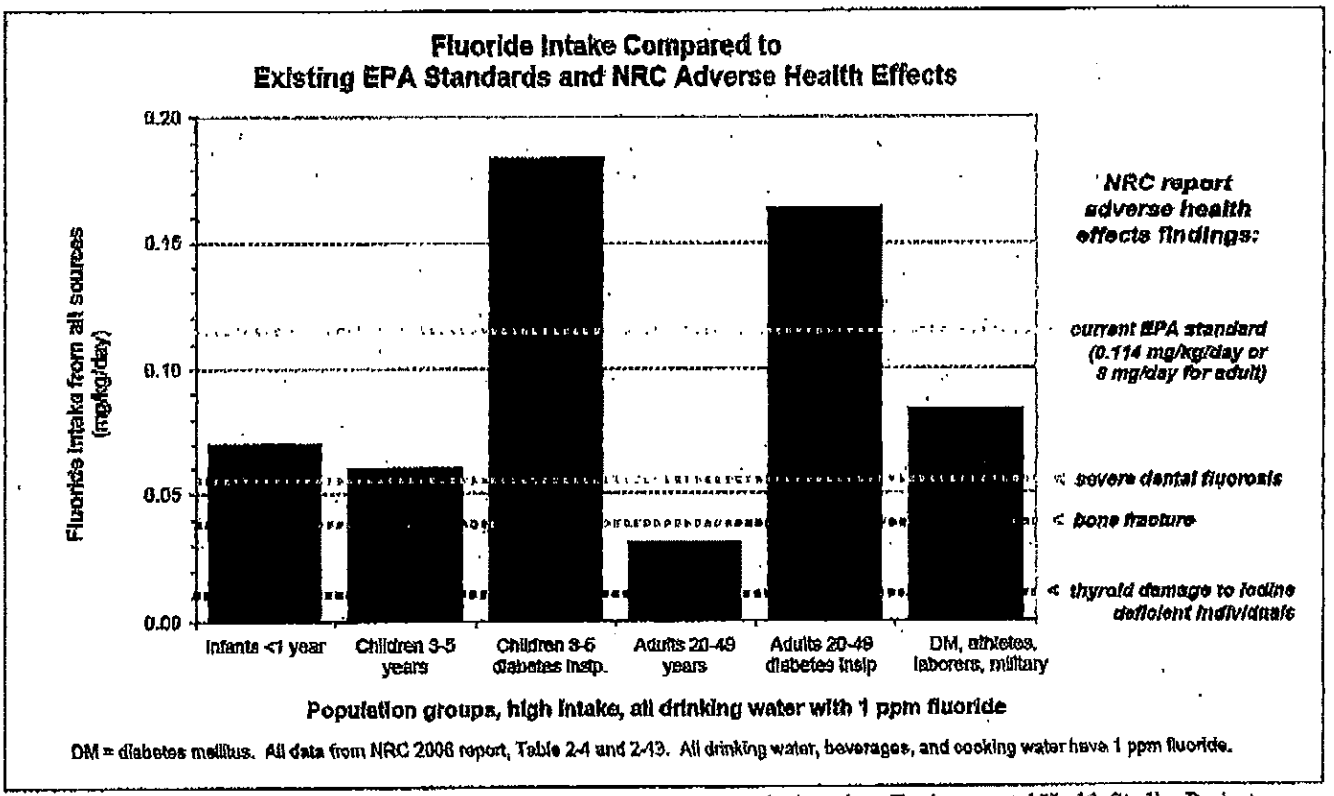

Table by Chris Neurath Director of Scientific Research, Fluoride Action Network, American Environmental Health Studies Project

US EPA commissioned the National Research Council (NRC), a branch of the National Academy of Sciences (NAS) to do this review. The National Academies is the most prestigious, independent scientific body in the US, founded to provide scientific advice to US government agencies. They used a "weight-of-evidence" approach. They did not examine efficacy. They only examined safety. The report was written by 12 experts and peer-reviewed by 14 experts. As well, public meetings were held.

The 12 committee members selected by the NAS reviewed over 1,000 research papers. The panel members selected for their recognized expertise in the fields of toxicology, risk assessment, epidemiology, and experience on fluoride health effects. The panel members spent thousands of hours over three years and received no compensation for their work. One Canadian panel member was chosen - Dr. Hardy Limeback, DDS, PhD, Head of Preventive Dentistry, U of Toronto, who has conducted several decades of primary research in biochemical effects of fluoride.

This is the most thorough review, of the highest quality ever done on this subject. It is a landmark review on the toxicology of fluoride in drinking water. 4 Types of scientific studies available for toxicological assessment: 1) studies on tissues or cells outside of living organisms (in vitro); 2) animal studies; 3) case reports on humans injured or diseased by fluoride; 4) epidemiological studies on humans. Randomized Controlled Trials of the harmful effects of fluoride do not exist. It is unethical to purposely expose humans to any medical treatment with the goal of determining the doses that produce harm.

Sprovieri, John Councillor

From: Sprovieri, John Councillor
Sent: 2017/04/04 10:54 AM
To: Sprovieri, John Councillor
Subject: FW: mass medication

The Supreme Court of Canada has found that the liberty interest protected by s. 7 includes the right to make fundamental personal choices free from state interference.30 ***In the context of medical treatment, the Ontario Court of Appeal has held that the right not to be subject to medical treatment without informed consent is an aspect of the security of the person interest under s. 7. 31 Section 7 thus protects "the right to be free from unwanted medical treatment."*** *32 To deprive individuals of the ability to make decisions with respect to their treatment and to force them to submit to medication against their competent wishes infringes the Charter right to security of the person as protected under s. 7 of the Charter.33*

Health Care Consent Act, 1996 (applies to the Medical Officers if they treat someone, but not Councillors, as far as I can tell): https://www.ontario.ca/laws/statute/96h02

"health practitioner" means a member of a College *under the Regulated Health Professions Act, 1991 or a member of a category of persons prescribed by the regulations as health practitioners; ("praticien de la santé")*

Consent to Treatment

No treatment without consent

10. (1) ***A health practitioner*** *who proposes a treatment for a person shall not administer the treatment, and shall take reasonable steps to ensure that it is not administered, unless,*

(a) he or she is of the opinion that the person is capable with respect to the treatment, and the person has given consent; or

....Elements of consent

11. (1) The following are the elements required for consent to treatment:

1. The consent must relate to the treatment.

2. The consent must be informed.

3. The consent must be given voluntarily.

4. The consent must not be obtained through misrepresentation or fraud. *1996, c. 2, Sched. A, s. 11 (1).*

From: Loh, Lawrence <lawrence.loh@peelregion.ca>
Sent: Tuesday, April 4, 2017 9:22 PM
To: Tovey, Jim; Parrish, Carolyn
Cc: Pedra, Inga; Polsinelli, Nancy
Subject: Re: 2017-03829 EPA Response to Paul Connett

Thank you for sending, Councillor Tovey.

Given our ongoing commitment to monitor for new evidence and positions on this topic, I feel an analysis of this document is warranted regardless of whether the committee is presently sitting.

We can certainly share that analysis with the committee if it reconvenes.

I will review with my staff and put together an analysis on this which should be available in the coming months - don't hesitate to reach out if you are interested in following on.

With thanks again for raising and best wishes,
Lawrence

Lawrence C. Loh, MD, MPH, CCFP, FRCPC, FACPM
Medical Officer of Health (A)
Peel Public Health
7120 Hurontario Street, 7th Floor
Mississauga, ON L5M 2C2

905-791-7800 extension 2566
lawrence.loh@peelregion.ca

From: Jim Tovey <Jim.Tovey@mississauga.ca>
Sent: April 4, 2017 21:15
To: Loh, Lawrence; Parrish, Carolyn
Subject: 2017-03829 EPA Response to Paul Connett

Hi Lawrence and Madam Chair,

This is a response from the EPA to the challenges to community water fluoridation from Paul Connett (Fluoride Action Network). What is interesting in the document, is that the EPA took considerable time and effort to examine and respond to all of Mr. Connett's claims. Claims which are the basis for arguments presented repeatedly to our CWF Committee by anti CWF proponents and Councillor Spovieri.
The EPA document is quite thorough and based on objective science. The 49 pages methodically correct the anti CWF activist statements. The report was made Public a month ago. Should we reconvene our CWF Committee, please put this on the Agenda with an analysis from the Medical Officer of Health.

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RECOMMENDED
DIRECTION REQUIRED _____
RECEIPT RECOMMENDED ✓_____

BILLING CODE 6560-50-P

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Chapter I

[EPA-HQ-OPPT-2016-0763; FRL-9959-74]

Fluoride Chemicals in Drinking Water; TSCA Section 21 Petition; Reasons for Agency Response

AGENCY: Environmental Protection Agency (EPA).

ACTION: Petition; reasons for Agency response.

SUMMARY: This document announces the availability of EPA's response to a petition it received on November 23, 2016, under section 21 of the Toxic Substances Control Act (TSCA). The TSCA section 21 petition was received from the Fluoride Action Network, Food & Water Watch, Organic Consumers Association, the American Academy of Environmental Medicine, the International Academy of Oral Medicine and Toxicology, and other individual petitioners. The TSCA section 21 petition requested that EPA exercise its authority under TSCA section 6 to "prohibit the purposeful addition of fluoridation chemicals to U.S. water supplies." After careful consideration, EPA has denied the TSCA section 21 petition for the reasons discussed in this document.

DATES: EPA's response to this TSCA section 21 petition was signed February 17, 2017.

FOR FURTHER INFORMATION CONTACT: *For technical information contact*: Darlene Leonard, National Program Chemicals Division (7404T), Office of Pollution Prevention and Toxics, Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460-0001; telephone number: (202) 566-0516; fax number: (202) 566-0470; email address: *leonard.darlene@epa.gov.*

For general information contact: The TSCA-Hotline, ABVI-Goodwill, 422 South Clinton Ave., Rochester, NY 14620; telephone number: (202) 554-1404; email address: *TSCA-Hotline@epa.gov*.

SUPPLEMENTARY INFORMATION:

I. General Information

A. Does this action apply to me?

This action is directed to the public in general. This action may, however, be of interest to individuals or organizations interested in drinking water and drinking water additives, including fluoride. Since other entities may also be interested, the Agency has not attempted to describe all the specific entities that may be affected by this action.

B. How can I access information about this petition?

The docket for this TSCA section 21 petition, identified by docket identification (ID) number EPA-HQ-OPPT-2016-0763, is available online at *http://www.regulations.gov* or in person at the Office of Pollution Prevention and Toxics Docket (OPPT Docket), Environmental Protection Agency Docket Center (EPA/DC), EPA West Bldg., Rm. 3334, 1301 Constitution Ave., NW., Washington, DC. Six binders containing copies of references were submitted along with the petition (Ref. 1). Those binders are not available electronically in the docket but may be reviewed in the Public Reading Room. The Public Reading Room is open from 8:30 a.m. to 4:30 p.m., Monday through Friday, excluding legal holidays. The telephone number for the Public Reading Room is (202) 566-1744, and the telephone number for the OPPT Docket is (202) 566-0280. Please review the visitor instructions and additional information about the docket available at *http://www.epa.gov/dockets*.

II. TSCA Section 21

A. What is a TSCA section 21 petition?

Under TSCA section 21 (15 U.S.C. 2620), any person can petition EPA to initiate a rulemaking proceeding for the issuance, amendment, or repeal of a rule under TSCA sections 4, 6, or 8 or an order under TSCA sections 4, 5(e), or 5(f). A TSCA section 21 petition must set forth the facts that are claimed to establish the necessity for the action requested. EPA is required to grant or deny the petition within 90 days of its filing. If EPA grants the petition, the Agency must promptly commence an appropriate proceeding that is "in accordance" with the underlying TSCA authority. If EPA denies the petition, the Agency must publish its reasons for the denial in the Federal Register. 15 U.S.C. 2620(b)(3). A petitioner may commence a civil action in a U.S. district court to compel initiation of the requested rulemaking proceeding within 60 days of either a denial or the expiration of the 90-day period. 15 U.S.C. 2620(b)(4).

B. What criteria apply to a decision on a TSCA section 21 petition?

TSCA section 21(b)(1) requires that the petition "set forth the facts which it is claimed establish that it is necessary" to issue the rule or order requested. 15 U.S.C. 2620(b)(1). Thus, TSCA section 21 implicitly incorporates the statutory standards that apply to the requested action. In addition, TSCA section 21 establishes standards a court must use to decide whether to order EPA to initiate rulemaking in the event of a lawsuit filed by the petitioner after denial of a TSCA section 21 petition. 15 U.S.C. 2620(b)(4)(B). Accordingly, EPA has relied on the standards in TSCA section 21 (and those in the provisions under which action has been requested) to evaluate this TSCA section 21 petition.

III. TSCA Section 6

Of particular relevance to this TSCA section 21 petition are the legal standards regarding TSCA section 6(a) rules. These standards were significantly altered in 2016 by the "Frank R. Lautenberg Chemical Safety for the 21st Century Act," Public Law No. 114-182 (2016), which amended TSCA. One of the key features of the new law is the requirement that EPA now systematically prioritize and assess existing chemicals, and manage identified risks. Through a combination of new authorities, a risk-based safety standard, mandatory deadlines for action, and minimum throughput requirements, TSCA effectively creates a "pipeline" by which EPA will conduct review and management of existing chemicals. This new pipeline - from prioritization to risk evaluation to risk management (when warranted) - is intended to drive forward steady progress on the backlog of existing chemical substances left largely unaddressed by the original law. (Ref. 2).

In the initial phase of the review pipeline, EPA is to screen a chemical substance for its priority status, propose a designation as either high or low priority, and then issue a final priority designation within one year of starting the screening process. 15 U.S.C. 2605(b)(1)(C). If the substance is high priority, EPA must initiate a risk evaluation for that substance. 15 U.S.C. 2605(b)(4)(C). EPA must define the scope of the risk evaluation within six months of starting, 15 U.S.C. 2605(b)(4)(D), and complete the risk evaluation within 3 to 3.5 years. 15 U.S.C. 2605(b)(4)(G). If EPA concludes that a chemical substance presents an unreasonable risk, EPA must propose a risk management rule under TSCA section 6(a) within one year and finalize that rule after another year, with limited provision for extension. 15 U.S.C 2605(c). As EPA completes risk

evaluations, EPA is to designate replacement high-priority substances, on a continuing basis. 15 U.S.C. 2605(b)(2)(C) and (b)(3)(C).

In general, to promulgate a rule under TSCA section 6(a), EPA must first determine "in accordance with section 6(b)(4)(A) that the manufacture, processing, distribution in commerce, use, or disposal of a chemical substance or mixture . . . presents an unreasonable risk." 15 U.S.C. 2605(a). TSCA section (b)(4)(A) is part of the risk evaluation process whereby EPA must determine "whether a chemical substance presents an unreasonable risk of injury to health or the environment," and thus, whether a rule under TSCA section 6(a) is necessary. 15 U.S.C. 2605(b)(4)(A). In particular, EPA must conduct this evaluation "without consideration of costs or other non-risk factors, including an unreasonable risk to a potentially exposed or susceptible subpopulation identified as relevant to the risk evaluation by the Administrator, under the conditions of use." Id. Unless EPA establishes an exemption under TSCA section 6(g) (whereby certain unreasonable risks may be allowed to persist for a limited period) or EPA is addressing a persistent, bioaccumulative, and toxic substance as set forth in TSCA section 6(h), the standard for an adequate rule under TSCA section 6(a) is that it regulates "so that the chemical substance or mixture no longer presents" unreasonable risks under the conditions of use. 15 U.S.C. 2605(a).

Prior to the 2016 amendment of TSCA, EPA completed risk assessments that were limited to selected uses of chemical substances. The amended TSCA authorizes EPA to issue TSCA section 6 rules that are not comprehensive of the conditions of use, so long as they are consistent with the scope of such pre-amendment risk assessments. 15 U.S.C. 2625(l)(4). But EPA has interpreted the amended TSCA as requiring that

forthcoming risk evaluations encompass all manufacture, processing, distribution in commerce, use, and disposal activities that the Administrator determines are intended, known or reasonably foreseen. (Ref. 2, p. 7565). EPA interprets the scope of post-risk-evaluation rulemaking under TSCA section 6(a) in a parallel fashion: while risk management rules for a certain subset of the conditions of use may be promulgated ahead of rulemaking for the remaining conditions of use, rules covering the complete set of conditions of use must be promulgated by the deadlines specified in TSCA section 6(c). 15 U.S.C 2605(c). While EPA has authority under TSCA section 6(a) to establish requirements that apply only to "a particular use," the restriction of just one particular use would not constitute an adequate risk management rule unless that particular use were the only reason that the chemical substance presented an unreasonable risk.

TSCA section 21(b)(4)(B) provides the standard for judicial review should EPA deny a request for rulemaking under TSCA section 6(a): "If the petitioner demonstrates to the satisfaction of the court by a preponderance of the evidence that . . . the chemical substance or mixture to be subject to such rule . . . presents an unreasonable risk of injury to health or the environment, without consideration of costs or other non-risk factors, including an unreasonable risk to a potentially exposed or susceptible subpopulation, under the conditions of use," the court shall order the EPA Administrator to initiate the requested action. 15 U.S.C 2620(b)(4)(B). EPA notes that bills preceding the final amendment to TSCA retained language in section 21 that resembled the pre-amendment criteria for rulemaking under section 6. Compare 15 U.S.C. 2620(b)(4)(B)(ii) (2015) (amended 2016), 15 U.S.C. 2605(a) (2015) (amended 2016), S. Rep. 114-67 at 135 (Ref. 3), and H.R. Rep. No. 114-176 at 81 (Ref. 4). But the effect of the revision in the final

bill is to align the standard for judicial review of a TSCA section 21 petition with the standard for EPA's preparation of risk evaluation under TSCA section 6(b)(4)(A). Consistent with these revisions, EPA concludes that Congress intended for a petition to set forth facts that would enable EPA to complete a risk evaluation under TSCA section 6(b).

In light of this, EPA interprets TSCA section 21 as requiring the petition to present a scientific basis for action that is reasonably comparable, in its quality and scope, to a risk evaluation under TSCA section 6(b). This requirement includes addressing the full set of conditions of use for a chemical substance and thereby describing an adequate rule under TSCA section 6(a) – one that would reduce the risks of the chemical substance "so that the chemical substance or mixture no longer presents" unreasonable risks under all conditions of use. 15 U.S.C. 2605(a). Specifically, EPA interprets section 21(a) – which authorizes petitions "to initiate a proceeding for the issuance. . . of a rule under. . . section 6" – as authorizing petitions for rules that *would comply with the requirements of* sections 6(a) and 6(c).

EPA recognizes that information on a single condition of use could, in certain instances, suffice to demonstrate that a chemical substance, as a whole, presents an unreasonable risk. Nonetheless, EPA concludes that such information does not fulfill a petitioner's burden to justify "a rule under [TSCA section 6]," under TSCA section 21, since the information would merely justify a subset of an adequate rule. To issue an adequate rule under section 6, EPA would need to conduct a catch-up risk evaluation addressing all the conditions of use not addressed by the petition, and either determine that those conditions do not contribute to the unreasonable risk or enlarge the scope of the

rule to address those further conditions of use. See 15 U.S.C. 2605(a). To issue this rule within the time required by section 6(c), EPA would have to proceed without the benefit of the combined 4 to 4.5-year period that TSCA section 6(b) would ordinarily afford EPA (i.e., time to prioritize a chemical substance, conduct a careful review of all of its conditions of use, and receive the benefit of concurrent public comment). Additionally, before even initiating the prioritization process for a chemical substance, EPA would generally screen the chemical substance to determine whether the available hazard and exposure-related information are sufficient to allow EPA to complete both the prioritization and the risk evaluation processes. (Ref. 5).

EPA's interpretation is most consonant with the review pipeline established in TSCA section 6. In particular, the prioritization process established in section 6(b) recognizes that a number of chemical substances may present an unreasonable risk of injury to health or the environment and charges EPA with prioritizing those that should be addressed first. EPA is required to have 10 chemical substances undergoing risk evaluation as of December 19, 2016, and must have a steady state of at least 20 high-priority substances undergoing risk evaluation by December 2019 (and as many as 10 substances nominated for risk evaluation by manufacturers). 15 U.S.C. 2605 (b)(2)(A), (B), 2605(b)(4)(E)(i). EPA is obligated to complete rulemakings to address any unreasonable risks identified in these risk evaluations within prescribed timeframes. 15 U.S.C. 2605(c)(1). These required activities will place considerable demands on EPA resources. Indeed, Congress carefully tailored the mandatory throughput requirements of TSCA section 6, based on its recognition of the limitations of EPA's capacity and resources, notwithstanding the sizeable number of chemical substances that will

ultimately require review. Under this scheme, EPA does not believe that Congress intended to empower petitioners to promote chemicals of particular concern to them above other chemicals that may well present greater overall risk, and force completion of expedited risk evaluations and rulemakings on those chemicals, based on risks arising from individual uses.

EPA recognizes that some members of the public may have safety concerns that are limited to a single condition of use for a chemical substance. But EPA's interpretation of TSCA section 21 does not deprive such persons of a meaningful opportunity to request that the Administrator proceed on their concerns. For example, such persons may submit a petition under the Administrative Procedure Act, requesting EPA to commence a "risk-based screening" of the chemical substance under TSCA section 6(b)(1)(A), motivated by their concern about a single condition of use.

IV. Summary of the TSCA Section 21 Petition

A. What action was requested?

On November 23, 2016, a TSCA section 21 petition was submitted by the Fluoride Action Network, Food & Water Watch, Organic Consumers Association, the American Academy of Environmental Medicine, the International Academy of Oral Medicine and Toxicology, Moms Against Fluoridation, and the following individuals signing on behalf of themselves and their children: Audrey Adams of Renton, Washington, Jacqueline Denton of Asheville, North Carolina, Valerie Green of Silver Spring, Maryland, Kristin Lavelle of Berkeley, California, and Brenda Staudenmaier of Green Bay, Wisconsin (Ref. 1). The general object of the petition is to urge EPA "to protect the public and susceptible subpopulations from the neurotoxic risks of fluoride by

banning the addition of fluoridation chemicals to water" (Ref. 1). The specific action sought is a rule, under TSCA section 6(a)(2), to "prohibit the purposeful addition of fluoridation chemicals to U.S. water supplies." However, such a restriction on the allowable use of fluoridation chemicals would actually be based on a rule under TSCA section 6(a)(5), not a rule under TSCA section 6(a)(2). In light of the discrepancy between the description of the rule sought and the cited authority, EPA interprets the petition as requesting *both* a TSCA section 6(a)(5) rule whereby the purposeful addition of any fluoridation chemical to a drinking water supply would be prohibited *and* a TSCA section 6(a)(2) rule whereby the manufacture, processing, or distribution in commerce of any fluoridation chemical for such use would be prohibited.

B. What support does the petition offer?

The petition is focused on the potential for fluoride to have neurotoxic effects on humans; it cites numerous studies bearing on this issue. The petition contends that the purposeful fluoridation of drinking water presents an unreasonable risk to human health from neurotoxicity, and that a ban on this use of fluoridation chemicals is necessary to curtail this unreasonable risk. The following is a summary of the primary support given in the petition for this view:

1. *Fluoride neurotoxicity at levels relevant to U.S. population.* The petition claims that fluoride poses neurotoxic risks to the U.S. population. The petition claims that the cited studies of fluoride-exposed human populations have consistently found neurotoxic effects (lower-than-average IQs) at water fluoride levels below the current Maximum Contaminant Level Goal of 4 mg/L set by EPA's Office of Water. The petition argues that the difference between the fluoride levels in the United States and the greater

levels in rural China (where most of the cited IQ studies were conducted) is "lessen[ed]" by the abundance of fluoridated toothpaste in the U.S.

2. *Recent epidemiological studies corroborate neurotoxic risk in Western populations.* The petition cites two studies from Western populations to attempt to corroborate the assertion that exposure to fluoride in drinking water presents unreasonable risks for neurotoxicity (Refs. 6 and 7).

3. *Neurotoxic risks supported by animal and cell studies.* The petition argues that studies on both experimental animals and cell cultures are consistent with cited human research linking fluoride exposure with neurotoxic effects in humans.

4. *Susceptible subpopulations are at heightened risk.* The petition argues that certain subpopulations (e.g., infants, the elderly, and persons with nutritional deficiencies, kidney disease or certain genetic predispositions) are more susceptible to fluoride neurotoxicity.

5. *RfD/RfC derivation and uncertainty factor application*. The petition argues that EPA's 1998 *Guidelines for Neurotoxicity Risk Assessment* support the need to apply a 10-fold uncertainty factor in deriving an oral Reference Dose (RfD) or inhalation Reference Concentration (RfC).

6. *Benefits to public health*. The petition bases, in part, its claim of unreasonable risk on the assertion that the fluoridation of drinking water confers little benefit to public health, relative to the alleged neurotoxic risks. The petition argues that since fluoride's primary benefit comes from topical contact with the teeth, there is little benefit from swallowing fluoride, in water or any other product. The petition argues that there is therefore "little justification" in exposing the public to "*any* risk" of fluoride

neurotoxicity.

7. *Extent and magnitude of risk from fluoridation chemicals*. The petition bases, in part, its claim of unreasonable risk on estimates of the extent and magnitude of risk posed to portions of the U.S. population living in areas where artificial fluoridation occurs.

8. *Consequences of eliminating use of fluoridation chemicals*. The petition argues that the risks of fluoride exposure from fluoridated drinking water are unreasonable, in part, because they could be easily and cheaply eliminated, and because alternative products containing topical fluoride are widely available.

9. *Link to elevated blood lead levels.* The petition argues that artificial fluoridation chemicals are linked with pipe corrosion and elevated blood lead levels. The petition interprets data in several studies as demonstrating an association between fluoridation chemicals and elevated blood lead levels.

In addition to supplying the petition, on January 30, 2017, the petitioners also delivered an in-person oral presentation of their views (Ref. 8). At their oral presentation, petitioners reiterated the information already supplied in writing, and requested that EPA also consider an additional study that was not part of the petition (Ref. 9). EPA has discretion (but not an obligation) to consider extra-petition materials when evaluating a petition submitted under TSCA section 21. In cases where the petitioners themselves attempt to enlarge the scope of materials under review while EPA's petition review is pending, EPA exercises its discretion to consider or not consider the additional material based on whether the material was submitted early enough in EPA's petition review process to allow adequate evaluation of the study prior to the petition deadline, the

relation of the late materials to materials already submitted. Given the particularly late submittal of the additional study, EPA conducted an abbreviated review of the study and found that the health concerns covered were substantially the same as those covered in other studies submitted with the petition. Based on this abbreviated review, EPA does not believe that the new study provided any new scientific grounds for granting the petition.

V. Disposition of TSCA Section 21 Petition

A. What was EPA's response?

After careful consideration, EPA denied the TSCA section 21 petition, primarily because EPA concluded that the petition has not set forth a scientifically defensible basis to conclude that any persons have suffered neurotoxic harm as a result of exposure to fluoride in the U.S. through the purposeful addition of fluoridation chemicals to drinking water or otherwise from fluoride exposure in the U.S. In judging the sufficiency of the petition, EPA considered whether the petition set forth facts that would enable EPA to complete a risk evaluation under TSCA section 6(b).

EPA also denied the petition on the independent grounds that the petition neither justified the regulation of fluoridation chemicals as a category, nor identified an adequate section 6 rule as the action sought. Rather than comprehensively addressing the conditions of use that apply to a particular chemical substance, the petition requests EPA to take action on a single condition of use (water fluoridation) that cuts across a category of chemical substances (fluoridation chemicals). A copy of the Agency's response, which consists of a letter to the petitioners, is available in the docket for this TSCA section 21 petition.

B. What were EPA's reasons for this response?

To take the actions under TSCA section 6 requested by the petitioners, EPA would need to make a determination of whether a chemical substance or substances present an unreasonable risk to human health or the environment. This section describes why the petitioners have not provided adequate and sufficient scientific information to make such a determination.

1. *Fluoride neurotoxicity at levels relevant to U.S. population.* The petition ignores a number of basic data quality issues associated with the human studies it relies upon. Many of the human studies cited in the petition are cross-sectional in design, and are affected by antecedent-consequent bias. The antecedent-consequent bias means it cannot be determined whether the exposure came before or after the health effects, since both are evaluated at the same time. Cross-sectional studies are most useful for developing hypotheses about possible causal relationships between an exposure and a health effect, but are rarely suitable for the development of a dose-response relationship for risk assessment. These studies are most useful in supporting more robust epidemiological studies in which defined exposures can be linked quantitatively to an adverse outcome.

The petition also does not properly account for the relatively poor quality of the exposure and effects data in the cited human studies (e.g., it appears to give all studies equivalent weight, regardless of their quality). When an association is suggested between an exposure and a disease outcome, the studies need to be assessed to determine whether the effect is truly because of exposure or if alternate explanations are possible. The way to do that is to adjust for potential confounders, such as diet, behavior, and socioeconomic status, in order to appropriately assess the real relationship between the

exposures to a specific substance and health effects. In other words, when these confounding factors are potentially present, but not recognized or controlled for, it is not possible to attribute effects to the contaminant of concern (fluoride) as opposed to other factors or exposures. The evidence presented did not enable EPA to determine whether various confounding factors (e.g., nutritional deficiencies) were indeed placing particular subpopulations at a "heightened risk of fluoride neurotoxicity," as alleged, because the evidence did not adequately account for the possibility that the *confounding factors themselves*, rather than concurrent fluoride exposure, were partly or wholly responsible for the health effects observed. Specific confounding factors or variables were noted by the National Research Council (NRC) (Ref. 10). They may include climate, drinking water intake, excessive dietary fluoride, low calcium intake, drinking water sources with fluctuating fluoride levels, and industrial pollution such as use of coal for domestic heating. These factors have the potential to confound efforts to identify a causal relationship between drinking water fluoride exposure and particular health effects, either by introducing additional, unaccounted for sources of fluoride exposure, by being associated with the pertinent health endpoint through some mechanism other than fluoride toxicity, or by directly affecting the health endpoint.

The petition relies heavily on two meta-analyses which include human cross-sectional (Ref. 11) and case control (Ref.1 9) studies. All of the studies listed in Table 1 of the petition were examined in detail by the 2012 Choi et al. study (Ref. 11) as part of their systematic review and meta-analysis to investigate the possibility that fluoride exposure delays neurodevelopment in children. The Choi et al. analysis analyzes studies in which IQ was measured using various IQ tests, compares children of various fluoride

exposure ranges without accounting for differences in susceptibility to fluoride by age, and used different exposure measures which only delineated between high and low exposure groups. A variety of measures of fluoride exposure were present across studies included in the Choi et al. study, including levels of fluoride in drinking water, observed dental fluorosis, coal burning in houses (i.e., air fluoride levels), and urine fluoride. Despite this disparate collection of types of measurements, all exposure measures were treated equally in the analysis (Ref. 11, Table 1). The authors of the analysis identified a variety of data quality issues associated with this collection of studies. For example, they recognized that several of the populations studied had fluoride exposures from sources other than drinking water (e.g., coal burning; Refs. 13-15); they therefore controlled for this confounding factor by excluding such studies from their analysis. Co-exposures to other potentially neurotoxic chemicals (e.g., iodine) (Refs. 16-18) and arsenic (Refs. 19-22) were also recognized and accounted for in the Choi et al. analysis to understand confounding by these factors. Yet the petitioners include such studies in making their assertion that fluoride is neurotoxic, but have not indicated any attempts to control for the confounding factors. Choi et al. also noted that basic information such as the study subjects' sex and parental education was missing in 80 percent of the studies and household income was missing in 93 percent of studies; they stated that they could not therefore control for these co-variables in their analysis. Consideration of these confounding factors and their impact on the applicability of these studies in a risk assessment context is evident in the authors' discussion. The authors caution readers that "our review cannot be used to derive an exposure limit, because the actual exposures of the individual children are not known" and they are measured in their conclusions (i.e.,

"our results support the possibility of adverse effects of fluoride exposures on children's neurodevelopment") (Ref. 11). The authors indicate that "further research should formally evaluate dose-response relationships based on individual-level measures of exposure over time, including more precise prenatal exposure assessment and more extensive standardized measures of neurobehavioral performance, in addition to improving assessment and control of potential confounders" (Ref. 11). EPA agrees with the conclusions by Choi et al. (Ref. 11) that the studies included in Table 1 of the petition are unsuitable for evaluating levels of fluoride associated with neurotoxic effects and for deriving dose-response relationships necessary for risk assessment.

The petition also cites an article by Grandjean and Landrigan (Ref. 23), for the proposition that fluoride is "known" to cause developmental neurotoxicity in humans. Grandjean and Landrigan refer only to the study of Choi et al. (2012), of which Grandjean is a co-author, in discussing fluoride. EPA's observations about the limitations of Choi et al. (2012) thus apply with equal force to the cited statement from Grandjean and Landrigan. Grandjean and Landrigan summarize that Choi et al. (2012) "*suggests* an average IQ decrement of about seven points in children exposed to raised fluoride concentrations." (Ref. 23). But Grandjean and Landrigan do not opine on whether fluoride exposures, arising from the purposeful addition of fluoridation chemicals to U.S. water supplies, are in fact causing developmental neurotoxic effects to persons in the U.S. The petition itself concedes that the actual existence of such effects is unestablished, in urging EPA to conduct "a diligent risk assessment, per EPA's *Guidelines*, to ensure that the general public, and sensitive subpopulations, are not ingesting neurotoxic levels" (Ref 1, p. 3).

The other meta-analysis cited in the petition (Ref. 12) showed that, based on 16 case-control studies in China, children living in an area with endemic fluorosis are more likely to have low IQ compared to children living in an area with slight fluorosis or no fluorosis. While this analysis may suggest an association between fluorosis and lowered IQ (both of which are possible effects of fluoride exposure at certain levels) any fluoride concentration-to-IQ effect relationship (i.e., dose-response relationship) is only inferred because actual fluoride exposures were not measured. Further, the two effects (fluorosis and lower IQ) both occur at fluoride exposures well above those found in fluoridated U.S. drinking water, such that any inference would only apply at fluoride concentrations not relevant to exposures in the U.S. The studies in the Tang et al. review (Ref. 12) correlate one effect (fluorosis) to another effect (neurotoxicity), but do not establish a dose-response relationship between fluoride exposure and neurotoxicity. This lack of a dose-dependent increase in effect with increasing exposure is a critical limitation of these data. Establishing a dose-response relationship between exposure to a toxicant and an effect "is the most fundamental and pervasive concept in toxicology. Indeed, an understanding of this relationship is essential for the study of toxic materials" (Ref. 12). Likewise, the IQ changes noted in Table 1 (Ref. 1) do not increase with increasing water fluoride concentration (e.g., dose) (Ref. 1).

The petition suggested that a dose-response relationship between urinary fluoride and IQ is seen in several studies (Refs. 24-26) shown in Figures 1-5 of the petition (Ref. 1). Assuming, as the petitioners claim, that all children were malnourished in the Das and Mondal (Ref. 26) study, it is not possible to determine whether effects on IQ were due to fluoride or to malnutrition (i.e., nutritional status may be an uncontrolled confounding

factor). The study authors caution that "it is difficult to determine with any degree of accuracy whether the difference of children's IQ scores solely depends on the exposure dose because many social and natural factors like economic condition, culture and geological environments are also responsible" (Ref. 26). Hence, extrapolating relationships from this study population to other populations is not scientifically defensible.

Choi et al. (2015) (Ref. 27) report that moderate and severe dental fluorosis was significantly associated with lower cognitive functions. However, associations between drinking water and urine fluoride and the same cognitive functions were not found to be significantly associated. They reached this conclusion from a study of 51 children in China and a comparison group of eight with dental fluorosis (Table 4 in Choi et al., 2015). The authors discuss potential problems associated with using these biomarkers of exposure to fluoride. For example, water samples may be imprecise because internal dose of fluoride depends on total water intake, and urine samples may be affected by the amount of water the subject drank prior to sampling. With regard to fluorosis, the degree of dental fluorosis is dependent not only on the total fluoride dose but also on the timing and duration of fluoride exposure. A person's individual response to fluoride exposure depends on factors such as body weight, activity level, nutritional factors, and the rate of skeletal growth and remodeling. These variables, along with inter-individual variability in response to similar doses of fluoride, indicate that enamel fluorosis cannot be used as a biological marker of the level of fluoride exposure for an individual (Ref. 28). Hence, the petitioner's use of fluorosis levels as a surrogate for evidence of neurotoxic harm to the U.S. population is inappropriate evidence to support an assertion of unreasonable risk to

humans from fluoridation of drinking water.

The petition also cites four studies (Refs. 24, 29-31) that rely on human urine or serum fluoride concentrations as biomarkers of exposure but does not discuss the limitations associated with the biomarkers used in the studies. In their report, *Human Biomonitoring for Environmental Chemicals*, NRC defines properties of biomarkers and created a framework for grouping biomarkers of exposure (Ref. 32). Figure 3-1 in the NRC report illustrates the relationship between external dose (e.g., water), internal dose (e.g., fluoride concentration) and biological effects, and indicates that internal dose is measured through biomonitoring (e.g., fluoride concentrations measured in urine or serum). NRC grouped the quality of biomarkers based on the robustness of these relationships. NRC designated biomarkers for substances that have been observed in bodily fluids, but that lack established relationships between external dose (e.g., water), internal dose (e.g., urine or serum) and biological effects (e.g., neurotoxicity) as "Group I" biomarkers. Although many human studies have been collated and reviewed in the petition, for the reasons outlined previously – particularly study design and confounding factors – relationships between urine and serum fluoride (internal doses), water fluoride concentration (external dose), and neurotoxic effects in humans have not been established. Further, serum and urine biomarkers for fluoride reflect only recent exposures, not long-term exposures, and may be different from the exposures during the specific time when developmental effects can occur. A lack of established sampling protocols and analytical methods are also hallmarks of "Group I" biomarkers. The main studies cited in the petition which attempt to relate urine or serum levels to possible neurotoxic effects suffer from either lack of good sampling protocols or absence of

documenting the sampling protocols. Important issues such as the timing and methods of sample collection were also often not reported in the studies. Using the NRC Framework, urine and serum fluoride levels would be at best "Group I" biomarkers for fluoride-related neurotoxicity. The NRC Framework states "[b]iomarkers in this category may be considered useless" for risk assessment purposes (Ref. 32, p. 78).

2. *Recent epidemiological studies corroborate neurotoxic risk in Western populations.* The petition cites two studies from Western populations to attempt to corroborate the assertion that exposure to fluoridated water presents unreasonable risks for neurotoxicity. Two population-level studies were cited which link fluoridated water to attention-deficit/hyperactivity disorder (ADHD) prevalence in the U.S. (Ref. 6) and drinking water exposures and hypothyroidism prevalence in England (Ref. 7). These studies use cross-sectional population-level data to examine the association between ADHD and hypothyroidism and fluoridated water levels. The studies make reasonable use the population-level data available, but causal inference cannot be made from these studies (Ref. 3).

As stated in the conclusion of Malin and Till, an association has been reported, but "[p]opulation studies designed to examine possible mechanisms, patterns and levels of exposure, covariates and moderators of this relationship are warranted" (Ref. 6, p. 8). In epidemiology, studies using cross-sectional data are most often used to generate hypotheses that need to be further studied to determine whether a "true" association is present. Ideally, the study designs and methods are improved by each study that is undertaken, such as, among other things, identifying additional potential confounders, considering timing issues or resolving ambiguity in collection of samples and disease

outcome, improving upon the exposure analysis, and evaluating the magnitude and consistency of the results, so that the evaluation can adequately assess the association (Ref. 34). For example, the authors assert that there are design issues with their study, especially related to the exposure categories, and they suggest how to address these issues in future studies. Although it is possible that there may be biological plausibility for the hypothesis that water fluoridation may be associated with ADHD, this single epidemiological study is not sufficient to "corroborate" neurotoxic health effects, as stated in the petition. More study would be needed to develop a body of information adequate to make a scientifically defensible unreasonable risk determination under TSCA.

The Peckham et al. study (Ref. 7) suffers from similar issues noted in Malin and Till (Ref. 6). Adjustment for some confounders was considered, including sex and age, but other potential confounders (such as iodine intake) were not assessed. Fluoride from other sources and other factors associated with hypothyroidism were not assessed in this study. Exposure misclassification, in which populations are placed in the wrong exposure categories based on the water fluoridation status, is very possible in either of the studies presented and is a limitation of the study designs.

3. *Neurotoxic risks supported by animal and cell studies.* The National Toxicology Program (NTP) conducted a systematic review of animal and cell studies on the effects of fluoride on learning and memory available up to January 2016 (Ref. 35). Almost all (159 out of 171) of the animal and cell culture studies cited in the petition in Appendix D-E were included in the NTP systematic review. From among 4,656 studies identified in the NTP database search, 4,552 were excluded during title and abstract

screening, 104 were reviewed at the full-text level and 68 studies were considered relevant and were included in the analysis. NTP assessed each study for bias, meaning a systematic error in the study that can over or underestimate the true effect and further excluded any studies with a high risk of bias. Of the 68 studies, including studies provided by the Fluoride Action Network, 19 were considered to pose a very serious overall risk of bias, primarily based on concern for at least three of the following factors: lack of randomization, lack of blinding at outcome assessment in conjunction with not using automated tools to collect information, lack of reporting on what was administered to animals (source, purity, chemical form of fluoride), lack of control for litter effects, lack of expected response in control animals, and lack of reporting of key study information such as the number or sex of animals treated. Of the studies cited in Table 4 in the petition, two were excluded from the NTP analysis because of serious concerns for study bias (Refs. 36 and 37). Based on its review of animal and cell studies, NTP concluded that "[t]he evidence is strongest (moderate level-of-evidence) in animals exposed as adults tested in the Morris water maze and weaker (low level-of-evidence) in animals exposed during development" and "[v]ery few studies assessed learning and memory effects at exposure levels near 0.7 parts per million, the recommended level for community water fluoridation in the United States." The animal studies cited in the petition (Ref. 1, p. 14, Table 4) reflect these high drinking water exposures ranging from 2.3 mg/L to 13.6 mg/L, equivalent to 3-20 times the levels to which drinking water is fluoridated in the U.S. Overall, NTP concluded that, "[r]esults show **low-to-moderate level-of-evidence** in developmental and adult exposure studies for a pattern of findings suggestive of an effect on learning and memory" (Ref. 35, p. 52). Based on this review of

available evidence, and the identified limitations in the database, NTP is currently pursuing experimental studies in rats to address key data gaps, starting with pilot studies that address limitations of the current literature with respect to study design (e.g., randomization, blinding, control for litter effects), and assessment of motor and sensory function to assess the degree to which impairment of movement may impact performance in learning and memory tests. If justified, follow-up studies would address potential developmental effects using lower dose levels more applicable to human intakes.

Two studies included in Table 4 (Ref. 1) were not included in the NTP review, but do not show neurotoxicity effects at doses relevant to U.S. populations. One study aimed to establish vitamin A as a marker for fluoride neurotoxicity (Ref. 38), but changes in vitamin A were measured only at an excessive fluoride dose of 20 mg/L. The other study dosed rats with fluoride in drinking water (Ref. 39) and showed effects on behavior and brain neurotransmitters at a dose of 5 mg/L, a level well above the 0.7 parts per million level recommended for community water fluoridation in the United States. Other studies in Table 4, which, according to the title of the table, are indicative of "Water Fluoride Levels Associated with Neurotoxic Effects in Rodents," erroneously report effect levels not supported by the studies themselves. In Wu et al. (Ref. 36), which NTP excluded based on high bias, no adverse effects were seen at a dose of 1 mg/kg-day as claimed in the petition. In fact, the behavioral effects occurred only at doses of 5 and 25 mg/L. In Chouhan et al. (Ref. 40), which NTP excluded in the initial screen for relevancy, no significant neurotoxicity was seen at 1 mg/L fluoride, in contrast to what the petition claims. In addition, the petition's statement that "rats require 5 times more fluoride in their water to achieve the same level of fluoride in their blood as humans"

(Ref. 1) as a rationale for why higher exposure levels in animals are relevant to lower levels in humans is not supported by the NTP review in the petition. The NTP review indicates that "assuming approximate equivalence [of drinking water concentrations in rodents and humans] is not unreasonable" (Ref. 35, p. 58). These several erroneously reported studies do not change EPA's agreement with the conclusions of the NTP report that their "[r]esults show **low-to-moderate level-of-evidence** in developmental and adult exposure studies for a pattern of findings suggestive of an effect on learning and memory" (Ref. 35, p. 52).

In cell studies cited in the petition, two studies demonstrated effects following exposure of artificial brain cells to fluoride at concentrations in the range purported to be in the bloodstream of humans. However, relevance of cell assays to humans is limited because the concentrations of fluoride experienced by cells by themselves in culture are not directly comparable to an animal or human exposure due to lack of metabolism, interactions between cells, and the ability to measure chronic (long-term) effects (Ref. 41). Extrapolation from concentrations in cell cultures to human exposures is not straightforward. Pharmacokinetic modeling is necessary to convert the concentrations to a human equivalent dose relevant to risk assessment (Ref. 42), but the petition did not address whether data are available or lacking to complete such an analysis.

4. *Susceptible subpopulations are at heightened risk.* The data and information provided in the petition do not support the claims that "nutritional status, age, genetics and disease are known to influence an individual's susceptibility to chronic fluoride toxicity." The only reference the petition presents that specifically addresses the claim that nutrient deficiencies (i.e., deficiencies in iodine and calcium) can "amplify fluoride's

neurotoxicity" is the study by Das and Mondal (Ref. 26). However, the study did not measure any nutrients in their test subjects. Rather, they measured Body Mass Index (BMI), acknowledging that "BMI is the most commonly used measure for monitoring the prevalence of overweight and obesity at population level" and "it is only a proxy measure of the underlying problem of excess body fat or underweight cases." Not only is the BMI an indirect proxy for the iodine and calcium deficiencies supposed in the petition, the BMI results presented in this study are themselves equivocal, as they show that BMIs ranged from underweight to overweight to obesity depending on the sex and age of the study subjects. Furthermore, the petition concedes that the Das and Mondal study data are only "suggestive" of an area with chronic malnutrition. A few human studies cited provide only suggestive evidence that low levels of iodine may increase the effects of high levels of fluoride in children, but these studies suffer from study design and confounding issues already described previously. Other cited studies describe the effects of iodine or calcium on rats or rat brain cells in addition to irrelevantly high fluoride levels. The petition also claims that a certain "COMT gene polymorphism greatly influences the extent of IQ loss resulting from fluoride exposure," citing a study by Zhang et al (Ref. 29) as support. The COMT gene encodes for the enzyme, catechol-O-methyltransferase, which is responsible for control of dopamine levels in the brain. Zhang et al. concludes that, "[t]he present study has several limitations. First, the cross-sectional observational design does not allow us to determine temporal or causal associations between fluoride and cognition. Second, the study has a relatively small sample size, which limits the power to assess effects of gene-environmental interactions on children's IQ" (Ref. 29). Zhang et al. continues "[d]espite the study limitations, this is the first gene-

environment study investigating the potential impact of COMT single-nucleotide polymorphism (SNP) on the relationship between children's cognitive performance and exposure to elemental fluoride" (Ref. 29). Several studies are cited in the petition to support the assertion that infants, the elderly and individuals with deficient nutritional intake and kidney disease are more susceptible to fluoride neurotoxicity. However, the level of supporting evidence from these studies (i.e., to specify the potentially greater susceptibility of any particular subpopulation) is insufficient to overcome the petition's broader failure to set forth sufficient facts to establish that fluoridation chemicals present an unreasonable risk to the general population, to allow EPA to reach a risk evaluation.

5. *RfD/RfC derivation and uncertainty factor application.* An oral Reference Dose or inhalation Reference Concentration is a daily exposure to the human population, including sensitive subgroups, that is likely to be without an appreciable risk of deleterious effects during a lifetime (Ref. 43). The petition cites EPA's 1998 guidance document, *Guidelines for Neurotoxicity Risk Assessment* (Ref. 44), purporting that it demonstrates the necessity of applying an uncertainty factor of at least 10. It appears that the petition has selected the eight studies presented in Table 5 (Ref. 1, p. 19) as candidates for deriving a Reference Dose (RfD) or Reference Concentration (RfC). The petition asserts that these dose or concentration values are relevant oral reference values for neurotoxic effects. However, the petition fails to recognize that the question of applying an uncertainty factor does not even arise until one has first appropriately performed a hazard characterization for all health endpoints of concern (Ref. 30, Section 3.1). As outlined in EPA's document, *A Review of the Reference Dose and Reference Concentration Processes* (Ref. 43), the first step in deriving an RfD or RfC is to evaluate

the available database. The petition does not set forth the strengths and limitations of each of the studies in the overall database of available studies nor any criteria or rationale for selecting the eight particular studies from which to derive an RfD or RfC. Without setting forth the strengths and limitations associated with each study and the weight of evidence provided by the available database, a necessary step in any assessment, it is not possible to determine whether uncertainty factors are necessary.

Following hazard characterization and identification of suitable studies for an RfD or RfC, uncertainty factors are generally applied to a lower limit dose or concentration on the continuum of observed effects (dose-response curve) in an individual study (e.g., NOAEL, LOAEL, Benchmark Dose, etc.). The selection of uncertainty factors and their magnitude should be based on the quality of the data, extent of the database and sound scientific judgment and consider the impact of having adverse effects from an inadequate exposure as well as an excess exposure. Uncertainty factor values may be considered appropriate to account for uncertainties associated with extrapolating from (1) a dose producing effects in animals to a dose producing no effects, (2) subchronic to chronic exposure in animals, (3) animal toxicological data to humans (interspecies), (4) sensitivities among the members of the human population (intraspecies), and (5) deficiencies in the database for duration or key effects (Ref. 43). Conflicting statements in the petition indicate that there is both a robust and certain dose-response relationship between fluoride exposure and IQ including for sensitive subpopulations. However, the petition does not clearly identify which sources/types of uncertainty in the data exist, nor which of the aforementioned uncertainty factors should be applied based on the review of the selected studies.

6. *Benefits to public health*. The petition asserts that the fluoridation of drinking water confers little benefit to public health, claiming that the primary benefit of fluoride comes from topical fluoride contact with the teeth and that there is thus little benefit from ingesting fluoride in water or any other product. The petition claims there are no randomized controlled trials on the effectiveness of fluoridation, and that few studies adequately account for potential confounding factors. In addition, the petition states that modern studies of fluoridation and tooth decay have found small, inconsistent and often non-existent differences in cavity rates between fluoridated and non-fluoridated areas. Further, the petition questions the cost-effectiveness of fluoridation relative to costs associated with what have been asserted to be fluoridation-related drops in IQ. The petition argues, then, that there is "little justification" in exposing the public to "*any* risk" of fluoride neurotoxicity (Ref. 1).

EPA does not believe that the petition has presented a well-founded basis to doubt the health benefits of fluoridating drinking water. The petition's argument about fluoridation benefits (i.e., that the risks of neurotoxic health effects from fluoridation are unreasonable in part because they outweigh the expected health benefits arising from exposure to fluoride) depends on first setting forth sufficient facts to establish the purported neurotoxic risks, to which the countervailing health benefits from fluoridation could be compared. But as noted earlier, EPA and other authoritative bodies have previously reviewed many of the studies cited as evidence of neurotoxic effects of fluoride in humans and found significant limitations in using them to draw conclusions on whether neurotoxicity is associated with fluoridation of drinking water. Irrespective of the conclusions one draws about the health benefits of drinking water fluoridation, the

petition did not set forth sufficient facts to justify its primary claims about purported neurotoxic effect from drinking fluoridated water.

The petition cites several studies as evidence that water fluoridation does not have any demonstrable benefit to the prevention of tooth decay (Refs. 45-49). However, EPA has found substantial concerns with the designs of each of these studies including small sample size and uncontrolled confounders, such as recall bias and socioeconomic status. Additionally, in Bratthall et al. (Ref. 45), for example, the appropriate interpretation of the responses of the 55 dental care professionals surveyed, based on the data provided in the paper, is that in places where water is fluoridated, the fluoridation is the primary reason for the reduction in dental caries. Diesendorf (Ref. 49) cites only anecdotal evidence and Cheng et al. (Ref. 46) is commentary only, with no supporting data.

EPA is mindful of the public health significance of reducing the incidence of dental caries in the U.S. population. Dental caries is one of the most common childhood diseases and continues to be problematic in all age groups. Historically, the addition of fluoride to drinking water has been credited with significant reductions of dental caries in the U.S. population. In 2000, the then-Surgeon General noted that "community water fluoridation remains one of the great achievements of public health in the twentieth century—an inexpensive means of improving oral health that benefits all residents of a community, young and old, rich and poor alike." The U.S. Surgeon General went on to note, "it [is] abundantly clear that there are profound and consequential disparities in the oral health of our citizens. Indeed, what amounts to a silent epidemic of dental and oral diseases is affecting some population groups." (Ref. 50).

At that time, among 5- to 17-year-olds, dental caries was more than five times as

common as a reported history of asthma and seven times as common as hay fever. Prevalence increases with age. The majority (51.6 percent) of children aged 5 to 9 years had at least one carious lesion or filling in the coronal portion of either a primary or a permanent tooth. This proportion increased to 77.9 percent for 17-year-olds and 84.7 percent for adults 18 or older. Additionally, 49.7 percent of people 75 years or older had root caries affecting at least one tooth (Ref. 50).

More recently, from the National Health and Nutrition Examination Survey (NHANES) for 2011-2012, approximately 23% of children aged 2–5 years had dental caries in primary teeth. Untreated tooth decay in primary teeth among children aged 2–8 was twice as high for Hispanic and non-Hispanic black children compared with non-Hispanic white children. Among those aged 6–11, 27% of Hispanic children had any dental caries in permanent teeth compared with nearly 18% of non-Hispanic white and Asian children. About three in five adolescents aged 12–19 years had experienced dental caries in permanent teeth, and 15% had untreated tooth decay (Refs. 51).

Further, in 2011-2012, 17.5 percent of Americans ages 5-19 years were reported to have untreated dental caries, while 27.4 percent of those aged 20-44 years had untreated caries (Ref. 52). For those living below the poverty line, 24.6 percent of those aged 5-19 years and 40.2 percent of those aged 20-44 years had untreated dental caries (Ref. 52). Untreated tooth decay can lead to abscess (a severe infection) under the gums which can spread to other parts of the body and have serious, and in rare cases fatal, results (Ref. 53). Untreated decay can cause pain, school absences, difficulty concentrating, and poor appearance, all contributing to decreased quality of life and ability to succeed (Ref. 54).

These data continue to suggest dental caries remains a public health problem affecting many people. Fluoride has been proven to protect teeth from decay by helping to rebuild and strengthen the tooth's surface or enamel. According to the Centers for Disease Control and Prevention and the American Dental Association, water fluoridation prevents tooth decay by providing frequent and consistent contact with low levels of fluoride (Refs. 55 and 56). Thus, the health benefits of fluoride include having fewer cavities, less severe cavities, less need for fillings and removing teeth, and less pain and suffering due to tooth decay (Ref. 55).

Fluoride protects teeth in two ways – systemically and topically (Ref. 57). Topical fluorides include toothpastes, some mouth rinse products and professionally applied products to treat tooth surfaces. Topical fluorides strengthen teeth already in the mouth by becoming incorporated into the enamel tooth surfaces, making them more resistant to decay. Systemic fluorides are those ingested into the body. Fluoridated water and fluoride present in the diet are sources of systemic fluoride. As teeth are developing (pre-eruptive), regular ingestion of fluoride protects the tooth surface by depositing fluorides throughout the entire tooth surface (Ref. 56). Systemic fluorides also provide topical protection as ingested fluoride is present in saliva which continually bathes the teeth (Ref. 56). Water fluoridation provides both systemic and topical exposure which together provide for maximum reduction in dental decay (Ref. 56).

The Surgeon General, the Public Health Service and the Centers for Disease Control and Prevention reaffirmed in 2015 the importance of community water fluoridation for the prevention of dental caries and its demonstrated effectiveness (Refs. 54 and 58). In the Public Health Service's 2015 *Recommendation for Fluoride*

Concentration in Drinking Water, they note "there are no randomized, double-blind, controlled trials of water fluoridation because its community-wide nature does not permit randomization of individuals to study and control groups or blinding of participants. However, community trials have been conducted, and these studies were included in systematic reviews of the effectiveness of community water fluoridation. As noted, these reviews of the scientific evidence related to fluoride have concluded that community water fluoridation is effective in decreasing dental caries prevalence and severity" (Ref. 59).

7. *Extent and magnitude of risk from fluoridation chemicals.* The petition argues that the purported risks of drinking water fluoridation are unreasonable in part because they are borne by a large population. The petition (in its discussion of the extent and magnitude of risk posed) cites the total U.S. population and estimates the number of U.S. children under the age of 18 years who live in areas where artificial fluoridation occurs. That estimate is then multiplied by an estimate of the average decrease in lifetime earnings associated with IQ point loss to calculate the overall potential IQ point loss and associated decrease in lifetime earnings for the segment of the U.S. population under the age of 18 years potentially exposed to artificially fluoridated water. The petition concludes, based on the potential extent and magnitude of exposure to fluoridation chemicals, that fluoridation would have caused "a loss of between 62.5 to 125 million IQ points" (Ref 1, p. 24).

The petition has not set forth a scientifically defensible basis to conclude that any persons have suffered neurotoxic harm as a result of exposure to fluoride in the U.S. through the purposeful addition of fluoridation chemicals to drinking water or otherwise

from fluoride exposure in the U.S. Still less has the petition set forth a scientifically defensible basis to estimate an aggregate loss of IQ points in the U.S, attributable to this use of fluoridation chemicals. As noted previously, EPA has determined the petition did not establish that fluoridation chemicals present an unreasonable risk of injury to health or the environment, arising from these chemical substances' use to fluoridate drinking water. The fact that a purported risk relates to a large population is not a basis to relax otherwise applicable scientific standards in evaluating the evidence of that purported risk. EPA and other authoritative bodies have previously reviewed many of the studies cited as evidence of neurotoxic effects of fluoride in humans and found significant limitations in using them to draw conclusions on whether neurotoxicity is associated with fluoridation of drinking water. In contrast, the benefits of community water fluoridation have been demonstrated to reduce dental caries, which is one of the most common childhood diseases and continues to be problematic in all age groups. Left untreated, decay can cause pain, school absences, difficulty concentrating, and poor appearance, all contributing to decreased quality of life and ability to succeed (Ref. 54).

8. *Consequences of eliminating use of fluoridation chemicals.* Apparently citing to a repealed provision of TSCA (15 U.S.C. 2605(c)[1](A) (2015)) and guidance issued with respect to that statutory provision, the petition argues that the following factors are germane to determining whether the alleged neurotoxic risks presented by fluoridation chemicals are unreasonable: "the societal consequences of removing or restricting use of products; availability and potential hazards of substitutes, and impacts on industry, employment, and international trade." Along these lines, the petition includes claims such as the following: that any risks of fluoridation chemicals could be easily reduced by

discontinuing purposeful fluoridation practices; that alternative topical fluoride products have widespread availability; and that the impacts on the requested rule on industry, employment, and international trade would be little, if any. In short, the petition urges EPA to conclude that the risks of fluoridation chemicals are unreasonable, in part because if EPA found that the risks were unreasonable, the cost and non-risk factors that EPA would need to address in ensuing risk management rulemaking could be readily addressed. But this sort of ends-driven reasoning is forbidden by the texts of section 6(b)(4)(A) and 21(b)(4)(B)(ii) of the amended TSCA, which exclude "costs or other non-risk factors" from the unreasonable risk determination. It is also plainly inconsistent with Congress' intent, in amending TSCA, to "de-couple" the unreasonable risk decision from the broader set of issues (e.g., chemical alternatives and regulatory cost-effectiveness) that may factor into how best to manage unreasonable risks, once particular risks have been determined to be unreasonable. See S. Rep 114-67 at 17 (Ref. 3); H.R. Rep. 114-176 at 23 (Ref. 4); and 162 Cong. Rec. S3516 (Ref. 60).

9. *Link to elevated blood lead levels.* To support the contention that TSCA (and not the Safe Drinking Water Act [SDWA]) is the appropriate regulatory authority, the petition asserts an association between fluoridation chemicals and elevated blood lead levels and claims that there is laboratory and epidemiological research linking artificial fluoridation chemicals with pipe corrosion. The petition then argues that issuing a rule under TSCA section 6 rather than SDWA would allow EPA to specifically target and prohibit the addition of fluoridation chemicals to drinking water. The petition argues that SDWA would not allow EPA to distinguish between intentionally-added, artificial and naturally-occurring fluoride. It is in the public interest, says the petition, to opt for the

regulatory option that is less expensive and can be more narrowly tailored.

Regarding the claims about the relative extent of legal authorities under TSCA and SDWA, EPA notes that the petition has not set forth any specific legal basis for its views on the purported limitations of SDWA. For this reason, and because the petition has not set forth facts sufficient to show that the fluoridation of drinking water presents an unreasonable risk under TSCA, the Agency need not resolve such legal questions in order to adjudicate this petition.

EPA has further observations about the petition's claims that drinking water fluoridation is linked to lead hazards. The Centers for Disease Control and Prevention (CDC) studied the relationship between fluoridation additives and blood lead levels in children in the United States (Ref. 61). More than 9,000 children between the ages of 1-16 years were included in the study's nationally representative sample. The petition argues that the study, and Table 4 in particular, shows that fluorosilicic acid was associated with increased risk of high blood lead levels. In fact, Macek et al. concluded that their detailed analyses did not support concerns that silicofluorides in community water systems cause high lead concentrations in children. The petition also points to another study (Ref. 62) which re-analyzed CDC's data and concluded that children exposed to "silicofluoridated" water had an elevated risk of having high blood lead levels. Coplan et al. (Ref. 62) criticized the Macek et al. approach as flawed and reevaluated the NHANES data comparing systems that used silicofluorides to all systems (e.g., a combination of fluoridated, nonfluoridated and naturally fluoridated) and found a small difference between the number of children in each group with blood lead levels >5 µg/dL; the results were not evaluated to see if the difference was statistically significant.

A number of other chemical characteristics are known to increase lead release into water sources such as pH, natural organic matter, water hardness, oxidant levels, and type of piping, age of housing; the Coplan et al. study did not evaluate these factors.

In any event, the Agency is not persuaded that the examination of the relationship between fluoridation chemicals, pipe corrosion, and elevated blood lead levels nor their bearing on the comparative efficacy of TSCA or SDWA is germane to the disposition of the petition. Under TSCA, where the EPA Administrator determines "that the manufacture, processing, distribution in commerce, use, or disposal of a chemical substance or mixture . . . presents an unreasonable risk of injury to health or the environment, the Administrator shall by rule [regulate a] . . . substance or mixture to the extent necessary so that the chemical substance or mixture no longer presents such risk" 15 U.S.C. 2605(a). As previously discussed, the petition does not demonstrate that purposeful addition of fluoridation chemicals to U.S. water supplies presents such unreasonable risk.

10. *Regulation of fluoridation chemicals as a category.* EPA has broad discretion to determine whether to regulate by category under TSCA section 26(c) rather than by individual chemical substances. In a prior evaluation of a section 21 petition seeking the regulation of a category of chemical substances, EPA explained that it does so in light of Congress' purpose in establishing the category authority: to "facilitate the efficient and effective administration" of TSCA. See 72 FR 72886 (Ref. 63) (citing Senate Report No. 94-698 at 31). It is of course self-evident that various chemical substances constituting "fluoridation chemicals" would have in common their use to fluoridate drinking water. But as discussed in Unit III., the inquiry does not end there. If EPA were to grant the

petitioner's request, the Agency would become obligated to address all conditions of use of the category. If certain chemical substances comprising the category present conditions of use that other members do not, and any of those conditions of use would be significant to whether the category as a whole presents an unreasonable risk to human health or the environment, then the overall approach of regulating by category is less suited to the efficient and effective administration of TSCA. But the petition does not set forth facts that would enable the Agency to reasonably evaluate whether a category approach on fluoridation chemicals would be consistent with the efficient and effective administration of TSCA. Nor does the petition set forth the specific chemical substances that should comprise the category of fluoridation chemicals.

11. *Specification of an adequate rule under TSCA section 6(a).* As discussed earlier, the petition does not set forth facts that satisfactorily demonstrate to the Agency that fluoridation chemicals present an unreasonable risk to human health, specifically arising from these chemical substances' use to fluoridate drinking water. But even if the petition had done so, it would still be inadequate as a basis to compel the commencement of section 6(a) rulemaking proceeding under TSCA section 21. This is because the petition does not address whether fluoridation chemicals would still present an unreasonable risk, even after implementing the requested relief, arising from other conditions of use. As discussed earlier in Unit III., EPA interprets TSCA section 21 as requiring a petition to address the full set of conditions of use for a chemical substance and thereby describe an adequate rule under TSCA section 6(a), as opposed to a rule that would merely address a particular subset of uses of special interest. The petition at issue pays little or no attention to the other conditions of use of the various fluoridation

chemicals (i.e., uses other than the eponymous use to treat drinking water) and makes no claim for any of these chemical substances that the risks to be addressed by curtailing drinking water fluoridation would be the only unreasonable risks or even the most significant unreasonable risks. This problem is compounded by the petition's lack of specificity as to which chemical substances are being construed as "fluoridation chemicals."

EPA acknowledges that its interpretation of the requirements of TSCA section 21, for petitions seeking action under TSCA section 6, was not available to petitioners at the time they prepared this petition. EPA has issued general guidance for preparing citizen's petitions, 50 FR 56825 (1985), but that guidance does not account for the 2016 amendments to TSCA. Particularly relevant under these circumstances, the Agency wishes to emphasize that its denial does not preclude petitioners from obtaining further substantive administrative consideration, under TSCA section 21, of a substantively revised petition under TSCA section 21 that clearly identifies the chemical substances at issue, discusses the full conditions of use for those substances, and sets forth facts that would enable EPA to complete a risk evaluation under TSCA section 6(b) for those substances.

VI. References

As indicated under **ADDRESSES**, a docket has been established for this document under docket ID number EPA-HQ-OPPT-2016-0763. The following is a listing of documents that are specifically referenced in this notice. The docket itself includes both these referenced documents and further documents considered by EPA. The docket also includes supporting documents provided by the petitioner and cited in the petition,

which are not available in the electronic version of the docket. For assistance in locating these printed documents, please consult the technical person listed under **FOR FURTHER INFORMATION CONTACT**.

1. Fluoride Action Network. Citizen Petition Under Section 21 of TSCA. November 2016.

2. EPA. Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act; Notice. **Federal Register** (82 FR 7562, January 19, 2017).

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List of Subjects

Environmental protection, fluoridation chemicals, drinking water, Toxic Substances Control Act (TSCA).

Dated: February 17, 2017,

Wendy Cleland-Hamnett,

Acting Assistant Administrator, Office of Chemical Safety and Pollution Prevention.

[FR Doc. 2017-03829 Filed: 2/24/2017 8:45 am; Publication Date: 2/27/2017]

From: Christine Massey
Sent: April 4, 2017 6:16 PM
To: Sprovieri, John; rbelgrave@thebramptonguardian.com; Thompson, Allan; Downey, Johanna; Groves, Annette; Innis, Jennifer; Shaughnessy, Barb; Jeffrey, Linda Mayor; Gibson, Grant; Medeiros, Martin; Miles, Gael; Moore, Elaine; Palleschi, Michael; Crombie, Bonnie; Carlson, George; Fonseca, Chris; Iannicca, Nando; Kovac, John; Mahoney, Matt; McFadden, Sue; Parrish, Carolyn; Ras, Karen; Saito, Pat; Starr, Ron; Tovey, Jim; Loh, Lawrence; Polsinelli, Nancy; Szwarc, David; Burkiewicz, Justyna; Hennings, Jeff; O'Connor, Patrick
Subject: MOECC: no "standard" saying any F level prevents cavities

Dear Peel Council / CWFC Members, Dr. Loh, Health Commissioner Polsinelli, Ms. Burkiewicz, Mr. Hennings, Mr. O'Connor and CAO Szwarc,

1. According to the MOECC in the emails below, there is no provincial "standard" stating that 0.5 to 0.8 mg/L fluoride in drinking water, or any other range, will prevent cavities. O. Reg. 169/03: ONTARIO DRINKING WATER QUALITY STANDARDS is the only set of drinking water standards for large municipal systems and it does not say anything about adding fluoride to water to prevent cavities.

The lowest level of fluoride that is in accordance with provincial standards is zero ppm, and Council's recent motion to lower the fluoride concentration to the lowest level in accordance with provincial standards implies that the Region will now cease fluoridation altogether.

2. The Region's website now says:

*The level of naturally-occurring fluoride in Peel's Lake-based municipal water supply is adjusted to an optimal concentration range to protect against tooth decay: 0.5 mg/L to 0.8 mg/L, as recommended by the Ministry of the Environment and Climate Change's **Technical Support Document for Ontario Drinking Water Standards, Objectives and Guidelines**.*

This technical document is not mentioned in the *Safe Drinking Water Act* or the actual drinking water standards, O. Reg. 169/03. It is not a standard. In conjunction with Council's recent motion, this statement is misleading to the public.

[This statement is also misleading because the Region is not adding more naturally-occurring calcium fluoride (a mineral) to our water, but a man-made acid. Material safety data sheets for HFSA say not to add it to domestic water supplies. The Region's expert, Mr. Jennings, admitted during Council's March 9th meeting that he does not know the long term effects of ingesting HFSA and will not argue that there are no adverse health effects.]

The technical document mentioned above makes this statement:

Where fluoride is added to drinking water, it is recommended that the concentration be adjusted to 0.5 -0.8 mg/L the optimum level for control of tooth decay.

This is only a recommendation for communities foolish enough to fluoridate, not a standard. There is no suggestion that it would be safe or wise to fluoridate at any concentration.

Also, on page 1 this document says:

REFERRAL TO _____
RECOMMENDED
DIRECTION REQUIRED _____
RECEIPT RECOMMENDED ✓ _____

Standards, objectives and guidelines are considered to be the minimum level of drinking-water quality and ***in no way should be regarded as implying that allowing the degradation of a high quality water supply to the specified level or range is acceptable.***

Best wishes,
Christine Massey
Fluoride Free Peel

---------- Forwarded message ----------
From: **Bekkout, Lamine (MOECC)** <Lamine.Bekkout@ontario.ca>
Date: Tue, Apr 4, 2017 at 2:12 PM
Subject: RE: Reply: Yes, Page: https://www.ontario.ca/page/ministry-environment-and-climate-change (Christine Massey)
To: Christine Massey

Hello Christine,

If by tap water you mean large municipal drinking water systems, then yes Ministry of the Environment and Climate Change has jurisdiction, but for small drinking water systems the oversight was transferred to the Ministry of Health as of December 1, 2008:

http://www.health.gov.on.ca/english/public/program/pubhealth/safewater/safewater_faq.html#1

Again the Fluoridation Act (1990) is under the jurisdiction of the Ministry of Health.

You may find the following web page of interest:

https://www.ontario.ca/page/rules-non-municipal-drinking-water-systems

Regards,

Mr. **Lamine Bekkout** *(pronounced La-meen Bee-koot)*
Bilingual Inquiry Support & Technology Officer | *Agent bilingue de support d'information et de technologie*
Ministry of the Environment and Climate Change | *Ministère de l'Environnement et de l'Action en matière de changement climatique*
Communications Branch | *Direction des communications*
2nd Floor, Macdonald Block | *Édifice Macdonald, 2e étage,*
900 Bay Street, Suite M2-22 | *900, rue Bay, bureau M2-22*
Toronto, ON, M7A 1N3
Tel | *Téléphone* : 416-325-4164
Toll free | *Sans frais* : 1-800-565-4923
TTY | *Numéro d'ATS* : 1-855-515-2759
Twitter: @EnvironmentOnt | Facebook: Facebook.com/OntarioEnvironment
Government of Ontario Employee and Organization Directory |Répertoire des employés et des bureaux du gouvernement de l'Ontario
To report a suspected act of pollution within the Province of Ontario, contact the Ministry of the Environment and Climate Change Pollution Hotline at 1-866-MOE-TIPS (663-8477) or email your concern to MOE.Tips.moe@ontario.ca | Pour signaler un présumé acte de la pollution

dans la province de l'Ontario, veuillez communiquer avec la ligne d'assistance MOE pollution au 1-866-MOE-TIPS (663-8477) ou par courriel : *MOE.Tips.moe@ontario.ca*.

From: Christine Massey
Sent: Tuesday, April 04, 2017 1:57 PM

To: Bekkout, Lamine (MOECC)
Subject: Re: Reply: Yes, Page: https://www.ontario.ca/page/ministry-environment-and-climate-change (Christine Massey)

Thank you very much, Lamine.

Does the Ministry of Health have any jurisdiction over tap water? I thought that only the MOECC has jurisdiction over tap water.

Best wishes,

Christine

---------- Forwarded message ----------
From: **Bekkout, Lamine (MOECC)** <Lamine.Bekkout@ontario.ca>
Date: Tue, Apr 4, 2017 at 1:48 PM
Subject: RE: Reply: Yes, Page: https://www.ontario.ca/page/ministry-environment-and-climate-change (Christine Massey)
To: Christine Massey [redacted]

Hello Christine,

I would suggest that you contact the Ministry of Health and Long Term Care for further details as the Fluoridation Act (1990) is under their jurisdiction.

Please feel free to contact me if you need any other assistance.

Regards,

Mr. **Lamine Bekkout** *(pronounced La-meen Bee-koot)*
Bilingual Inquiry Support & Technology Officer | *Agent bilingue de support d'information et de technologie*
Ministry of the Environment and Climate Change | *Ministère de l'Environnement et de l'Action en matière de changement climatique*
Communications Branch | *Direction des communications*
2nd Floor, Macdonald Block | *Édifice Macdonald, 2e étage,*
900 Bay Street, Suite M2-22 | *900, rue Bay, bureau M2-22*
Toronto, ON, M7A 1N3
Tel | *Téléphone* : 416-325-4164
Toll free | *Sans frais* : 1-800-565-4923
TTY | *Numéro d'ATS* : 1-855-515-2759
Twitter: @EnvironmentOnt | Facebook: Facebook.com/OntarioEnvironment

From: Christine Massey
Sent: Tuesday, April 04, 2017 1:20 PM

To: Bekkout, Lamine (MOECC)
Subject: Re: Reply: Yes, Page: https://www.ontario.ca/page/ministry-environment-and-climate-change (Christine Massey)

Thank you very much, Lamine.

Which legal provincial standard states that 0.5 to 0.8 mg/L fluoride in drinking water will prevent dental caries, and/or that systems that fluoridate for the prevention of cavities are required to maintain a range of 0.5 to 0.8 mg/L fluoride?

Best wishes,

Christine

On Tue, Apr 4, 2017 at 1:11 PM, Bekkout, Lamine (MOECC) <Lamine.Bekkout@ontario.ca> wrote:

Hello Christine,

Thank you for following up.

As you may know, it is the municipalities which are responsible for deciding if they will or not fluoridate their water supply.

Under the Fluoridation Act (1990), which is administered by the Ministry of Health and Long Term Care, a local municipality may enact a by-law to discontinue fluoridation of its municipal drinking water supply. The municipality may also hold a referendum asking electors if they are in favour of fluoridation of the public water supply in their municipality.

The current Ontario Drinking Water Quality Standards of 1.5 milligram per Litre (mg/L) is consistent with the other provinces and territories.

In Ontario drinking water systems that fluoridate for the protection of dental health are required to maintain a range of 0.5 to 0.8 mg/L fluoride, a level about one-half of the Ontario Drinking Water Quality Standard.

Please feel free to contact me if you need any other assistance.

Regards,

Mr. **Lamine Bekkout** *(pronounced La-meen Bee-koot)*
Bilingual Inquiry Support & Technology Officer | *Agent bilingue de support d'information et de technologie*
Ministry of the Environment and Climate Change | *Ministère de l'Environnement et de l'Action en matière de changement climatique*
Communications Branch | *Direction des communications*
2nd Floor, Macdonald Block | *Édifice Macdonald, 2e étage,*
900 Bay Street, Suite M2-22 | *900, rue Bay, bureau M2-22*
Toronto, ON, M7A 1N3
Tel | *Téléphone* : 416-325-4164
Toll free | *Sans frais* : 1-800-565-4923
TTY | *Numéro d'ATS* : 1-855-515-2759
Twitter: @EnvironmentOnt | Facebook: Facebook.com/OntarioEnvironment
Government of Ontario Employee and Organization Directory |Répertoire des employés et des bureaux du gouvernement de l'Ontario

To report a suspected act of pollution within the Province of Ontario, contact the Ministry of the Environment and Climate Change Pollution Hotline at 1-866-MOE-TIPS (663-8477) or email your concern to MOE.Tips.moe@ontario.ca | Pour signaler un présumé acte de la pollution dans la province de l'Ontario, veuillez communiquer avec la ligne d'assistance MOE pollution au 1-866-MOE-TIPS (663-8477) ou par courriel : *MOE.Tips.moe@ontario.ca*.

From: Christine Massey
Sent: Tuesday, April 04, 2017 12:20 PM
To: Bekkout, Lamine (MOECC)
Subject: Re: Reply: Yes, Page: https://www.ontario.ca/page/ministry-environment-and-climate-change (Christine Massey)

Thank you very much, Lamine.

Is there a provincial standard specifying a concentration of fluoride in drinking water that will prevent dental caries (cavities)?

Best wishes,

Christine

On Tue, Apr 4, 2017 at 9:51 AM, Bekkout, Lamine (MOECC) <Lamine.Bekkout@ontario.ca> wrote:

Hello Ms. Massey,

Thank you for contacting the Ministry of the Environment and Climate Change.

There are many regulations in Ontario covering drinking water, but if you are referring to the one dealing with the drinking water quality standards, acceptable limits of elements in drinking water, then O. Reg. 169/03: ONTARIO DRINKING WATER QUALITY STANDARDS is the one that deals with this specific issue.

I would need more details to be able to properly respond to your request.

Regards,

Mr. **Lamine Bekkout** *(pronounced La-meen Bee-koot)*
Bilingual Inquiry Support & Technology Officer | *Agent bilingue de support d'information et de technologie*
Ministry of the Environment and Climate Change | *Ministère de l'Environnement et de l'Action en matière de changement climatique*
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Government of Ontario Employee and Organization Directory |Répertoire des employés et des bureaux du gouvernement de l'Ontario
To report a suspected act of pollution within the Province of Ontario, contact the Ministry of the Environment and Climate Change Pollution Hotline at 1-866-MOE-TIPS (663-8477) or email your concern to MOE.Tips.moe@ontario.ca | Pour signaler un présumé acte de la pollution dans la province de l'Ontario, veuillez communiquer avec la ligne d'assistance MOE pollution au 1-866-MOE-TIPS (663-8477) ou par courriel : *MOE.Tips.moe@ontario.ca*.

From: PICEmail (MOECC)
Sent: Tuesday, April 04, 2017 9:21 AM
To: Bekkout, Lamine (MOECC)
Subject: FW: Reply: Yes, Page: https://www.ontario.ca/page/ministry-environment-and-climate-change (Christine Massey)

From: do.not.reply@ontario.ca [mailto:do.not.reply@ontario.ca]
Sent: Monday, April 03, 2017 6:30 PM
To: PICEmail (MOECC)
Subject: Reply: Yes, Page: https://www.ontario.ca/page/ministry-environment-and-climate-change (Christine Massey)

Referring page: page/ministry-environment-and-climate-change

Message:

Hello, What drinking water "standards" exist in the province of Ontario? Please reply via email. Christine

Reply Request: Yes

Name: Christine Massey

E-mail:

Address:

Brampton, ON

User agent:

From: Christine Massey
Sent: Friday, April 7, 2017 4:07 PM
To: Sprovieri, John; Polsinelli, Nancy; O'Connor, Patrick; Parrish, Carolyn; Palleschi, Michael; Ras, Karen; Loh, Lawrence; Dale, Frank; Tovey, Jim; Downey, Johanna; Groves, Annette; Moore, Elaine; Szwarc, David
Cc: [redacted]
Subject: Region's fraudulent dental fluorosis statistic

Dear CWFC Members, Chair Dale, Dr. Loh, Health Commissioner Polsinelli and CAO Szwarc,

On page 61 of the Region's new oral health report, Staff reported a fraudulent dental fluorosis statistic. This should have been obvious to anyone with a basic understanding of dental fluorosis.

See page 42 for the ages of the children examined: "*Routine data about the oral health status of Peel's population is limited to children in junior kindergarten (JK), senior kindergarten (SK) and Grade 2.*" The majority of these children were too young to have the teeth erupted that need to be examined for proper evaluation of dental fluorosis, yet they were included in the denominator when calculating the percentage of children affected by dental fluorosis.

I've attached for you CAO Szwarc's reply to my request for details on this new statistic. In his letter you can see the details I had asked for.

Also attached is the reply from Public Health Staff saying that they cannot provide a breakdown on how many of the children they reported on were in each age group, nor how many of them had the teeth erupted that are needed for proper evaluation of fluorosis, nor how many of them had the various degrees of dental fluorosis.

Note that in the earlier 2003 Peel report, page 14/21, 7 year old children were the youngest reported on regarding dental fluorosis. In the new report they are the oldest, which is unscientific, grossly misleading, and makes clear the false nature of Staff's claim that they have been monitoring the water fluoridation situation carefully.

It is also fraudulent to classify children as 'unaffected by fluorosis' when they do not have the indicator teeth erupted yet.

Also note that Staff indicated they followed the province's child health program oral health guidance document when assigning fluorosis scores. Page 13 of this document states that the fluorosis score is an "optional field". Hence, for all we know at this point, Staff also cherry-picked which scores they would record in order to further lower the fraudulent statistic.
This report needs to be removed from circulation until the dental fluorosis section has been made as clear as possible, and a notice needs to be provided to everyone to whom it was already circulated.

Further, the Staff member(s) responsible for the unscientific data collection and reporting need to be held accountable.

Best wishes,
Christine Massey M Sc
(Graduate of the Dalla Lana School of Public Health, University of Toronto)
Spokesperson for Fluoride Free Peel

REFERRAL TO _____
RECOMMENDED
DIRECTION REQUIRED _____
RECEIPT RECOMMENDED ✓ _____

Newbert, Kathleen

From: Pedra, Inga
Sent: March 2, 2017 8:56 AM
To: Newbert, Kathleen
Cc: Sharma, Paul; Cheema, Debbie
Subject: Re: Request for Documents for I23-17-059
Attachments: childhealth_oralhealth_gd.pdf

Kathleen,

Staff have looked into this request and the following response has been prepared.
Thank you
Inga

1a The scale for measuring fluorosis that is used is outlined in the Provincial Child Health Program Oral Health Guidance Document (attached).

1c The reported figure of 2.1% in the following statement in the Oral Health Status report - "In Peel, dental fluorosis affects about 2.1% (representing 1,113 children) of the 52,462 children that were screened during the 2014-2015 school year." - was determined by dividing the number of children provided with a dental screening at schools in Peel in the 2014-2015 school year with a fluorosis index of 1,2,3 or 4 (as defined in the Provincial Child Health Program Oral Health Guidance Document) by the total number of children provided with a dental screening at schools in Peel in the 2014-2015 school year and multiplying the result by 100.

p913.

There is a NIL response for the other requests.

> From: Newbert, Kathleen
> Sent: February 22, 2017 11:01 AM
> To: Sharma, Paul; Pedra, Inga
> Cc: Cheema, Debbie
> Subject: FW: Request for Documents for I23-17-059
>
>
> Hello,
>
> The Clerk's Division received a freedom of Information request for records that may be in the custody of you or your staff. The request under the Municipal Freedom of Information and Protection of Privacy Act (the Act) was for:
>
>
> 1. Records showing the details how the fluorosis diagnoses reported in the new 2017 Oral Health Report was carried out including:
>
> a. the scale for measuring dental fluorosis;
>
> b. criteria used to determine whether a child has been assessed; and
>
> c. how the reported figures of 2.1% was determined.

Region of Peel
Working for you

March 22, 2017

Christine Massey
Via email

Dear Ms. Massey,

This responds to your complaint of February 24, 2017 which was directed to me and which, as has been previously indicated when acknowledging receipt of your complaint, falls for me to deal with under the Region's formal complaint policy. I have considered the content of your email of that date and the text of your email of February 10, 2017 which you included with your complaint. Your complaint is that the Medical Officer of Health and the Commissioner of Health Services "failed to acknowledge my serious concerns conveyed to them on Feb. 10 2017, shown further below".

Upon review, your email of February 10, 2017 consists largely of assertions in support of your position on the use of fluoride in drinking water. Your advocacy for changes to Peel's current practice on the use of fluoride in Peel's drinking water has been considered by Regional Council throughout its recent protracted review of that practice, and where requested by Council, Peel's Medical Officer of Health has provided Council with information as requested in response to your advocacy. I find a non-response to these aspects of your email to have been entirely appropriate

Your February 10 email does contain one request for information which in my view does call for a response. That was stated by you in these terms:

> *"Please also let me know how many JK, SK and Grade 2 children were examined, how many in each age group had the teeth to be evaluated for fluorosis, the number in each age group with fluorosis, the degrees of fluorosis recorded, and whether any of the 1113 kids with fluorosis were from higher grades."*

Also, in your complaint itself you have posed as an additional question warranting a response, the following:

> *"whether the Region has <u>any</u> post-2001/2 data on dental fuorosis (sic)"*

I am accordingly responding to your complaint by asking staff through the Acting Medical Officer of Health, Dr. Lawrence Loh to answer these questions. It may (or may not) be that the information you have requested or some part of it is unavailable. If so, I anticipate that that will be addressed in the response. I am advised that you may expect a direct response within 9 working days. In all other respects I find your complaint to be without merit.

Yours sincerely,

David Szwarc

David Szwarc
Chief Administrative Officer

C: Regional Clerk

Office of the Chief Administrative Officer
10 Peel Centre Dr., Suite A, Brampton, ON L6T 4B9
Tel: 905-791-7800 Web: peelregion.ca

TOWNSHIP OF NAIRN AND HYMAN

64 McIntyre Street • Nairn Centre, Ontario • P0M 2L0 ☎ 705-869-4232 🖷 705-869-5248
Established: March 7, 1896 Office of the Clerk Treasurer, CAO E-mail: nairncentre@personainternet.com

April 13, 2017

Region of Peel
10 Peel Centre Drive, Suite A
Brampton, ON L6T 4B9

RECEIVED
April 13, 2017
REGION OF PEEL
OFFICE OF THE REGIONAL CLERK

Attention: Summer MacGregor, Legislative Assistant

RE: Water Fluoridation

Dear Ms:

Please be advised that our Council adopted the following resolution at their meeting of April 10, 2017:

ADVOCATING TO THE PROVINCIAL GOVERNMENT THAT THEY CLARIFY AND ASSUME THEIR LEGISLATIVE ROLE IN COMMUNITY WATER FLUORIDATION
RESOLUTION #2017-4-104
MOVED BY: Brigita Gingras
SECONDED BY: Charlene Y. Martel
RESOLVED: that Council supports the resolution adopted by the Peel Regional Council on March 9, 2017 regarding their concerns with water fluoridation.

CARRIED

Sincerely Yours,

Robert Deschene,
CAO-Clerk-Treasurer

LF/lc
cc: Michael Mantha, MPP, Algoma-Manitoulin

REFERRAL TO _____
RECOMMENDED
DIRECTION REQUIRED _____
RECEIPT RECOMMENDED ✓

6.22-2

14B

nairncentre@personainternet.com

From: "ZZG-RegionalClerk" <zzg-regionalclerk@peelregion.ca>
Date: March-31-17 10:56 AM
To: "Undisclosed recipients:"
Subject: Resolution 2017-185

I am writing to advise that Peel Regional Council approved the below resolution at its meeting held on Thursday, March 9, 2017. This resolution is provided to you for your information only.

Resolution 2017-185:

Whereas the Community Water Fluoridation Committee (CWFC) was established on February 11, 2016 to closely examine the current practice of water fluoridation in the Region of Peel and make recommendations to Regional Council on community water fluoridation in Peel;

And whereas, over the past year the CWFC has reviewed information and research related to the effectiveness, safety and cost of community water fluoridation using hydrofluorosilicic acid and heard from a number of experts and stakeholders;

And whereas, Regional Council has supported the Committee's recommendation to advocate to the provincial government that they clarify and assume their legislative role in community water fluoridation;

Therefore be it resolved, that while waiting for the Province to respond to the above request:

a) The Region of Peel undertake to reduce the concentration of fluoride in Peel's lake-based municipal water supply, adjusting it to the lowest level in accordance with provincial standards for the prevention of tooth decay;

b) And further, that the Region of Peel modify the fluoride additive used in the Region's water supply to reduce the levels of residual components; substituting a fluoride additive from calcium fluoride or such other source as will have the desired effect of reducing the levels of residual components;

c) And further, that Peel Public Health reaffirms its commitment to ongoing monitoring of the oral health status of Peel residents – especially children of school age – as well as relevant evidence on the effectiveness and safety of community water fluoridation;

d) And further, that the CWFC suspend meetings until such time as the Province clarifies its role in community fluoridation; or until such time as Regional Council reconvenes the Committee;

e) And further, that copies of this resolution be circulated to the Region of York (which receives a portion of their water supply from the Region of Peel), all Ontario municipalities and all Peel-area MPPs.

Thank you

Summer MacGregor

From: Christine Massey
Sent: April 28, 2017 8:21 PM
To: Loh, Lawrence; Polsinelli, Nancy; Sprovieri, John; O'Connor, Patrick; Parrish, Carolyn; Palleschi, Michael; Ras, Karen; Dale, Frank; Tovey, Jim; Downey, Johanna; Groves, Annette; Moore, Elaine; Szwarc, David; Hennings, Jeff
Cc: Ghandour, Victoria; Thomson, Christine; Roth, Julie; Burkiewicz, Justyna
Subject: Re: Response to Formal Complaint 5-17

Dear CWFC Members, Chair Dale, Dr. Loh, Health Commissioner Polsinelli, Mr. Hennings and CAO Szwarc,

Please see Dr. Loh's attached letter of April 6, 2017.

Dr. Loh has failed to provide even one single valid experiment to support the claim made over and over again that industrial waste HFSA dissociates 100% in tap water.

1. As pointed out *in my complaint*, the study by Finney et al is not generalizable to the reality of artificial water fluoridation because 'Nanopure' water is entirely different from tap water. It is de-ionized water devoid of impurities while our tap water has many impurities.

Further, the high grade HFSA used in the study is quite different from the industrial waste HFSA contaminated with various known toxins that the Region added to our water for years. [Since the Region has not provided any published studies on the new HFSA used by the Region, I would assume Finney's HFSA is different from the new acid also.]

All of you should realize that an experiment conducted under one set of conditions cannot scientifically be assumed to reflect what happens under an entirely different set of conditions. It is disturbing that a Medical Officer would cite this study in response to my complaint, *especially since this problem has been pointed out repeatedly*.

2. Urbansky 2002 is a review**,** not a primary study.

3. Further, Commissioner Polsinelli inappropriately dismissed the request I made of Dr. de Villa to provide all studies relied upon to prove that any dissociated HFSA stays dissociated even in acidic conditions such as coffee, tea and GI tracts and in the presence of many contaminants. This was a fair request given that Dr. de Villa repeatedly insisted that residents are not exposed to any HFSA.

Please advise what you intend to do about the glaring lack of evidence on the alleged safety of water fluoridation.

Best wishes,
Christine Massey
Fluoride Free Peel

REFERRAL TO _____
RECOMMENDED
DIRECTION REQUIRED _____
RECEIPT RECOMMENDED ✓_____

On Fri, Apr 7, 2017 at 11:31 AM, Loh, Lawrence <lawrence.loh@peelregion.ca> wrote:

Dear Ms. Massey,

Please find attached correspondence regarding your complaint of March 9, 2017.

Lawrence C. Loh, MD MPH CCFP FRCPC FACPM

Acting Medical Officer of Health

lawrence.loh@peelregion.ca

Region of Peel
Working for you

April 6, 2017

Dear Ms. Massey,

Further to the correspondence you received on April 3, 2017 from Nancy Polsinelli, Commissioner of Health Services in response to your March 9, 2017 complaint, below is my response to your request for information. Specifically, you asked the following "…*please provide all the 'studies' you rely upon when insisting that industrial waste HFSA dissociates 100% in our drinking water and that ph level is the only determining factor*".

As presented at the February 2, 2017 Community Water Fluoridation Committee meeting, Finney et al. (2006) and Urbansky (2002) are studies that support the statement that HFSA dissociates 100 per cent in tap water. The references and links to these studies include:

- Finney, W.F., Wilson, E., Callender, A., Morris, M.D., & Beck, L.W. (2006). Re-examination of hexafluorosilicate hydrolysis by Fluoride NMR and pH measurement. *Environmental Science & Technology*, 40(8), 2572-2577.
- Urbansky, E.T. (2002). Fate of fluorosilicate drinking water additives. *Chemical Reviews*, 102 (8), 2837-2854.

I trust you will find this helpful.

Sincerely,

Lawrence Loh, MD MPH CCFP FRCPC FACPM
Acting Medical Officer of Health

Health Services
PO Box 667 RPO Streetsville, Mississauga, ON L5M 2C2
Tel: 905-799-7700 peelregion.ca

Public Health
Office of the Medical Officer of Health

Inaccurate Information Provided to Council by Regional Staff, Regarding

the Mass Medication of Peel Residents Using Toxic Waste from the Smokestacks of the Phosphate Fertilizer Industry

and

the Unlawfully Closed Fluoridation Session of January 21st, 2016

Christine Massey
Fluoride Free Peel
www.fluoridefreepeel.ca

Hydrofluorosilicic acid (HFSA) is the phosphate fertilizer industry's hazardous waste, added to our tap water and framed by some as "*free dental care for the poor*".

For years, residents have sought from Public Health Staff the toxicological studies needed to show that HFSA is safe for human consumption over a lifetime for all members of our community when added to municipal tap water. No studies have ever been provided, even by NSF.
http://www.fluoridefreepeel.ca/wp-content/uploads/2013/07/Health-Canada-FOI-Response-Letter-June2014.pdf

The Region's Public Health Staff claim there is no need for toxicological studies because HFSA dissociates 100% in drinking water (see this 2014 memo:
http://www.stoppsychotherapytakeover.ca/wp-content/uploads/2016/09/agarewal_8-19-2016_16-19-32.pdf**) and therefore the public do not come in contact with it.**

This assertion is not supported by the scientific literature, including the 2006 Finney et al (Michigan) study cited by Staff: http://www.ncbi.nlm.nih.gov/pubmed/16683594

1975: Westendorf found that under physiological conditions, dissociation of silicafluorides was no more than 66% in the concentration range considered optimum for fluoridated water.

2001: Senior EPA research staff acknowledged that their *"longstanding confidence in the "virtually total" dissociation of SiFs (silicofluorides) may have been misplaced."* **http://fluoridealert.org/studies/westendorf-foreword/**

<u>2006: The Finney et al (Michigan) study cited by Regional Staff used a higher-than-pharmaceutical grade HFSA, AND, high purity deionized water devoid of impurities:</u>
http://www.ncbi.nlm.nih.gov/pubmed/16683594

<u>The Michigan study does not remotely reflect fluoridation in Peel</u>, as pointed out at a Committee meeting to the Regional Medical Officer of Health, Dr. Eileen de Villa, by Councillor Sprovieri.

Further, it has been demonstrated that

- **dissociation depends on a number of factors such as temperature, presence of other substances (metal cations), water hardness and most importantly pH, as shown in the Michigan study, and**

❖ **it has been shown that re-association may occur under acidic pH conditions (see Urbansky, 2002 and Morris, 2004), for example in our gut or in acidic beverages such as tea or coffee prepared using fluoridated water, and**

❖ **Mullenix, in 2014, stressed the potential generation of *"decomposition products with toxicity greater than that of the original compounds"*.**

THIS SLIDE IS FROM DECLAN WAUGH, Chartered Environmental Scientist Chartered Waste Manager, Chartered Water and Environmental Manager

At normal stomach pH range additional peer reviewed studies have found silicon tetrafluoride, (SiF4) acid molecules.

Gabovich RD; "Fluorine in Stomatology and Hygiene"; translated from the original Russian and published in Kazan (USSR); printed by the US Govt Printing Office on behalf of the Dept of Health Education and Welfare. US Public Health Service, National Institute of Dental Health; DHEW pub no (NIH) 78-785, 1977

Roholm K; "Fluorine Intoxication; A Clinical-Hygiene Study"; H. K. Lewis & Co. Ltd, London; 1937

Lewis RJ, jr.; "Hazardous Chemicals Desk Reference": Van Nostrand Reinhold; Fourth Edition.

Matheson Gas Products; 30 Seaview Drive, Secaucus, NJ; "Effects of Exposure to Toxic Gases" and MSDS for CAS # 7783-61-1; created 1/24/89.

Voltaix, Inc.; Material Safety Data Sheet for Silicon Tetrafluoride (SiF4).

Rumyantseva GI et al; "Experimental Investigation of The Toxic Properties of Silicon Tetrafluoride"; *Gig Sanit ;(5):31-33, 1991*

Further, allowed limits of toxins do not ensure safety, rather they take into account the difficulty & expense in keeping toxins at levels that are completely safe.

HFSA's contaminants include arsenic & lead:
http://www.fluoridefreepeel.ca/wp-content/uploads/2013/07/20130705121108426.pdf

An MCLG (Maximum Contaminant Level Goal) is the maximum level in drinking water at which no known or anticipated adverse human health effects would occur. The EPA's MCLG for arsenic & lead is ZERO:
https://www.epa.gov/ground-water-and-drinking-water/table-regulated-drinking-water-contaminants

World Health Organization: "There is no known level of lead exposure that is considered safe."
http://www.who.int/mediacentre/factsheets/fs379/en/

Health Canada: "Because arsenic can cause cancer, every effort should be made to keep arsenic levels in drinking water as low as possible".
http://www.hc-sc.gc.ca/hl-vs/iyh-vsv/environ/arsenic-eng.php

Mullenix, in 2014, stressed the possibility of synergistic effects between various contaminants fostering an underestimation of health risks:

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4090869/pdf/oeh-20-02-157.pdf

Some studies show lead uptake in blood using HFSA:

http://www.fluoridefreepeel.ca/wp-content/uploads/2013/07/Roger-Masters-Bibliography-Publications-on-Silicofluorides.pdf

Questions:

Were these facts discussed at Jan. 21st closed meeting? If not, we want them on record today.

Who is responsible for the Region's determination that toxicology studies are not necessary?

Another Questionable Statement from Staff

Published in the April 2016 fluoridation committee minutes, from non-expert, ALPHA member, Dr. Eileen de Villa:

"...at current levels of fluoride added to the water system, a person would have to drink 15 litres of water, every day for ten years before any potential toxicity concerns (i.e. skeletal fluorosis)."

REBUTTAL

Dr. Hardy Limeback, fluoride toxicity expert, recently retired full professor, head of Preventive Dentistry at University of Toronto, for 18 years, co-author of the NRC's highly regarded 2006 review of fluoride in drinking water:

"..the models estimated that bone fluoride concentrations resulting from lifetime exposure to fluoride in drinking water at 2 mg/L (4,000 to 5,000 mg/kg ash) or 4 mg/L (10,000 to 12,000 mg/kg ash) fall within or exceed the ranges historically associated with stage II and stage III skeletal fluorosis (4,300 to 9,200 mg/kg ash and 4,200 to 12,700 mg/kg ash, respectively).

That means <u>stage II skeletal fluorosis can occur in someone consuming</u>

1. 1 L of 2 ppm Fwater/day
2. 2 L of 1 ppm Fwater/day
3. <u>2.86 L of 0.7 ppm Fwater/day</u>

<u>Dr. de Villa is over-estimating by 5.25 FOLD.</u>
<u>Further, a baby only has to drink an average day's worth of 0.75 L of 0.7 ppm infant formula made with Peel tap water and it would have a very high probability of getting dental fluorosis."</u>

Unlawfully Closed Fluoridation Session: January 21st, 2016

In a legitimate open democracy:

- **the public, media are free to attend, record, report on meetings that affect decision-making of elected officials**
- **able to follow up, hold accountable, challenge, critique any experts, staff, representatives and their statements**
- **NOT required to wait months, make special requests, pay to access information presented, or pay for expenses incurred strictly as a result of Region's unlawful behaviour**

<u>But Regional Staff gave Council inaccurate advice & the meeting was closed.</u>

In reply to a recent FOI request, I've been told that I must pay the Region an estimated fee of over $850 in order to obtain the audio recording of the Region's unbalanced fluoridation meeting of January 21st, even though, according to the *Municipal Act* and the Region's own investigation, the Region unlawfully prevented myself and others from attending said meeting.

Requests:

- **Council question the reliability of info provided by Staff relating to safety, efficacy, legality of fluoridation**

- **Impose an immediate moratorium on fluoridation**

- **Ensure that experts from both sides of fluoridation issue are heard from regarding issues around toxic waste HFSA**

- **Automatically waive/refund all fees associated with the illegally closed Jan. 21st meeting, including FOI request #123-16-317, and including all $5 application fees**

- **Immediately make the Jan. 21st audio recording freely available to the public, along with a written transcript when available, any presentations made during the meeting, and any handouts that were distributed, by posting them on the Region's existing webpage that provides links to Council meeting minutes**

Requests:

- **Council hold accountable whoever is responsible for the illegal closing of the Jan. 21st fluoridation meeting, especially given that the illegality was pointed out to Regional officials ONE WEEK prior to the meeting.**

- **Council hold accountable whoever is responsible for the unbalanced nature of the Jan. 21st fluoridation meeting**

- **Council hold accountable all Staff who have provided false assurances regarding toxic waste HFSA and fluoridation in general, including its alleged safety, efficacy and legality**

- **Council ensure that future meetings, including Committee meetings, and Regional publications on the issue of fluoridation, are BALANCED to include input from BOTH SIDES, and that all existing and future website materials also be BALANCED**

From: Sprovieri, John Councillor [mailto:John.Sprovieri@brampton.ca]
Sent: April 28, 2017 2:12 PM
To: Lockyer, Kathryn
Cc: Parrish, Carolyn; Sprovieri, John
Subject: RE: Community Water Fluoridation

REFERRAL TO _____
RECOMMENDED
DIRECTION REQUIRED _____
RECEIPT RECOMMENDED ✓

Thank you Kathryn.
Can you also place the following issues on the next Community water Fluoridation Committee agenda for discussion.

#1, Staffs assertion that HFSA Disassociates in the drinking water supply.

#1, Health Canada's recommendation that Toxicology Reviews be done on the Fluoridation agents to ensure its safety at the minimum use level.

#2, Staffs assertion that no Toxicology Reviews are necessary because HFSA Dissociates when added to the drinking water supply.

#3, The 1957 Supreme Court ruling that water Fluoridation is a medication.

#4, Who gives Peel Region Council the authority to Force medicate the inhabitants.
John.

John Sprovieri
Regional Councillor for wards 9 & 10
City of Brampton
(905) 874-2610

From: Lockyer, Kathryn [mailto:kathryn.lockyer@peelregion.ca]
Sent: 2017/04/27 3:07 PM
To: Sprovieri, John Councillor <John.Sprovieri@brampton.ca>
Subject: RE: Community Water Fluoridation

Good afternoon Councillor Sprovieri,

Thank you for your email. I draw your attention to the below resolution wherein all requests related to community water fluoridation are being referred to the Committee for determination upon it being reconvened. I have added your request to the list for the Committee.

> Moved by Councillor Parrish,
> Seconded by Councillor Tovey;
>
> Whereas Regional Council passed Resolution 2017-68 on February 9, 2017, on recommendation from the Community Water Fluoridation Committee, to request that the Province of Ontario both test for water toxicity due to the use of hydrofluorisilicic acid (HFSA) and take legislative responsibility for the regulation and administration of HFSA in water fluoridation treatments across the province;
>
> And whereas, Regional Council passed Resolution 2017-185, on March 9, 2017, on recommendation from the Community Water Fluoridation Committee, to both reduce the concentration in Peel's lake-based municipal water supply, adjusting it

to the lowest level in accordance with provincial standards for the prevention of tooth decay, and modify the fluoride additive used in the Region's water supply to reduce the levels of residual components;

And whereas, Resolution 2017-185 also suspended the Committee from meeting again until the Province had responded to the request contained with Resolution 2017-68;

Therefore be it resolved, that the requests for delegation related to community water fluoridation appearing on the Regional Council Agenda for March 30, 2017, and all further requests for delegation, correspondence and requests of any nature from any source on this matter, be referred to the Community Water Fluoridation Committee, when they reconvene, as per the Committee's process, for determination.

Carried

2017-234

Thanks,
Kathryn

Kathryn Lockyer
Regional Clerk and Director
Regional Municipality of Peel
Telephone: 905-791-7800 x4325
Fax: 905-791-1693

From: Sprovieri, John Councillor [mailto:John.Sprovieri@brampton.ca]
Sent: April 27, 2017 8:28 AM
To: Polsinelli, Nancy
Cc: Parrish, Carolyn; Tovey, Jim; Lockyer, Kathryn; ; Sprovieri, John; Moore, Elaine; Palleschi, Michael; Dale, Frank; Downey, Johanna; Groves, Annette; Ras, Karen
Subject: RE: Community Water Fluoridation

Hi Nancy,
I have not received a reply to my request below. Have you received the E Mail and have you located one study that you can provide me that proves Water Fluoridation is safe for people with health problems.
John.

John Sprovieri
Regional Councillor for wards 9 & 10

City of Brampton
(905) 874-2610

From: Sprovieri, John Councillor
Sent: 2017/04/02 8:28 AM
To: Polsinelli, Nancy <nancy.polsinelli@peelregion.ca>
Cc: Parrish, Carolyn <carolyn.parrish@mississauga.ca>; Lockyer, Kathryn <kathryn.lockyer@peelregion.ca>; ; Sprovieri, John Councillor <John.Sprovieri@brampton.ca>
Subject: Re: Community Water Fluoridation

Thank you Nancy.
While I appreciate your suggestion I doubt Dr. Mohanta will come back to answer the questions, just like Dr. Allukian did not accept committees invitation to come back and address some unanswered questions from his presentation to the Council educational workshop.
In any event, the questions need to be answered by someone before Council makes a final decision.
My concern is that if the questions are not addressed and Council decides to continue water fluoridation, we will all end up in court to justify our positions on water fluoridation.
Nancy, you may recall Dr. De Villa's answer some of my questions with, "there are over 400 studies that prove water fluoridation is safe" but never provided any studies for the committee to review. Can you provide me one such study for my review?
Regards, John.

Sent from my BlackBerry 10 smartphone on the Rogers network.

From: Polsinelli, Nancy
Sent: Saturday, April 1, 2017 6:34 PM
To: Sprovieri, John Councillor
Cc: Parrish, Carolyn; Lockyer, Kathryn;
Subject: Re: Community Water Fluoridation

Good Evening Councillor Sprovieri,

Thank you for copying me on this email. I will refer your questions to the Community Water Fluoridation Committee as directed by Council and I suggest that the Committee can decide if they want to invite Dr Mohanta to respond to the questions when it reconvenes.

Kind Regards,

Nancy

Nancy Polsinelli
Commissioner, Health Services
Region of Peel
647-339-6091

Sent from my iPad

On Apr 1, 2017, at 11:00 AM, Sprovieri, John Councillor <John.Sprovieri@brampton.ca> wrote:

Hello Dr. Mohanta,
I hope that you are doing well. I must let you know that I am very disappointed that you have not replied to my message below. I would expect that you being a professional would at least acknowledge my E Mail and perhaps try to correct any information that may be incorrect.
In addition to the last questions, are you aware that the FDA has not approved Fluoride as a mineral Nutrient in the U.S. because no toxicology studies have been done on the substance?
Are you aware that Health Canada has approved Fluoride as Mineral Nutrient even though no Toxicology Studies have been done on the substance. Does that concern you?
As you may recall, I pointed out at the Council meeting that you delegated that Lead, Arsenic and Fluoride have close Toxicity Levels, yet the FDA and Health Canada allows 400 times more Fluoride in our drinking water then Arsenic and 265 times more Fluoride in the drinking water then Lead.
Are you aware that the EPA's ''Public Health Goal''/ Maximum Contaminant Level Goal'' [MCLG] for both Arsenic and Lead is ZERO?
Why do you suppose the EPA has set the Goal for Lead and Arsenic to ZERO? Why is the EPA only concerned about Lead and Arsenic when Fluoride is more Toxic then Lead and slightly less toxic then Arsenic.
Dr. Mohanta, If you are truly concerned about the health and wellbeing of the children and people of Ontario, I hope that you have answers to my questions and that you will share the answers with the Community Water Fluoridation Committee..
Regards, John.

John Sprovieri
Regional Councillor for wards 9 & 10
City of Brampton
(905) 874-2610

From: Sprovieri, John Councillor
Sent: 2017/03/13 2:04 PM
To: 'sanjukta mohanta' ; Johanna Downey <johanna.downey@caledon.ca>; Annette Groves <annette.groves@caledon.ca>; Carolyn Parrish <carolyn.parrish@mississauga.ca>; Karen Ras <karen.ras@mississauga.ca>; jim.tovey@mississauga.ca; Palleschi, Michael - Councillor <Michael.Palleschi@brampton.ca>; frank.dale@mississauga.ca
Cc: Sprovieri, John Councillor <John.Sprovieri@brampton.ca>; 'Rushowy, Kris' <krushowy@thestar.ca>; 'Belgrave, Roger' <RBelgrave@thebramptonguardian.com>; Polsinelli, Nancy <nancy.polsinelli@peelregion.ca>; Loh, Lawrence <lawrence.loh@peelregion.ca>
Subject: RE: Community Water Fluoridation

Hello Dr. Mohanta,
Thank you for your message. Further to the discussion of last Thursday at Peel Region Council, you may recall my comments regarding the 2006 U.S. National Research Council review finding, that Fluoride is most effective when applied topically. The CDC is also on record that Fluoride is most effective when applied topically and not when ingested.
The NRC review also stated that ''Randomized Controlled Trials of the Harmful Effects of Fluoride do not exist. It is unethical to purposely expose humans to any medical treatment with the goal of determining the doses that produce harm.
The Cochrane review found that 97% of the 155 studies were at high risk of bias, which reduces the overall quality of the results. There was also substantial variation between studies in terms of their results.

I also have an audio recording of Dr. Peter Cooney who was Canada's Chief Dental Officer of Health, where he admits that Water Fluoridation reduces cavity rates by less than half a cavity per child / adolescent / permanent teeth.
Should the NRC, the CDC and Dr. Cooney be wrong about the effectiveness of Water Fluoridation, the Province needs to legislate water fluoridation, in order to provide the benefit to the 30% of the population in Ontario that does not have access to Water Fluoridation.
Regards, John.

John Sprovieri
Regional Councillor for wards 9 & 10
City of Brampton
(905) 874-2610

From: sanjukta mohanta
Sent: 2017/03/13 12:32 PM
To: Johanna Downey <johanna.downey@caledon.ca>; Annette Groves <annette.groves@caledon.ca>; Carolyn Parrish <carolyn.parrish@mississauga.ca>; Karen Ras <karen.ras@mississauga.ca>; jim.tovey@mississauga.ca; Palleschi, Michael - Councillor <Michael.Palleschi@brampton.ca>; Sprovieri, John Councillor <John.Sprovieri@brampton.ca>; frank.dale@mississauga.ca
Subject: Community Water Fluoridation

Good Morning

I appreciate the work of the Community Water Fluoridation and for recommending the continuation of water fluoridation in Peel.

Thank you very much for the opportunity to delegate.

The Region of Peel continues to be the envy of others with the oral health programs it supports and the preventive measures it takes to decrease the risk of dental disease.

Thank you very much.

Dr. Sanjukta Mohanta

The Corporation of the Township of Minden Hills

Regular Council

Resolution **May 25, 2017**

Moved by: Lisa Schell

Seconded by: Ron Nesbitt

RECEIVED
May 25, 2017
REGION OF PEEL
OFFICE OF THE REGIONAL CLERK

Be it resolved that Council receive Report #17-019 EPO – Fluoridation of Municipal Water Systems as information.

And further that Council supports the Region of Peel's resolution number 2017-68 requesting the Premier of Ontario, and the Minister of Health and Long Term Care, whose mandate is to protect the health of Ontarians, to:

• undertake appropriate and comprehensive toxicity testing necessary to reassure the public that the use of HFSA in water fluoridation treatments is safe; and

• take legislative responsibility for the regulation and administration of HFSA in water fluoridation treatments across the province relieving local governments from what is a provincial responsibility.

REFERRAL TO _____
RECOMMENDED
DIRECTION REQUIRED _____
RECEIPT RECOMMENDED ✓

Certified under the hand of
The Deputy Clerk and seal of
The Corporation of the
Township of Minden Hills
to be a true copy of resolution 17-288

Dated this 12 day of June 2017

Victoria Bull,
Deputy Clerk, Township of Minden Hills

CARRIED ✓ DEFEATED _____ DEFERRED _____ RECORDED VOTE _____

ABSTAIN	YEA	VOTING	NAY
		ANTHON	
		MURDOCH	
		NESBITT	
		NEVILLE	
		SAYNE	
		SCHELL	
		DEVOLIN	

REEVE

MOTION NO.: 17-288

From: Jim Tovey [mailto:Jim.Tovey@mississauga.ca]
Sent: July 4, 2017 3:16 PM
To: Lockyer, Kathryn
Subject: Re: Notification of Agenda Delivery - July 6, 2017 - Regional Council Meeting

Perfect

Sent from my iPhone

On Jul 4, 2017, at 3:11 PM, Lockyer, Kathryn <kathryn.lockyer@peelregion.ca> wrote:

Good afternoon,

I suggest that this report be added to the list of information, correspondence, etc. that is being accumulated for when the Committee reconvenes. The resolution that all requests for delegation related to community water fluoridation and all correspondence, communications, items and requests of any nature from any source on this matter, be referred to the Community Water fluoridation Committee, when they reconvene, as per the Committee's process, for determination is still in full force and effect. Instead of listing the below item on Thursday's agenda, we will add it to the Committee agenda when it reconvenes. Please confirm that this is satisfactory.

For your information, we have also received a request to delegate on the matter.

Thanks,
Kathryn

REFERRAL TO _____
RECOMMENDED
DIRECTION REQUIRED _____
RECEIPT RECOMMENDED ✓_____

Kathryn Lockyer
Regional Clerk and Director
Regional Municipality of Peel
Telephone: 905-791-7800 x4325
Fax: 905-791-1693

From: Jim Tovey [mailto:Jim.Tovey@mississauga.ca]
Sent: July 2, 2017 1:28 PM
To: Sprovieri, John; Lockyer, Kathryn
Cc: Polsinelli, Nancy; Loh, Lawrence; Szwarc, David; Parrish, Carolyn; Dale, Frank; Downey, Johanna; Palleschi, Michael; Groves, Annette; Ras, Karen; Smith, Janette
Subject: Re: Notification of Agenda Delivery - July 6, 2017 - Regional Council Meeting

Hi Kathryn and Nancy,
Can you please include the study contained in the link below as an item for information related to the "Update-Water Fluoridation" Report.

https://www.scimex.org/__data/assets/file/0017/106523/16399-NHMRC-Fluoride-Information.pdf

Regards,
Councillor Jim Tovey, Ward 1
City of Mississauga
Telephone: 416-989-2255
Email: Jim.tovey@mississauga.ca

On Jul 1, 2017, at 4:02 PM, Sprovieri, John Councillor <John.Sprovieri@brampton.ca> wrote:

Thank you Nancy.
Happy Canada Day to everyone.
John.

John Sprovieri
Regional Councillor for wards 9 & 10
City of Brampton
(905) 874-2610

From: Polsinelli, Nancy [mailto:nancy.polsinelli@peelregion.ca]
Sent: 2017/07/01 11:49 AM
To: Sprovieri, John Councillor <John.Sprovieri@brampton.ca>
Cc: Loh, Lawrence <lawrence.loh@peelregion.ca>; Szwarc, David <david.szwarc@peelregion.ca>; Parrish, Carolyn <carolyn.parrish@mississauga.ca>; Dale, Frank <frank.dale@peelregion.ca>; Downey, Johanna <johanna.downey@caledon.ca>; Palleschi, Michael - Councillor <Michael.Palleschi@brampton.ca>; Groves, Annette <annette.groves@caledon.ca>; Tovey, Jim <jim.tovey@mississauga.ca>; Ras, Karen <karen.ras@mississauga.ca>; Smith, Janette <janette.smith@peelregion.ca>
Subject: Re: Notification of Agenda Delivery - July 6, 2017 - Regional Council Meeting

Good morning Councillor Sprovieri,

We are happy to gather this information for you in time for Thursday's Council meeting. Happy Canada Day!

Regards,

Nancy

Nancy Polsinelli
Commissioner, Health Services
647-339-6091

Sent from my iPhone

On Jul 1, 2017, at 9:54 AM, Sprovieri, John Councillor <John.Sprovieri@brampton.ca> wrote:

Hi Nancy,
According to your attached report, the Region has transitioned from a fluoride additive derived from Phosphate Rock to a fluoride additive derived from Calcium Fluoride. Can you provide me the following documentation for Thursdays Council meeting:
#1, The specifications of the new Fluoridation Agent that Peel has switched to.

#2, The Quality Certificate that is provided by the supplier and certified by NSF.
#3, The Material Safety Data Sheet provided by the manufacturer.
John.

From: Cheema, Reetu (Navreet)
Sent: 2017/06/30 10:32 AM
To: Sprovieri, John Councillor <John.Sprovieri@brampton.ca>
Cc: Garewal, Anahadjeet (Jeet) <Anahadjeet.Garewal@brampton.ca>
Subject: RE: Notification of Agenda Delivery - July 6, 2017 - Regional Council Meeting

Hello Councillor,

There was a report titled “update- Water Fluoridation” in the agenda. Please find the report attached.

Thank-you,

Navreet

From: Sprovieri, John Councillor
Sent: 2017/06/29 9:20 PM
To: Cheema, Reetu (Navreet) <Reetu.Cheema@brampton.ca>
Cc: Sprovieri, John Councillor <John.Sprovieri@brampton.ca>
Subject: FW: Notification of Agenda Delivery - July 6, 2017 - Regional Council Meeting

Hi Navreet,
F.Y.I. Can you check the Regional agenda to see if there is any material on Water Fluoridation.
John.

John Sprovieri
Regional Councillor for wards 9 & 10
City of Brampton
(905) 874-2610

From: ZZG-RegionalClerk [mailto:zzg-regionalclerk@peelregion.ca]
Sent: 2017/06/29 4:41 PM
Subject: Notification of Agenda Delivery - July 6, 2017 - Regional Council Meeting

Please be advised that the agenda packages for the Regional Council meeting scheduled for July 6, 2017 have been uploaded:

Please Note: Bound hard copies of the Community for Life Annual Report related to Item 6.10, Advancement of the Regional Council Strategic Plan, will be provided to Regional Council at the July 6, 2017 Regional Council Meeting.

Please login to your Tempo Box account to download and save the agenda packages:
https://tempobox.peelregion.ca/

Region of Peel staff:
Access the agenda package(s) via EIM

Help and Support for iPad/Mobile Device Access: Kris Dubuque, Legislative Specialist, 905-791-7800 x4369, kris.dubuque@peelregion.ca or contact the Service Desk at 905-791-7800 x4020, Help4020@peelregion.ca.

Please Note: The electronic agenda package will be available online for a total of 7 business days after which time they will be deleted in order to accommodate the next meeting's material. Please ensure that you save the downloaded documents to your device or local drive to ensure access to the agenda and related reports on the meeting date.

Please do not hesitate to contact Ava Macintyre, Manager, Legislative Services, if you have any questions about this program at (905) 791-7800, ext. 4462 or via email at ava.macintyre@peelregion.ca

Thank you.

<ROP AGENDA 2017-07-06- WF.pdf>

From: Christine Massey [redacted]
Sent: July 5, 2017 10:01 AM
To: Lockyer, Kathryn
Subject: Re: Request to Delegate at July 6th Regional Council Meeting

Thank you, Kathryn.

Have you already included the list of questions/issued I previously sent you (i.e. why are the new certificates of analysis not posted, and the old ones are not dated, how is the new chemical manufactured, what are its contaminants and their levels, etc.)?

Also, will you please answer my other questions?

Is the Chair legally obligated to honour her assurance to reconvene if/when "a pile" of delegation requests have been received, and if so, how will she find out when this has happened? Are you going to alert her, and if so, what do you consider to be "a pile"? Are you counting only delegation requests... or also letters, emails.... ?

How often does the Region get "a pile" of delegation requests on any particular topic? Would this be an extremely rare occurrence?

If the Province never "*clarifies its role in community fluoridation*", can anything else ever trigger the Chair or Regional Council to reconvene the Committee now that Council has been prevented from receiving communications on the topic of water fluoridation?

Please note that the MOECC has actually already clarified the province's role to me in an email dated April 9th, 2017. I will paste it below for you. Please include this email from me in your list if you are including emails, since it contains this important email from the province.

Note that the MOHLTC protocol mentioned in this email does not contain any "standards" stating that fluoride in drinking water at *any* concentration prevents cavities or that it is acceptable or legal to degrade water quality by increasing the level of potent regulated contaminants such as fluoride, arsenic, lead, etc. for the purpose of preventing cavities. It simply *"outlines the action(s) required when fluoride levels are below the* [alleged] *therapeutic range... or above the Maximum Acceptable Concentration (MAC)"* in communities reckless enough to illegally fluoridate their drinking water. Also note it contains a different alleged therapeutic range from the technical document mentioned on the Region's website (which also contains no such standards). Is this sufficient to reconvene the CWFC?

Deshpande, Satish (MOECC) <Satish.Deshpande@ontario.ca>
Apr 10
to **Michael**, **Tim**, me

Dear Ms. Massey,

The short answer to your question is that there is no legal provincial standard to add fluoride to the drinking water within the 0.5-0.8 mg/L range. Our “Technical Support

REFERRAL TO _____
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RECEIPT RECOMMENDED ✓ _____

Document for Ontario Drinking Water Standards, Objectives and Guidelines" does recommend a range but we rely on the drinking water system to set the level for fluoride addition.

Here is some general information which might be useful:

The Ministry of the Environment and Climate Change (MOECC) in the Safe Drinking Water Act, 2002 has Ontario Drinking Water Quality Standards (ODWQSs) listed in Ontario Regulation 169/03.

The ODWQS for fluoride is 1.5 mg/L and is based on the protection of dental fluorosis. More information can be obtained from Health Canada's Technical Guideline document for Fluoride in Drinking Water.

The English version of this document can be found at:

https://www.canada.ca/en/health-canada/services/publications/healthy-living/guidelines-canadian-drinking-water-quality-guideline-technical-document-fluoride.html

The basis of the guideline value (ODWQS) for fluoride taken from the above document is:

Moderate dental fluorosis has been chosen as the endpoint of concern for fluoride. It is not considered to be a toxicological end-point because it is not a health concern, but it is significant because it correlates with cosmetic problems. Dental fluorosis is the effect occurring at the lowest level of exposure in the population, and is the most widely and frequently studied of all adverse effects of fluoride.

It should be noted that the role of MOECC is to inspect the performance of drinking water systems for compliance purposes with respect to all operational aspects including fluoridation equipment if it is used. However, it is the Municipality in consultation with its health unit (Board of Health) that has the jurisdiction over the fluoridation of drinking water.

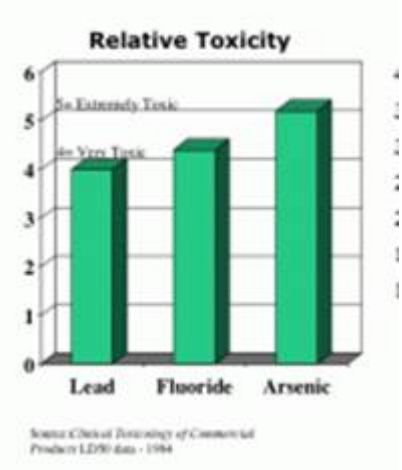
The Ministry of Health and Long-Term Care (MOHLTC) has provided a protocol on fluoridation which municipalities typically consult; it can be found at:

http://www.health.gov.on.ca/en/pro/programs/publichealth/oph_standards/docs/water_fluoride_levels.pdf

The protocol from MOHLTC "…outlines the action(s) required when fluoride levels are below the therapeutic range (TR) of 0.6 to 0.8 ppm or above the Maximum Acceptable Concentration (MAC) of 1.5 ppm (mg/L)." Consequently, MOHLTC considers the therapeutic range to be between 0.6-0.8 mg/L fluoride. The recommended range is considered to be best practice rather than an enforceable (hence legal) standard.

I trust that this information is useful.

Satish Deshpande



Best wishes,
Christine Massey, M.Sc. (Dalla Lana School of Public Health, University of Toronto)

On Wed, Jul 5, 2017 at 8:52 AM, Lockyer, Kathryn <kathryn.lockyer@peelregion.ca> wrote:

Good morning,

I have reviewed the items that have been referred to the Committee for when it reconvenes and note that there are the two delegations from the March meeting that were referred to the Committee and your subsequent request to delegate. No other requests to delegate have been received on this topic.

The resolution referring items to the Committee is broad and includes "…correspondence, communications, items and requests of any nature from any source…" be referred to the Committee. If you have any such items, you can provide them to me and I will add them to the list of items to be referred to the Committee.

Thanks,

Kathryn

Kathryn Lockyer

Regional Clerk and Director

Regional Municipality of Peel

Telephone: 905-791-7800 x4325

Fax: 905-791-1693

From: Christine Massey [redacted]]
Sent: July 4, 2017 10:25 PM
To: Lockyer, Kathryn
Cc: Sprovieri, John; Tovey, Jim; Parrish, Carolyn; Downey, Johanna; Groves, Annette; Palleschi, Michael; Ras, Karen; Dale, Frank
Subject: Re: Request to Delegate at July 6th Regional Council Meeting

Dear Kathryn,

Thank you. I'm confused as to how this is going to work.

Council passed a motion saying that "*.. the Community Water Fluoridation Committee suspend meetings* ***until such time as the Province clarifies its role in community fluoridation; or until such time as Regional Council reconvenes the Committee****;*

And a March 30th motion initiated by the pro-fluoridation CWFC Chair Carolyn Parrish states: *"...that the requests for delegation related to community water fluoridation appearing on the Regional Council Agenda for March 30, 2017, and all further correspondence, communications, items and requests of any nature from any source on this matter,* ***be referred to the Community Water Fluoridation Committee, when they reconvene,*** *as per the Committee's process, for determination."*

Chair Parrish assured Councillor Sprovieri on March 30th that she would reconvene the CWFC when he points out to her that "a pile" of delegation requests have been received, yet this claim is not reflected in any motion that I know of and it's not clear to me how Councillor Sprovieri can be expected to know when "a pile' of requests have been made, or what is meant by "a pile". Is the Chair legally obligated to honour her assurance, and if so, how will Councillor Sprovieri know when "a pile' of requests have been made?

Also, if the Province never "*clarifies its role in community fluoridation*" (which would not be surprising since the province was not asked to "clarify" anything, rather the Health Minister was asked to 1) perform toxicology studies on HFSA and 2) to "*take*" legislative responsibility for the regulation and administration of HFSA... something he will never do since adding HFSA to drinking water violates multiple federal and provincial laws), what else could ever trigger Regional Council to reconvene the Committee given that no one on the face of the planet is allowed to communicate with Council on the topic of water fluoridation and Chair Parrish's stated attitude was that it was "not productive" to even allow the public to ask questions about the mysterious new industrial fluoride acid drug added to their drinking water.

Also, who *is* the public able to communicate with on this topic at the Region? Anyone besides yourself? Or do all communications, even to staff members, Commissioners and the CAO, now get referred to the indefinitely-suspended CWFC?

Best wishes,

Christine

On Tue, Jul 4, 2017 at 8:05 PM, Lockyer, Kathryn <kathryn.lockyer@peelregion.ca> wrote:

Good evening,

I apologize for the lateness of my reply. You are correct, I was on vacation but am now back.

As per the existing Council resolution, I will add your request to delegate to the next meeting of the Community Water Fluoridation Committee when it reconvenes.

Thank you.

Kathryn Lockyer

Regional Clerk

Sent from my iPhone

On Jul 4, 2017, at 6:55 PM, Christine Massey [redacted] wrote:

Hi Curtiss,

The Clerk has not replied to my emails below. Is she on holiday?

Thank you,

Christine

---------- Forwarded message ----------
From: **Christine Massey** [redacted]
Date: Tue, Jul 4, 2017 at 11:08 AM
Subject: Request to Delegate at July 6th Regional Council Meeting
To: "ZZG-Regionalclerk@peelregion.ca" <ZZG-Regionalclerk@peelregion.ca>, "Montesdeoca, Veronica" <veronica.montesdeoca@peelregion.ca>

Dear Kathryn and Veronica,

I wish to delegate to Council on July 6th.

Please let me know if I can do this, as I will need time to prepare.

Christine Massey

Spokesperson

Fluoride Free Peel
905 230 4155

Topic:
Questions regarding Peel's water fluoridation program.

I will need equipment for a formal Powerpoint presentation.

Best wishes,
Christine

On Fri, Jun 30, 2017 at 5:34 PM, Christine Massey [redacted] wrote:

Correction: I wish to delegate to Council on **July 6th**.

On Fri, Jun 30, 2017 at 12:57 PM, Christine Massey [redacted] wrote:

Correction: I wish to delegate to Council on June 6th, as mentioned in my subject line.

On Fri, Jun 30, 2017 at 12:27 PM, Christine Massey [redacted] wrote:

Dear Kathryn and Veronica,

I wish to delegate to Council on March 30th:

Christine Massey

Spokesperson

Fluoride Free Peel
905 230 4155

Topic:
Questions regarding Peel's water fluoridation program.

I will need equipment for a formal Powerpoint presentation.

The Region's website states:

*"Any individual who wishes to appear before a Committee or Council meeting may request to do so by notifying the Regional Clerk's office in writing **or** by completing the Request for Delegation Form"*

Best wishes,
Christine

From: Dobush, Olha
Sent: July 17, 2017 4:36 PM
To: Sprovieri, John
Cc: Loh, Lawrence; Polsinelli, Nancy; Lockyer, Kathryn; Pedra, Inga; Fry, Scott; Fitzpatrick, Sandra
Subject: RE: Studies - Community Water Fluoridation

Good afternoon Councillor Sprovieri,

As requested, please find attached examples of studies demonstrating the effectiveness and safety of community water fluoridation.

While these are the examples of just a few studies, Peel Public Health utilizes a systematic and objective process to review all research evidence. This approach ensures that the highest quality and most relevant evidence is used and that our assessment is based on the totality of evidence.

Please note, that due to copyright laws, we are unable to email PDFs with restricted access. The attached studies are 'open access'. A librarian can assist you, should you be interested in reviewing additional studies that have restricted access.

Sincerely,

Olha Dobush
Director, Chronic Disease and Injury Prevention
Public Health
Region of Peel
905-791-7800 ext. 2617

From: Loh, Lawrence
Sent: July 11, 2017 4:57 PM
To: Sprovieri, John
Cc: John Councillor Sprovieri; Pedra, Inga; Dobush, Olha; Fitzpatrick, Sandra; Fry, Scott; Polsinelli, Nancy
Subject: Re: Community Water Fluoridation

Hi Councillor Sprovieri
A number of studies were used to support our view that CWF is safe. I am copying in the team who can provide you with some PDFs of the key studies and reviews that were used in preparing summaries for your review.
If you have questions or a specific study in mind, don't hesitate
With best,
Lawrence

Sent from my BlackBerry 10 smartphone on the Bell network.

REFERRAL TO _____
RECOMMENDED
DIRECTION REQUIRED _____
RECEIPT RECOMMENDED ✓_____

From: Sprovieri, John Councillor
Sent: Tuesday, July 11, 2017 10:49 PM
To: Loh, Lawrence
Cc: John Councillor Sprovieri
Subject: FW: Community Water Fluoridation

Hello Dr. Loh,
Further to our discussion of last Thursday, below you will see my request to Commissioner Polsinelli to provide me a scientific study that supports Health Canada and Regional medical staff's Claim that Water Fluoridation is safe and effective.
Can you provide me an actual Scientific study and not some reference number for a study.
Regards, John.

John Sprovieri
Regional Councillor for wards 9 & 10
City of Brampton
(905) 874-2610

From: Sprovieri, John Councillor
Sent: 2017/04/27 8:28 AM
To: Polsinelli, Nancy <nancy.polsinelli@peelregion.ca>
Cc: Parrish, Carolyn <carolyn.parrish@mississauga.ca>; 'Jim Tovey' <Jim.Tovey@mississauga.ca>; Lockyer, Kathryn <kathryn.lockyer@peelregion.ca>; sanjuktamohanta@hotmail.com; Sprovieri, John Councillor <John.Sprovieri@brampton.ca>; Moore, Elaine - Councillor <Elaine.Moore@brampton.ca>; Palleschi, Michael - Councillor <Michael.Palleschi@brampton.ca>; Dale, Frank (Frank.Dale@peelregion.ca) <Frank.Dale@peelregion.ca>; Johanna Downey <johanna.downey@caledon.ca>; Annette Groves <annette.groves@caledon.ca>; Karen Ras <Karen.Ras@mississauga.ca>
Subject: RE: Community Water Fluoridation

Hi Nancy,
I have not received a reply to my request below. Have you received the E Mail and have you located one study that you can provide me that proves Water Fluoridation is safe for people with health problems.
John.

John Sprovieri
Regional Councillor for wards 9 & 10
City of Brampton
(905) 874-2610

From: Sprovieri, John Councillor
Sent: 2017/04/02 8:28 AM
To: Polsinelli, Nancy <nancy.polsinelli@peelregion.ca>
Cc: Parrish, Carolyn <carolyn.parrish@mississauga.ca>; Lockyer, Kathryn <kathryn.lockyer@peelregion.ca>; [redacted]; Sprovieri, John Councillor <John.Sprovieri@brampton.ca>
Subject: Re: Community Water Fluoridation

Thank you Nancy.
While I appreciate your suggestion I doubt Dr. Mohanta will come back to answer the questions, just like Dr. Allukian did not accept committees invitation to come back and address some unanswered questions from his presentation to the Council educational workshop.
In any event, the questions need to be answered by someone before Council makes a final decision.
My concern is that if the questions are not addressed and Council decides to continue water fluoridation, we will all end up in court to justify our positions on water fluoridation.
Nancy, you may recall Dr. De Villa's answer some of my questions with, "there are over 400 studies that prove water fluoridation is safe" but never provided any studies for the committee to review. Can you provide me one such study for my review?
Regards, John.

Cochrane Library

Cochrane Database of Systematic Reviews

Water fluoridation for the prevention of dental caries (Review)

Iheozor-Ejiofor Z, Worthington HV, Walsh T, O'Malley L, Clarkson JE, Macey R, Alam R, Tugwell P, Welch V, Glenny AM

Iheozor-Ejiofor Z, Worthington HV, Walsh T, O'Malley L, Clarkson JE, Macey R, Alam R, Tugwell P, Welch V, Glenny AM.
Water fluoridation for the prevention of dental caries.
Cochrane Database of Systematic Reviews 2015, Issue 6. Art. No.: CD010856.
DOI: 10.1002/14651858.CD010856.pub2.

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[Intervention Review]

Water fluoridation for the prevention of dental caries

Zipporah Iheozor-Ejiofor[1], Helen V Worthington[1], Tanya Walsh[2], Lucy O'Malley[2], Jan E Clarkson[3], Richard Macey[2], Rahul Alam[4], Peter Tugwell[5], Vivian Welch[6], Anne-Marie Glenny[1]

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ABSTRACT

Background

Dental caries is a major public health problem in most industrialised countries, affecting 60% to 90% of school children. Community water fluoridation was initiated in the USA in 1945 and is currently practised in about 25 countries around the world; health authorities consider it to be a key strategy for preventing dental caries. Given the continued interest in this topic from health professionals, policy makers and the public, it is important to update and maintain a systematic review that reflects contemporary evidence.

Objectives

To evaluate the effects of water fluoridation (artificial or natural) on the prevention of dental caries.

To evaluate the effects of water fluoridation (artificial or natural) on dental fluorosis.

Search methods

We searched the following electronic databases: The Cochrane Oral Health Group's Trials Register (to 19 February 2015); The Cochrane Central Register of Controlled Trials (CENTRAL; Issue 1, 2015); MEDLINE via OVID (1946 to 19 February 2015); EMBASE via OVID (1980 to 19 February 2015); Proquest (to 19 February 2015); Web of Science Conference Proceedings (1990 to 19 February 2015); ZETOC Conference Proceedings (1993 to 19 February 2015). We searched the US National Institutes of Health Trials Registry (ClinicalTrials.gov) and the World Health Organization's WHO International Clinical Trials Registry Platform for ongoing trials. There were no restrictions on language of publication or publication status in the searches of the electronic databases.

Selection criteria

For caries data, we included only prospective studies with a concurrent control that compared at least two populations - one receiving fluoridated water and the other non-fluoridated water - with outcome(s) evaluated at at least two points in time. For the assessment of fluorosis, we included any type of study design, with concurrent control, that compared populations exposed to different water fluoride concentrations. We included populations of all ages that received fluoridated water (naturally or artificially fluoridated) or non-fluoridated water.

Data collection and analysis

We used an adaptation of the Cochrane 'Risk of bias' tool to assess risk of bias in the included studies.

We included the following caries indices in the analyses: decayed, missing and filled teeth (dmft (deciduous dentition) and DMFT (permanent dentition)), and proportion caries free in both dentitions. For dmft and DMFT analyses we calculated the difference in mean change scores between the fluoridated and control groups. For the proportion caries free we calculated the difference in the proportion caries free between the fluoridated and control groups.

For fluorosis data we calculated the log odds and presented them as probabilities for interpretation.

Main results

A total of 155 studies met the inclusion criteria; 107 studies provided sufficient data for quantitative synthesis.

The results from the caries severity data indicate that the initiation of water fluoridation results in reductions in dmft of 1.81 (95% CI 1.31 to 2.31; 9 studies at high risk of bias, 44,268 participants) and in DMFT of 1.16 (95% CI 0.72 to 1.61; 10 studies at high risk of bias, 78,764 participants). This translates to a 35% reduction in dmft and a 26% reduction in DMFT compared to the median control group mean values. There were also increases in the percentage of caries free children of 15% (95% CI 11% to 19%; 10 studies, 39,966 participants) in deciduous dentition and 14% (95% CI 5% to 23%; 8 studies, 53,538 participants) in permanent dentition. The majority of studies (71%) were conducted prior to 1975 and the widespread introduction of the use of fluoride toothpaste.

There is insufficient information to determine whether initiation of a water fluoridation programme results in a change in disparities in caries across socioeconomic status (SES) levels.

There is insufficient information to determine the effect of stopping water fluoridation programmes on caries levels.

No studies that aimed to determine the effectiveness of water fluoridation for preventing caries in adults met the review's inclusion criteria.

With regard to dental fluorosis, we estimated that for a fluoride level of 0.7 ppm the percentage of participants with fluorosis of aesthetic concern was approximately 12% (95% CI 8% to 17%; 40 studies, 59,630 participants). This increases to 40% (95% CI 35% to 44%) when considering fluorosis of any level (detected under highly controlled, clinical conditions; 90 studies, 180,530 participants). Over 97% of the studies were at high risk of bias and there was substantial between-study variation.

Authors' conclusions

There is very little contemporary evidence, meeting the review's inclusion criteria, that has evaluated the effectiveness of water fluoridation for the prevention of caries.

The available data come predominantly from studies conducted prior to 1975, and indicate that water fluoridation is effective at reducing caries levels in both deciduous and permanent dentition in children. Our confidence in the size of the effect estimates is limited by the observational nature of the study designs, the high risk of bias within the studies and, importantly, the applicability of the evidence to current lifestyles. The decision to implement a water fluoridation programme relies upon an understanding of the population's oral health behaviour (e.g. use of fluoride toothpaste), the availability and uptake of other caries prevention strategies, their diet and consumption of tap water and the movement/migration of the population. There is insufficient evidence to determine whether water fluoridation results in a change in disparities in caries levels across SES. We did not identify any evidence, meeting the review's inclusion criteria, to determine the effectiveness of water fluoridation for preventing caries in adults.

There is insufficient information to determine the effect on caries levels of stopping water fluoridation programmes.

There is a significant association between dental fluorosis (of aesthetic concern or all levels of dental fluorosis) and fluoride level. The evidence is limited due to high risk of bias within the studies and substantial between-study variation.

PLAIN LANGUAGE SUMMARY

Water fluoridation to prevent tooth decay

Background

Tooth decay is a worldwide problem affecting most adults and children. Untreated decay may cause pain and lead to teeth having to be removed. In many parts of the world, tooth decay is decreasing. Children from poorer backgrounds still tend to have greater levels of decay. Fluoride is a mineral that prevents tooth decay. It occurs naturally in water at varying levels. Fluoride can also be added to the water with the aim of preventing tooth decay. Fluoride is present in most toothpastes and available in mouthrinses, varnishes and gels. If young children swallow too much fluoride while their permanent teeth are forming, there is a risk of marks developing on those teeth. This is called 'dental fluorosis'. Most fluorosis is very mild, with faint white lines or streaks visible only to dentists under good lighting in the clinic. More noticeable fluorosis, which is less common, may cause people concern about how their teeth look.

Review question

We carried out this review to evaluate the effects of fluoride in water (added fluoride or naturally occurring) on the prevention of tooth decay and markings on teeth (dental fluorosis).

Study characteristics

We reviewed 20 studies on the effects of fluoridated water on tooth decay and 135 studies on dental fluorosis. The evidence is up to date at 19 February 2015.

Nineteen studies assessed the effects of starting a water fluoridation scheme. They compared tooth decay in two communities around the time fluoridation started in one of them. After several years, a second survey was done to see what difference it made. Around 70% of these studies were conducted before 1975. Other, more recent studies comparing fluoridated and non-fluoridated communities have been conducted. We excluded them from our review because they did not carry out initial surveys of tooth decay levels around the time fluoridation started so were unable to evaluate changes in those levels since then. We reviewed one study that compared tooth decay in two fluoridated areas before fluoridation was stopped in one area. Again, after several years, a second survey was done to see what difference it made.

Around 73% of dental fluorosis studies were conducted in places with naturally occurring - not added - fluoride in their water. Some had levels of up to 5 parts per million (ppm).

Key results

Our review found that water fluoridation is effective at reducing levels of tooth decay among children. The introduction of water fluoridation resulted in children having 35% fewer decayed, missing and filled baby teeth and 26% fewer decayed, missing and filled permanent teeth. We also found that fluoridation led to a 15% increase in children with no decay in their baby teeth and a 14% increase in children with no decay in their permanent teeth. These results are based predominantly on old studies and may not be applicable today.

Within the 'before and after' studies we were looking for, we did not find any on the benefits of fluoridated water for adults.

We found insufficient information about the effects of stopping water fluoridation.

We found insufficient information to determine whether fluoridation reduces differences in tooth decay levels between children from poorer and more affluent backgrounds.

Overall, the results of the studies reviewed suggest that, where the fluoride level in water is 0.7 ppm, there is a chance of around 12% of people having dental fluorosis that may cause concern about how their teeth look.

Quality of the evidence

We assessed each study for the quality of the methods used and how thoroughly the results were reported. We had concerns about the methods used, or the reporting of the results, in the vast majority (97%) of the studies. For example, many did not take full account of all the factors that could affect children's risk of tooth decay or dental fluorosis. There was also substantial variation between the results of the studies, many of which took place before the introduction of fluoride toothpaste. This makes it difficult to be confident of the size of the effects of water fluoridation on tooth decay or the numbers of people likely to have dental fluorosis at different levels of fluoride in the water.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Initiation of water fluoridation compared with low/non-fluoridated water for the prevention of dental caries

Patient or population: people of all ages
Settings: community setting
Intervention: initiation of water fluoridation
Comparison: low/non-fluoridated water

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk in area with low/non-fluoridated water	Risk in area with initiation of water fluoridation				
Caries in deciduous teeth (dmft)[1] Scale from: 0 to 20 (lower = better) Follow-up: range from 3-12 years	The mean dmft at follow-up in the low/non-fluoridated areas ranged from 1.21 to 7.8 (median 5.1)	The mean dmft in the areas with water fluoridation was 1.81 lower (1.31 lower to 2.31 lower)		44,268[2] (9 observational studies)	⊕⊕◯◯[3,4,5,6]	This indicates a reduction in dmft of 35% in the water fluoridation groups over and above that for the control groups We have limited confidence in the size of this effect due to the high risk of bias within the studies and the lack of contemporary evidence
Caries score in permanent teeth (DMFT)[7] Scale from: 0 to 32 (lower better) Follow-up: range from 8-11 years	The mean DMFT at follow-up in the low/non-fluoridated areas ranged from 0.7 to 5.5 (median 4.4)	The mean DMFT in the areas with water fluoridation was 1.16 lower (0.72 lower to 1.61 lower)		78,764[2] (10 observational studies)	⊕⊕◯◯[3,4,5,6]	This indicates a reduction in DMFT of 26% in the water fluoridation groups over and above that for the control groups We have limited confidence in the size of this

					effect due to the high risk of bias within the studies and the lack of contemporary evidence
Change in proportion of caries-free children (deciduous teeth) Scale: 0 to 1 Follow-up: range 3-12 years	The proportion of caries-free children at follow-up in the low/non-fluoridated areas ranged from 0.06 to 0.67 (median 0.22)	The proportion of caries-free children increased in the areas with water fluoridation 0.15 (0.11 to 0.19)		39,966[2] (10 observational studies)	⊕⊕◯◯[3,4,5,6]	We have limited confidence in the size of this effect due to the high risk of bias within the studies and the lack of contemporary evidence
Change in proportion of caries-free children (permanent teeth) Scale: 0 to 1 Follow-up: range 8-12 years	The proportion of caries-free children at follow-up in the low/non-fluoridated areas ranged from 0.01 to 0.67 (median 0.14)	The proportion of caries-free children increased in the areas with water fluoridation 0.14 (0.05 to 0.23)		53,538[2] (8 observational studies)	⊕⊕◯◯[3,4,5,6]	We have limited confidence in the size of this effect due to the high risk of bias within the studies and the lack of contemporary evidence
Disparities in caries by socioeconomic status (SES)[8]				> 35,399[9] (3 observational studies)	⊕⊕◯◯[3]	There is insufficient information to determine whether initiation of a water fluoridation programme results in a change in disparities in caries levels across SES
Adverse effects Dental fluorosis of aesthetic concern[10] (measured by Dean's Index, TFI, TSIF)[11]	For a fluoride level of 0.7 ppm the percentage of participants with dental fluorosis of aesthetic concern was estimated to be 12% (95% CI 8% to 17%) Controlling for study effects, we would expect the odds of dental fluorosis to increase by a factor of 2.90 (95% CI 2.05 to 4.10) for each one unit increase in fluoride level (1 ppm F)			59,630 (40 observational studies)	⊕⊕◯◯[3,12]	The estimate for any level of dental fluorosis at 0.7ppm was 40% (95% CI 35% to 44%; 90 studies). This includes dental fluorosis that can only be detected under clinical conditions and other

			enamel defects We have limited confidence in the size of this effect due to the high risk of bias and substantial between-study variation

⊕⊕⊕⊕: We are very confident that the true effect lies close to that of the estimate of the effect. Further research is very unlikely to change the estimate of effect.
⊕⊕⊕◯: We are moderately confident in the effect estimate. Further research may change the estimate.
⊕⊕◯◯: Our confidence in the effect estimate is limited. Further research is likely to change the estimate.
⊕◯◯◯: We are very uncertain about the estimate.

1. dmft - decayed, missing and filled deciduous teeth
2. Total number of participants measured. Analysis undertaken on average number of participants measured at baseline and follow-up for each study
3. Studies at high risk of bias; quality of the evidence downgraded
4. Substantial heterogeneity present, however, given that the direction of effect was the same in all but on of the studies/ outcomes we did not downgrade due to heterogeneity
5. Indirectness of evidence due to lack of contemporary evidence; quality of the evidence downgraded. 71% of the studies conducted prior 1975; the use of fluoridated toothpaste, the availability of other caries prevention strategies, diet and tap water consumption are all likely to have changed in the populations in which the studies were conducted. No studies on the effect of water fluoridation in adults met the inclusion criteria
6. Very large effect size; quality of the evidence upgraded twice
7. DMFT - decayed, missing and filled permanent teeth
8. SES - socioeconomic status
9. Number of participants not stated in one study
10. Data come from studies of both naturally occurring and artificially fluoridated areas (i.e. not just areas where water fluoridation has been initiated). Dental fluorosis of aesthetic concern only with levels of reported fluoride exposure of 5 ppm or less
11. TFI - Thylstrup-Fejerskov Index: TSIF - Tooth Surface Index of Fluorosis
12. Substantial heterogeneity; quality of the evidence downgraded

BACKGROUND

Description of the condition

Dental caries is a chronic and progressive disease of the mineralised and soft tissues of the teeth. Its aetiology is multifactorial and is related to the interactions over time between tooth substance and certain micro-organisms and dietary carbohydrates, producing plaque acids. Demineralisation of the tooth enamel (non-cavitated dental caries) follows and in the absence of successful treatment, can extend into the dentine and the dental pulp, impairing its function (Ten Cate 1991). Despite reductions in the prevalence and severity of dental caries over time (CDC 2005), social inequalities in dental health persist (OECD 2011), with significant numbers of individuals and communities having a clinically significant burden of preventable dental disease. Dental caries is associated with pain, infection, tooth loss and reduced quality of life (Sheiham 2005). In children, the burden of dental disease also includes lost school time and restricted activity days, as well as problems in eating, speaking and learning. This especially affects those from lower income families owing to their higher prevalence of caries (Feitosa 2005). Given the progressive nature of the condition and widespread prevalence in adulthood, most children are at risk of dental caries.

Dental caries is a major public health problem in most industrialised countries, affecting 60% to 90% of school children (Petersen 2003). It has been estimated that in the USA 42% of children aged between two to 11 years have caries experience in their primary teeth and 59% of those aged 12 to 19 years have caries experience in their permanent teeth (Dye 2007). Prevalence studies in South America, Asia and Europe have indicated that caries may affect between 20% and 100% of the population (Bagramian 2009). Increasing levels of dental caries are observed in some developing countries, especially those where community-based preventive oral care programmes are not established (Petersen 2004). Studies also suggest that the growing retention of teeth has also been accompanied by a rise in dental caries among ageing adults in different parts of the world (Selwitz 2007). This has major implications especially in high-income countries experiencing an increase in life expectancy.

The link between fluoride and the prevention of dental caries dates back to the 1930s. There are many ways in which fluoride can be provided, including toothpastes, gels, varnishes, milk and water. An adverse effect associated with the use of fluoride is the development of dental fluorosis due to the ingestion of excessive fluoride by young children with developing teeth. Dental fluorosis occurs due to the hypomineralisation of the dental enamel caused by the chronic ingestion of sufficiently high concentrations of fluoride while the dentition is still forming (Pendrys 2001). Clinically, the appearance of teeth with fluorosis depends on the severity of the condition. In its mildest form, there are faint white lines or streaks visible only to trained examiners under controlled examination conditions. In more involved cases, fluorosis manifests as mottling of the teeth in which noticeable white lines or streaks often have coalesced into larger opaque areas. In the more severe forms, brown staining or pitting of the tooth enamel may be present and actual breakdown of the enamel may occur (Rozier 1994).

Description of the intervention

Water can be artificially fluoridated (also known as community water fluoridation) through the controlled addition of a fluoride compound to a public water supply (Department of Health and Human Services 2000). Water that is artificially fluoridated is set at the 'optimum level', considered to be around 1 ppm (Dean 1941; WHO 2011). The European Union water quality directive specifies 1.5 ppm as the maximum level for human consumption (European Union 1998). Community water fluoridation was initiated in the USA in 1945 and is currently practiced in about 25 countries around the world (The British Fluoridation Society 2012). Health authorities consider it to be a key strategy for preventing dental caries. In Western Europe around 3% of the population receive water with added fluoride (Cheng 2007), mainly in England, Ireland, and Spain. In the USA, over 70% of the population on public water systems receive fluoridated water (CDC 2008), as do a similar proportion of Australians (NHMRC 2007). The rationale behind the role of community water fluoridation is that it benefits both children and adults by effectively preventing caries, regardless of socioeconomic status or access to care. It is believed to have played an important role in the reductions in tooth decay (40% to 70% in children) and of tooth loss in adults (40% to 60%) in the USA (Burt 1999). Fluoridation is an intervention that occurs at the environmental level, meaning that individual compliance is not relied upon. Interventions at this level can have greater impact upon populations than those at the individual and clinical levels (Frieden 2010), although concerns have been raised around the ethics of 'mass intervention' (Cheng 2007).

Fluoride is also naturally present in the soil, in water and the atmosphere at varying levels depending on geographic location. In areas of Africa, Asia, the Middle East, Southern Europe and the Southern USA, ground waters have been found to contain particularly high concentrations of fluoride, well above the 'optimum level' of 1 ppm. However, while ground waters in some areas can contain high concentrations of fluoride, fluoride content in drinking water in many locations is too low to prevent and control tooth decay.

How the intervention might work

Fluoride impedes the demineralisation of the enamel and also enhances its remineralisation, if it is present in high enough concentrations in the saliva (Ten Cate 1991). This function is very important in caries prevention as the progression of cavities depends on the balance of the demineralisation and remineralisation

processes (Selwitz 2007). The presence of fluoride in drinking water therefore confers the advantage of providing a constant exposure to fluoride ions in the oral cavity. The effectiveness of fluoridated water (McDonagh 2000; Truman 2002), and other fluoride sources, such as toothpastes and varnishes, have previously been documented (Marinho 2013; Walsh 2010). Some adverse effects of fluoridated water that have been explored are widely perceived to be dependent on dose, duration and/or time of exposure (Browne 2005). Within community water fluoridation programmes, maximum fluoride concentrations are set to prevent other harms related to very high fluoride concentrations. Supra-optimal levels of fluoride (occurring naturally) have been linked to severe dental fluorosis and skeletal fluorosis. There is a lack of evidence for other postulated harms such as cancer and bone fractures; no evidence of a strong association with water fluoridation has been shown for these conditions (McDonagh 2000).

Why it is important to do this review

Water fluoridation was identified as a priority topic in the Cochrane Oral Health Group's international priority setting exercise, incorporating views from clinicians, guideline developers and members of the public.

The use of water fluoridation as a means of improving dental health has been endorsed by many national and international health institutions, including the World Health Organization (MRC 2002). It has been hailed by the US Surgeon General as "one of the most effective choices communities can make to prevent health problems while actually improving the oral health of their citizens" (ADA 2013). Opponents have raised concerns about ethical issues and its potential harms (Cheng 2007), as a result of which the practice has remained controversial. A comprehensive systematic review of water fluoridation has previously been published (McDonagh 2000). The review showed a benefit in terms of a reduction in caries as well as an increased risk of dental fluorosis. However, there was insufficient evidence to draw conclusions regarding other potential harms or health disparities. The review findings have often been misinterpreted and have been used to support arguments on both sides of the water fluoridation debate (Cheng 2007). In addition, little comment has been made on the applicability of the evidence to today's society. Many of the caries studies presented in the McDonagh 2000 review were conducted prior to the widespread use of fluoride toothpastes in the late 1970s, and the introduction and uptake of other preventative strategies, such as fluoride varnish. The McDonagh 2000 review was conducted 15 years ago. Given the continued interest in this topic, from both health professionals, policy makers and the public, it is important to update and maintain a systematic review that reflects any emerging, contemporary evidence.

This review updates the McDonagh 2000 review. It aims to contextualise the evidence to inform current national and international guidelines.

It should be noted, the original systematic review had a broader remit and aimed to evaluate the differential effects of natural and artificial fluoridation as well as adverse effects other than dental fluorosis (McDonagh 2000). The inclusion criteria for the objectives covered in this review follow those stated in McDonagh 2000.

OBJECTIVES

To evaluate the effects of water fluoridation (artificial or natural) on the prevention of dental caries.

To evaluate the effects of water fluoridation (artificial or natural) on dental fluorosis.

METHODS

Criteria for considering studies for this review

Types of studies

Water fluoridation for the prevention of dental caries

For caries data, we included only prospective studies with a concurrent control, comparing at least two populations, one receiving fluoridated water and the other non-fluoridated water, with at least two points in time evaluated. Groups had to be comparable in terms of fluoridated water at baseline. For studies assessing the initiation of water fluoridation the groups had to be from non-fluoridated areas at baseline, with one group subsequently having fluoride added to the water. For studies assessing the cessation of water fluoridation, groups had to be from fluoridated areas at baseline, with one group subsequently having fluoride removed from the water.

For the purposes of this review, water with a fluoride concentration of 0.4 parts per million (ppm) or less (arbitrary cut-off defined a priori) was classified as non-fluoridated.

Water fluoridation and dental fluorosis

For the assessment of dental fluorosis, we included any study design, with concurrent control, comparing populations exposed to different water fluoride concentrations.

It should be noted that, due to the nature of the research question, randomised controlled trials are unfeasible.

Types of participants

Populations of all ages receiving fluoridated water (naturally or artificially) and populations receiving non-fluoridated water.

Types of interventions

Water fluoridation for the prevention of dental caries

Caries data: a change in the level of fluoride in the water supply of at least one of the study areas within three years of the baseline survey. Exposure to fluoridated water or non-fluoridated water (less than 0.4 ppm) could be in conjunction with other sources of fluoride (e.g. fluoridated toothpaste), provided the other sources were similar across groups. Where specific information on the use of other sources of fluoride was not supplied, we assumed that populations in studies conducted after 1975 in industrialised countries had been exposed to fluoridated toothpaste.

Water fluoridation and dental fluorosis

Fluoride at any concentration present in drinking water.

Types of outcome measures

Primary outcomes

Any measure of dental caries including the following.

- Change in the number of decayed, missing and filled deciduous, and permanent teeth, (dmft and DMFT, respectively).
- Change in the number of decayed, missing and filled deciduous, and permanent, tooth surfaces (dmfs and DMFS, respectively).
- Incidence of dental caries.
- Percentage of caries-free children.

We also recorded data on disparities in dental caries across different groups of people, as reported in the included studies.
An a priori set of rules regarding the prioritisation of caries measures has been developed previously (Marinho 2013). We would have adopted these, if the data had required.

Secondary outcomes

Dental fluorosis, as measured by the following.

- Percentage of children with fluorosis (any level of fluorosis, or fluorosis of aesthetic concern).
- Dean's Fluorosis Index.
- Tooth Surface Index of Fluorosis (TSIF).
- Thylstrup and Fejerskov index (TFI).
- Modified Developmental Defects of Enamel (DDE).

We aimed to record the prevalence of dental fluorosis for each dentition if reported in the studies. In measuring the percentage prevalence of dental fluorosis, we classified children with dental fluorosis according to the index used in the individual studies. As measured by the common epidemiologic indices for dental fluorosis (Rozier 1994), we classified children with a DDE, TSIF, TFI score greater than zero or Dean's classification of 'questionable' or higher as having dental fluorosis. If other indices had been used, we would have considered and adopted the percentage prevalence of dental fluorosis as reported by the original investigators using other methods (e.g. photographic method or other index). Any dental fluorosis scoring ≥ 3 (TFI), ≥ 2 (TSIF) and 'mild' or worse (Dean's) were considered to be of aesthetic concern. We restricted analysis on dental fluorosis of aesthetic concern to TFI, TSIF and Dean's indices as it is not easily determined from the modified DDE index.
Within the context of this review dental fluorosis is referred to as an 'adverse effect'. However, it should be acknowledged that moderate fluorosis may be considered an 'unwanted effect' rather than an adverse effect. In addition, mild fluorosis may not even be considered an unwanted effect.
We also recorded data on any other adverse effects (e.g. skeletal fluorosis, hip fractures, cancer, congenital malformations, mortality) reported in the included studies. However, this review did not aim to provide a comprehensive systematic review of adverse effects other than dental fluorosis.

Search methods for identification of studies

The original review involved searching a wide range of databases from their starting date to June/October 1999 (Appendix 1). Full details of all the strategies initially used have been published previously (McDonagh 2000).
For the identification of studies included or considered for this updated review, we developed detailed search strategies combining controlled vocabulary and free text terms for each database searched. These were based on the search strategy developed for MEDLINE (Appendix 4) but revised appropriately for each database to take account of differences in controlled vocabulary and syntax rules.

Electronic searches

We searched the following electronic databases (from inception):

- The Cochrane Oral Health Group's Trials Register (to 19 February 2015; see Appendix 2);
- The Cochrane Central Register of Controlled Trials (CENTRAL; *The Cochrane Library* 2015, Issue 1; see Appendix 3);
- MEDLINE via OVID (1946 to 19 February 2015; see Appendix 4);

- EMBASE via OVID (1980 to 19 February 2015; see Appendix 5);
- Proquest (all databases; to 19 February 2015; Appendix 6);
- Web of Science Conference Proceedings (1990 to 19 February 2015; see Appendix 7);
- ZETOC Conference Proceedings (1993 to 19 February 2015; see Appendix 8).

There were no restrictions on language of publication and non-English studies were translated, unless a translator could not be found through Cochrane.

Searching other resources

We searched the following databases for ongoing trials (see Appendix 9):

- US National Institutes of Health Trials Register (clinicaltrials.gov to 19 February 2015);
- The WHO Clinical Trials Registry Platform (apps.who.int/trialsearch/default.aspx to 19 February 2015).

Only handsearching conducted as part of the Cochrane Worldwide Handsearching Programme and uploaded to CENTRAL was included (see the Cochrane Masterlist for the details of journals searched to date). We reviewed the reference lists of identified trials and review articles for additional appropriate studies.

Data collection and analysis

Selection of studies

Two review authors independently and in duplicate screened the titles and abstracts (when available) of all reports identified through the electronic search update. We obtained the full report for all studies that appeared to meet the inclusion criteria, or for which there were insufficient data in the title and abstract to make a clear decision. Two review authors independently assessed the full reports obtained from the electronic and other methods of searching to establish whether or not the studies met the inclusion criteria. Disagreements were resolved by discussion. Where resolution was not possible, a third review author was consulted. Studies rejected at this or subsequent stages were recorded in the 'Characteristics of excluded studies' table, and reasons for their exclusion recorded.

Data extraction and management

Two review authors extracted data independently using specially designed data extraction forms (produced in Excel). We piloted the data extraction forms on several papers and modified them as required before use. Any disagreements were discussed and a third review author consulted where necessary.
For each study we aimed to record the following data.

- Year of publication, country of origin and source of study funding.
- Details of the participants including demographic characteristics (socioeconomic status (SES), ethnicity), age, deciduous/permanent dentition and criteria for inclusion and exclusion.
- Details of the type of intervention, comparator and co-interventions.
- Details of the outcomes reported, including method of assessment, and time intervals.
- Details of confounding factors considered (potential confounders of relevance to this review include sugar consumption/dietary habits, SES, ethnicity and the use of other fluoride sources).
- Details on comparability of groups with regard to confounding factors.
- Details on methods used to control for confounding.
- Details regarding both unadjusted and adjusted effect estimates.

Assessment of risk of bias in included studies

McDonagh 2000 used specially designed validity assessment checklists that provided a 'validity score' and assigned a 'level of evidence' for each study. In this update, we aimed to assess all included studies (including those from the previous review by McDonagh 2000) for risk of bias using the Cochrane 'Risk of bias' assessment tool adapted for non-randomised controlled studies (Higgins 2011). The domains assessed for each included study included: sampling, confounding, blinding of outcome assessment, completeness of outcome data, risk of selective outcome reporting and risk of other potential sources of bias. We did not include random sequence generation or allocation concealment, as these were not relevant for the study designs included and are covered by the domain for confounding. We had identified the following factors as important confounders for the primary and secondary outcomes: sugar consumption/dietary habits, SES, ethnicity and the use of other fluoride sources.
We tabulated a description of the 'Risk of bias' domains for each included trial, along with a judgement of low, high or unclear risk of bias.
We undertook a summary assessment of the risk of bias for the primary outcome (across domains) across studies (Higgins 2011). Within a study, we gave a summary assessment of low risk of bias when there was a low risk of bias for all key domains, unclear risk of bias when there was an unclear risk of bias for one or more key domains, and high risk of bias when there was a high risk of bias for one or more key domains.

Measures of treatment effect

We included the following caries indices in the analyses: dmft, DMFT, and proportion caries free in both dentitions. For dmft

and DMFT analyses we calculated the difference in mean change scores between fluoridated and control groups. For the proportion caries free, we calculated the difference in the proportion caries free between the fluoridated and control groups.
For dental fluorosis data we calculated the log odds and presented them as probabilities for interpretation.
We have presented data on other adverse effects, reported in the included studies, as a narrative.
We intended to present data on both adjusted and unadjusted results, but the data allowed only for unadjusted values.

Dealing with missing data

Where outcome data were missing from the published report, or could not be calculated from the information presented in the report of a trial, we attempted to contact the authors to obtain the data and clarify any uncertainty. The analyses generally included only the available data (ignoring missing data). When the number of participants evaluated was not reported, we did not include outcome data in the analyses. Where standard deviations were missing for DMFT and dmft data we used the equation: log(SD) = 0.17 + 0.56 x log(mean) to estimate the standard deviations for both the before and after mean caries values. This equation was estimated from available data where the standard deviations were given (R^2 = 0.91; Appendix 10). We undertook no other imputations.
We undertook sensitivity analyses to determine the effect of the imputed standard deviations.

Assessment of heterogeneity

We planned to explore differences in fluoridation technique, fluoride concentration, outcome measurement index and technique as possible sources of heterogeneity. Initial consideration of heterogeneity would be via the DerSimonian-Laird model (commonly referred to as a random-effects meta-analysis). When between study variance was deemed to be both robustly estimated and substantial (judged as the estimate being larger than twice its standard error), we favoured the random-effects model over a fixed-effect approach. We would have investigated any heterogeneity further via Baujat and normal quantile-quantile (Q-Q) plots, alongside influence diagnostics (for example **dif**ference in **fit**ted values (DFFITS), Cook's distance, hat values and leave-one-out methods) as appropriate. However, due to the limited data and lack of clarity in reporting we were unable to undertake any of these analyses for the caries data. Fluoride concentration was explored as part of the fluorosis analysis.

Assessment of reporting biases

If more than 10 trials had been identified for any meta-analysis of the primary outcome caries, we would have assessed publication bias according to the recommendations described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Had asymmetry been identified in the contour-enhanced funnel plots, we would have investigated possible causes. The number of studies presented in each caries meta-analyses precluded this.

Data synthesis

The primary analyses was based on all included studies, irrespective of risk of bias.

Caries

For the analyses of mean dmft and DMFT severity data, we used Review Manager (RevMan 2014; not shown) to calculate weighted (for age) mean change score for water fluoridation and control group separately, and the summary effect estimates across all age groups for each study (we only analysed data for dmft for children eight years and younger). The resulting effect estimates for the water fluoridation and control groups were then entered into RevMan for each study to calculate the mean difference in change scores for the review (see Analysis 1.1; Analysis 1.2). We decided to display this data using the average n for the before and after data for each study to give an indication of the size of the studies. The raw data and summary statistics are shown in Table 1; Table 2.
Where standard deviations (SDs) are missing for the dmft, DMFT data we used the equation: log(SD) = 0.17 + 0.56 x log(mean) to estimate the SDs for both before and after mean caries values. We undertook a sensitivity analysis omitting all the data for studies/age groups where the standard deviation was imputed.
For the caries free data for both dentitions, we calculated the risk differences in RevMan (not shown) for water fluoridation and control groups separately, for each study, undertaking a meta-analyses across age groups. These summary effect estimates and standard deviations were then combined in a meta-analysis in RevMan (not shown) as continuous data to provide summary estimates of the change in the proportion caries free for both groups. For each dentition (rather than age group), we then combined the resulting data as a meta-analysis in the review. Once again we decided to display this data using the average n for the before and after data for each study to give an indication of the size of the studies. Table 3 and Table 4 provide the raw data and summary estimates of the risk differences for each water fluoridation and control group separately, for each study, across age groups.

Fluorosis

In line with the previous systematic review (McDonagh 2000), the primary analysis was carried out on data where fluoride exposure was 5 ppm or less, for reasons of applicability and robustness of evidence (the concentration of most naturally occurring fluoride will be below than this threshold, and the paucity of information from higher exposures leads to less precise estimates). We analysed

two aspects of fluorosis: aesthetic concerns of fluorosis (as defined in Types of outcome measures), and any level of fluorosis. We used random-effects models with random intercept and random slope to model the log odds of fluorosis as a function of fluoride exposure. In this model we allowed the intercept and slope to vary from study to study. The slope of the linear relationship between fluoride level (the predictor) and the log odds of fluorosis is the value of the coefficient for fluoride level plus the study specific random effect for that specific study. Fluoride exposure was centred upon the grand mean, and results presented as probabilities to aid interpretation.

Subgroup analysis and investigation of heterogeneity

We undertook subgroup analyses according to whether data were collected prior to the widespread use of fluoride toothpaste, or after: we used a cut-off of 1975 for this purpose. We made the decision to undertake subgroup analyses by date of study conduct post hoc, following peer review comments.

We had planned to use meta-regression to investigate and explain sources of heterogeneity among studies where possible (potential confounders of relevance to this review include sugar consumption/dietary habits, SES, ethnicity and the use of other fluoride sources). Dental caries results were to be analysed using meta-regression in order to assess the impact of potential sources of heterogeneity and estimate the underlying effect of water fluoridation. We also planned to conduct subgroup analyses by study design. However, due to the small number of studies and lack of clarity in the reporting within the caries studies, we did not undertake these sub-group analyses

Sensitivity analysis

We would have undertaken sensitivity analyses based on risk of bias if sufficient trials had been included. We had planned to undertake further sensitivity analyses to determine if the results of the meta-analysis were influenced by the timing of baseline measurement, as appropriate. We did undertake sensitivity analyses to determine the effect of the imputed standard deviations.

Presentation of main results

We assessed the quality of the evidence for the primary and secondary outcomes for this review using GRADE methods (gdt.guidelinedevelopment.org). Due to the observational nature of the studies included in the review, GRADE stipulates that the quality of the body of evidence starts at 'low'. We considered subsequent downgrading of the quality of the body of evidence with reference to the overall risk of bias of the included studies, the directness of the evidence, the inconsistency of the results and the precision of the estimates. We considered upgrading the quality of the evidence on the basis of an assessment of the risk of publication bias, the magnitude of the effect and whether or not there was evidence of a dose response.

We presented the results and quality of evidence for each outcome in a 'Summary of findings' table. We made a post hoc decision not to use the GRADE terminology of high, moderate, low and very low to describe the quality of the evidence (see Quality of the evidence).

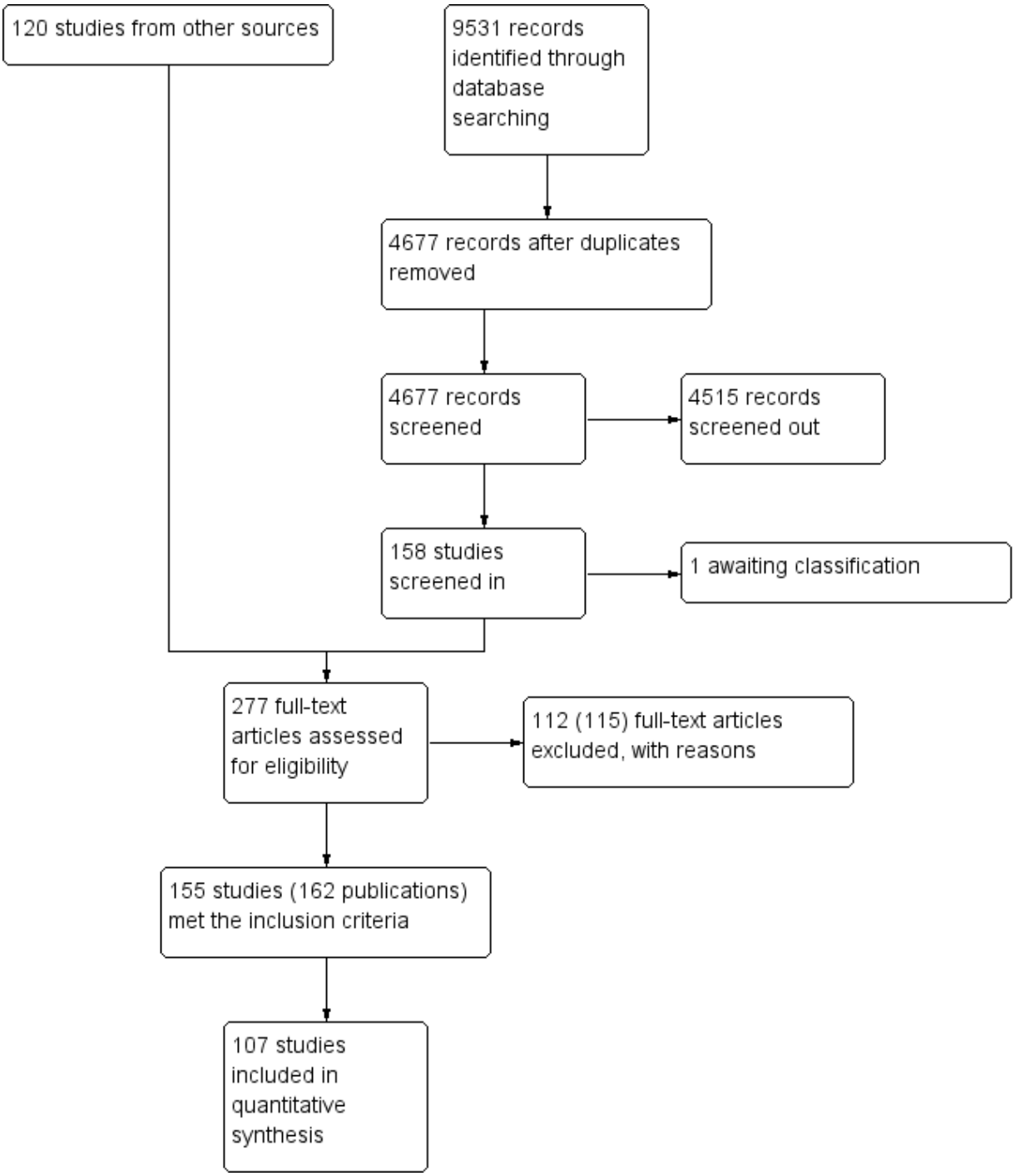
RESULTS

Description of studies

Results of the search

The search for literature produced a total of 4677 records after de-duplication. Two reviewers in duplicate screened these records independently. Any disagreements were resolved by a third reviewer. After this initial screening, we obtained 158 articles, combined with 120 articles from additional sources (including McDonagh 2000; NHMRC 2007 and an unpublished paper, Blinkhorn (unpublished)) and read them in detail. We assessed 277 of these 278 articles for eligibility; 155 studies (162 publications) met the inclusion criteria for the review. However, only 107 studies (15 caries studies; 92 studies reporting data on either all fluorosis severities or fluorosis of aesthetic concern) presented sufficient data for inclusion in the quantitative syntheses. One study awaits classification. The search, screening results and selection of included studies are illustrated in the PRISMA flow diagram (Figure 1).

Figure 1. Figure 1. Study flow diagram.



Included studies

A total of 20 prospective observational studies provided data on caries or disparities in caries, or both (Adriasola 1959; Arnold 1956; Ast 1951; Backer-Dirks 1961; Beal 1971; Beal 1981; Blinkhorn (unpublished); Brown 1965; DHSS England 1969; DHSS Scotland 1969; DHSS Wales 1969; Gray 2001; Guo 1984; Hardwick 1982; Holdcroft 1999; Kunzel 1997; Loh 1996; Maupome 2001; Pot 1974; Tessier 1987).

Caries

Nineteen prospective observational studies (22 publications) published between 1951 and 2015 met the inclusion criteria for the caries outcome. Eighteen of these studies looked at the effect of the initiation of water fluoridation programme on dental caries (Adriasola 1959; Arnold 1956; Ast 1951; Backer-Dirks 1961; Beal 1971; Beal 1981; Blinkhorn (unpublished); Brown 1965; DHSS England 1969; DHSS Scotland 1969; DHSS Wales 1969; Gray 2001; Guo 1984; Hardwick 1982; Kunzel 1997; Loh 1996; Pot 1974; Tessier 1987), and one study focused on the effect of cessation of fluoridation on caries (Maupome 2001). Only one study followed the same participants over time (Hardwick 1982), evaluating 12-year old children in a fluoridated and a non-fluoridated area and following them for four years. All other studies evaluated specific age groups within three years of a change in fluoridation status and undertook a follow-up evaluation of the same age groups (different children) at at least one other time point. A low/non-fluoridated area was used as a control. These have been analysed as controlled before-and-after studies.

The studies were conducted in multiple centres in Europe (Backer-Dirks 1961; Beal 1971; Beal 1981; DHSS England 1969; DHSS Scotland 1969; DHSS Wales 1969; Gray 2001; Hardwick 1982; Kunzel 1997; Pot 1974), North America (Arnold 1956; Ast 1951; Brown 1965; Maupome 2001; Tessier 1987), South America (Adriasola 1959), Australia (Blinkhorn (unpublished)) and Asia (Guo 1984; Loh 1996). Five studies were funded by research grants from research organisations, health authorities and government organisations (Beal 1971; Blinkhorn (unpublished); Booth 1991; Kunzel 1997; Maupome 2001), one study was funded in collaboration with members of the committee pro-fluoridation (Adriasola 1959), while the other studies did not state their funding sources. Participants, aged from three to 16 years, were mostly recruited from schools; the period of time between baseline and final measurement ranged from two to 12 years.

The intervention groups in all 'fluoride initiation' studies were exposed to naturally low fluoride at baseline and artificially fluoridated water at follow-up, while the control groups were exposed to naturally low fluoride at both time points. In studies where it was not stated clearly, fluoride concentration was reported as 'high' or 'fluoridated' for the intervention group and 'low' or 'non-fluoridated' for the control group. For the 'fluoride cessation' study that met our inclusion criteria, the intervention group was exposed to artificially fluoridated water at baseline and naturally low fluoride at follow-up, while the control group remained artificially fluoridated at both time points.

Measures of dental caries reported were dmft (decayed missing and filled deciduous teeth), DMFT (decayed missing and filled permanent teeth), DMFS (decayed missing and filled surfaces in permanent teeth), and proportion of caries-free children (deciduous and permanent dentition).

Disparities in caries

Three prospective observational studies (four publications) met the inclusion criteria for disparities in caries but did not provide data suitable for analysis (Beal 1971; Gray 2001; Holdcroft 1999). They all assessed the effect of the initiation of water fluoridation on caries in different SES groups receiving fluoridated and non-fluoridated water. All three studies evaluated specific age groups within three years of a change in fluoridation status and undertook a follow-up evaluation of the same age groups (different children) at a least one other time point. A low/non-fluoridated area was used as a control. All these studies were conducted in the UK. Caries measures reported were decayed, extracted and filled deciduous teeth (deft; Beal 1971), dmft (Gray 2001; Holdcroft 1999), and percentage of caries-free children (Beal 1971; Gray 2001).

Dental fluorosis

For dental fluorosis, 135 studies were included. These were published between 1941 and 2014. Of these studies, 28% were conducted in Europe, 23% in Asia, 19% in North America, 13% in South America, 10% in Africa, 5% in Australia and 2% in multiple centres in Europe and Asia. Forty-four studies were supported by research grants from government organisations and health authorities, non-governmental organisations, research organisations, universities or a combination of these sources (Adair 1999; Alarcon-Herrera 2001; AlDosari 2010; Angelillo 1999; Awadia 2000; Azcurra 1995; Bao 2007; Butler 1985; Chen 1989; Clark 1993; Correia Sampaio 1999; de Crousaz 1982; Garcia-Perez 2013; Hernandez-Montoya 2003; Ibrahim 1995; Indermitte 2007; Indermitte 2009; Kanagaratnam 2009; Kumar 1999; Kumar 2007; Mackay 2005; Mandinic 2010; Milsom 1990; Nanda 1974; Narwaria 2013; Nunn 1992; Pontigo-Loyola 2008; Ray 1982; Riordan 2002; Ruan 2005; Rwenyonyi 1999; Skinner 2013; Stephen 2002; Szpunar 1988; Tsutsui 2000; Vilasrao 2014; Villa 1998; Vuhahula 2009; Wang 1999; Wang 2012; Warren

2001; Whelton 2004; Whelton 2006; Wondwossen 2004); six studies were funded by: a sugar association (McInnes 1982), a water company (Firempong 2013; Warnakulasuriya 1992), the dental industry (Machiulskiene 2009; Wenzel 1982), or associated with a dental industry through authorship (McGrady 2012). Sources of support were not explicitly stated in 86 studies. One study explicitly stated that no funding had been obtained (Shanthi 2014).

Out of the 135 studies that met the inclusion criteria for fluorosis we aimed to extract cross-sectional data. Ninety studies reported sufficient data for inclusion in the analysis for all severities of dental fluorosis (Appendix 11). Forty studies were included in the analysis for fluorosis of aesthetic concern (Appendix 11). The remaining studies did not report sufficient data for inclusion in the analysis, typically due to failure to indicate water fluoride concentration of the study areas or reporting inappropriate measure of fluorosis (e.g. mean value or Community Fluorosis Index (CFI)). Where studies reported fluorosis outcomes as CFI only, we could not use the data. The CFI is a composite score calculated by summing the scores of Dean's Index and dividing the total by the sample size. This gives an indication of the experience and severity of fluorosis at a population level, but individual level data cannot be derived from it alone.

Dean's index, TFI, TSIF, DDE were reported in 41%, 19%, 10%, 6% of the included studies, respectively, while 23% of the studies either reported on other indices, specific enamel defects, or did not state the index used at all.

Other adverse effects

Five studies that reported on the dental fluorosis outcome also presented data on other adverse effects associated with water fluoridation (Table 5). The outcomes reported were skeletal fluorosis (Chen 1993; Jolly 1971; Wang 2012), bone fracture (Alarcon-Herrera 2001), and skeletal maturity (Wenzel 1982). Outcomes were assessed in participants using radiographs (Chen 1993; Jolly 1971; Wenzel 1982), the diagnostic criteria of endemic skeletal fluorosis (WS 192-2008; Wang 2012), or methods that were not clearly stated (Alarcon-Herrera 2001).

Excluded studies

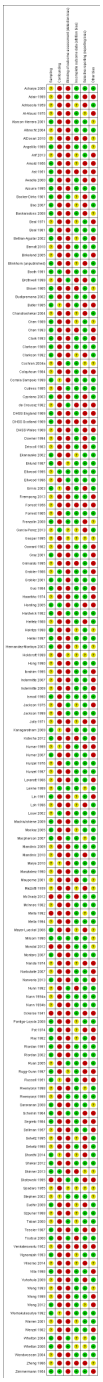
Of the 277 studies that were assessed for eligibility, we excluded 112 studies (115 publications; see Characteristics of excluded studies). The reasons for exclusion were most frequently due to inappropriate study design, including:

- absence of data from two time points for one or both study groups (Agarwal 2014; Ajayi 2008; Aldosari 2004; Antunes 2004; Archila 2003; ARCPOH 2008; Armfield 2004; Armfield 2005; Arora 2010; Bailie 2009; Baldani 2002; Baldani 2004; Binbin 2005; Blagojevic 2004; Bradnock 1984; Carmichael 1980; Carmichael 1984; Carmichael 1989; Evans 1995; Gillcrist 2001; Gushi 2005; Han 2011; Jones 1997; Jones 2000a; Jones 2000b; Kirkeskov 2010; Kumar 2001; Lee 2004; Peres 2006; Provart 1995; Rihs 2008; Riley 1999; Rugg-Gun 1977; Sagheri 2007; Sales-Peres 2002; Saliba 2008; Sampaio 2000; Slade 2013; Tagliaferro 2004; Tiano 2009; Tickle 2003; Zimmermann 2002);
- unsuitable control group (Attwood 1988; Hobbs 1994; Kalsbeek 1993; Seppa 1998; Wragg 1999; Murray 1984; Murray 1991);
- absence of concurrent control group (Buscariolo 2006; Kunzel 2000a; Wong 2006).

Risk of bias in included studies

The review authors' judgements about each risk of bias item for each included study is summarised in Figure 2.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Caries outcome

We judged that all the 20 studies included for the caries outcome (including disparities in caries) were at high risk of bias overall. The bias may occur in either direction.

Sampling

We judged 13 of the studies as being at low risk of bias in terms of sampling (Arnold 1956; Ast 1951; Backer-Dirks 1961; Beal 1981; Blinkhorn (unpublished); Brown 1965; DHSS England 1969; DHSS Scotland 1969; Gray 2001; Guo 1984; Hardwick 1982; Pot 1974; Tessier 1987). For these studies, sampling was achieved either randomly or by including the entire eligible population of the study area. We judged seven studies to be at unclear risk of bias for sampling (Adriasola 1959; Beal 1971; DHSS Wales 1969; Holdcroft 1999; Kunzel 1997; Loh 1996; Maupome 2001). This judgement was based on insufficient or unavailable information in most cases, however in the study by Kunzel 1997, there was an unexplained exclusion of disabled children. In the DHSS Scotland 1969 study, different age criteria were used for each group resulting in an imbalance between the groups; the reason for this was not explained. No studies were found to be at high risk for selection bias for this outcome.

Confounding

We found all studies to be at high risk of bias for confounding. We considered confoundng factors for this outcome to be sugar consumption/dietary habits, SES, ethnicity and the use of other fluoride sources. We would have judged studies to be at low risk of confounding bias only if they had successfully controlled for all factors. Six of the studies attempted to control for none of these factors (Adriasola 1959; Ast 1951; Brown 1965; Guo 1984; Loh 1996; Pot 1974). Eight controlled for SES, but not for other sources of fluoride or for dietary habits (Arnold 1956; Backer-Dirks 1961; Beal 1971; Beal 1981; DHSS England 1969; DHSS Scotland 1969; DHSS Wales 1969; Gray 2001). Hardwick 1982 matched for SES and reported the use of fluoride from other sources to be broadly similar across groups, but did not report on dietary habits. Maupome 2001 reported on dietary habits and the use of fluoride from other sources; this study showed that dietary habits did not confound the relationship between water fluoridation and caries.

Detection bias

The majority of the studies did not blind outcome assessors. This is perhaps unsurprising when considering the efforts that may be required to blind assessors for this type of study. We judged only two studies to be at low risk of bias for this domain (Backer-Dirks 1961; Hardwick 1982). Backer-Dirks 1961 utilised radiographs in order to blind assessors, and in the Hardwick 1982 study children were brought to a central examination centre for assessment.

Incomplete outcome data

Eight studies were judged as being at low risk of bias (Beal 1971; Beal 1981; Brown 1965; Gray 2001; Guo 1984; Hardwick 1982; Kunzel 1997; Maupome 2001), or unclear risk of bias for the domain of incomplete outcome data (Adriasola 1959; Arnold 1956; Backer-Dirks 1961; Beal 1971; Blinkhorn (unpublished); Holdcroft 1999; Loh 1996; Pot 1974). We found four studies to be at high risk. In two studies (Ast 1951; Maupome 2001), the outcome data for participants was substantially lower than at baseline. The Brown 1965 study, which ran from 1948 to 1959, sampled and examined children aged six to eight years up until 1957, but ceased this activity after 1957 as no significant differences were found to exist in that age group. The DHSS Scotland 1969 study did not present data for all children examined.

Selective reporting

We found 11 of the studies to be at high risk of bias for selective reporting. Four studies recorded data on dental fluorosis, but this was not reported (Arnold 1956; DHSS England 1969; DHSS Scotland 1969; DHSS Wales 1969). Six studies did not report standard deviations (Arnold 1956; Blinkhorn (unpublished); DHSS England 1969; DHSS Wales 1969; Kunzel 1997; Tessier 1987), and Adriasola 1959 did not report complete baseline data for the proportion of caries-free children aged six, seven, 11 and 15 years. Eight studies were found to be at low risk of bias for this domain with all expected data having been reported (Beal 1971; Beal 1981; Brown 1965; Gray 2001; Guo 1984; Hardwick 1982; Kunzel 1997; Maupome 2001). For one study the risk of bias remains unclear (Holdcroft 1999).

Other bias

We found 12 studies to be at high risk of other bias; for ten of these studies this was due to an apparent lack of reliability or consistency of the outcome assessments in terms of either calibration of examiners or tests for inter- and intra-rater reliability (Arnold 1956; Ast 1951; Beal 1971; DHSS England 1969; DHSS Scotland 1969; DHSS Wales 1969; Gray 2001; Guo 1984; Pot 1974; Tessier 1987). In the Gray 2001 study the baseline fluoridation status of the children was determined by the location of the school they attended, which may not have taken into account any children attending schools in fluoridated areas who residede outside those areas. We assessed four studies as being at unclear risk of bias (Beal 1981; Brown 1965; Holdcroft 1999; Maupome

2001). The remaining six studies were not assessed as having any other apparent risk of bias.

Dental fluorosis outcome

Of the 135 studies included for this outcome, we found 131 to be at high risk of bias and four to be at unclear risk overall (Ellwood 1995; Levine 1989; Milsom 1990; Stephen 2002). We judged no studies as being at low risk.

We assessed five studies as being at high risk for sampling bias, 60 as being at low risk of bias and the remainder as 'unclear'. We found the majority of studies (114) to be at high risk for confounding; we assessed 11 as being at low risk of bias for this domain. For detection bias, we assessed 103 as being at high risk of detection bias, and 15 at low risk of bias. Overall, we found studies to be at low risk of bias for incomplete outcome data (92), with only 12 assessed as being at high risk of bias. For selective reporting, we assessed 42 as being at high risk of bias, with 82 at low risk of bias. With regard to other bias, we assessed 48 studies as being at high risk, 66 at low risk and all others at unclear risk. In most cases the reason for studies having high risk of other bias was that they did not report on the reliability or consistency of the outcome assessments.

Effects of interventions

See: **Summary of findings for the main comparison**; **Summary of findings 2**

Caries

Nineteen studies met the inclusion criteria (18 fluoride initiation studies and one fluoride cessation studies), with 15 providing sufficient data for analysis of caries levels following a change in fluoridation status. Only one of these studies examined the effect of water fluoridation on adults (Pot 1974); the reported outcome for this study was the percentage of participants with dentures. There are no data to determine the effect of water fluoridation on caries levels in adults.

Four studies provided insufficient data for analysis (Backer-Dirks 1961; DHSS Scotland 1969; Loh 1996; Pot 1974).

Initiation of water fluoridation

The caries studies are presented in forest plots, sub-grouped according to when they were conducted (those conducted in 1975 or before, and those conducted after 1975; Figure 3; Figure 4; Figure 5; Figure 6). Given the limited data post-1975 and this being a post-hoc analysis, the results presented below are for the overall body of evidence for each outcome.

Figure 3. Initiation of water fluoridation compared with low/non-fluoridated water: change in dmft

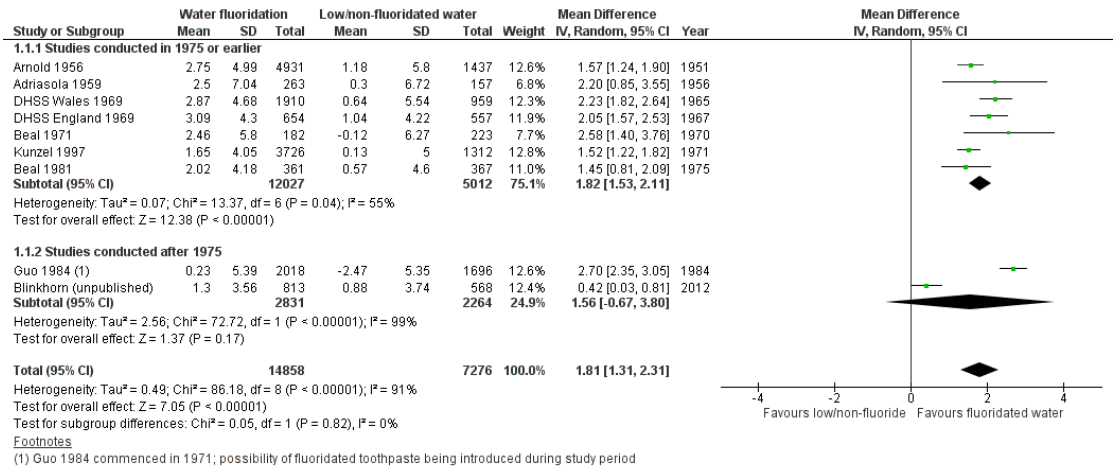
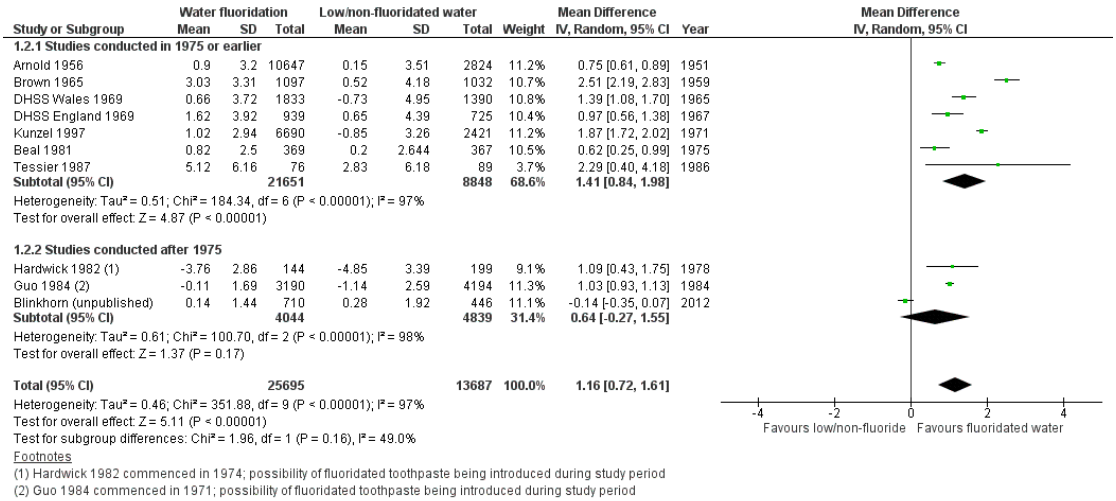


Figure 4. Initiation of water fluoridation compared with low/non-fluoridated water: change in DMFT

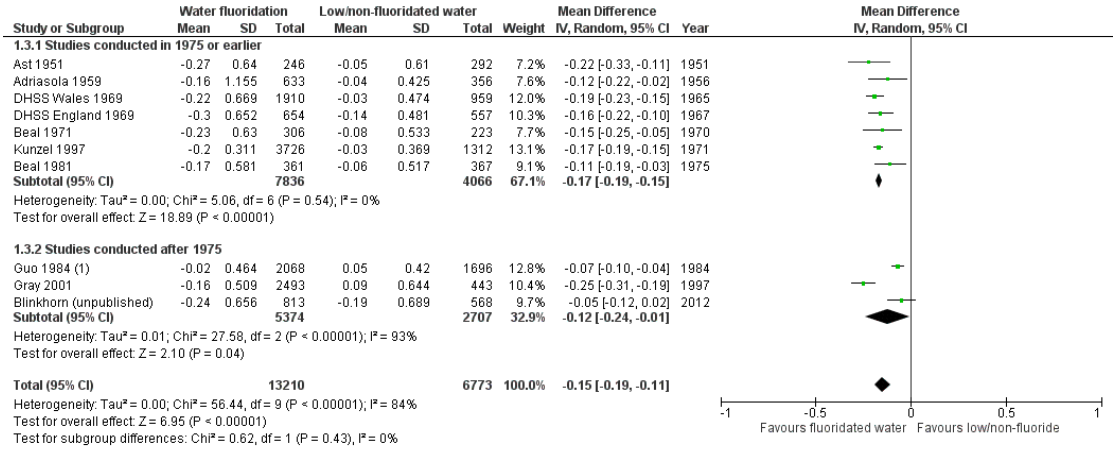


Footnotes

(1) Hardwick 1982 commenced in 1974; possibility of fluoridated toothpaste being introduced during study period

(2) Guo 1984 commenced in 1971; possibility of fluoridated toothpaste being introduced during study period

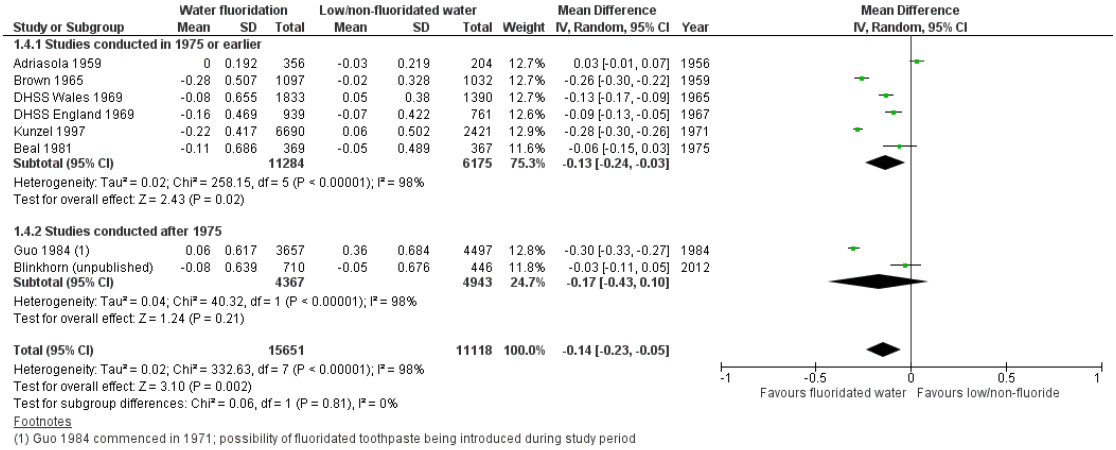
Figure 5. Initiation of water fluoridation compared with low/non-fluoridated water: change in proportion of caries-free children (deciduous teeth)



Footnotes

(1) Guo 1984 commenced in 1971; possibility of fluoridated toothpaste being introduced during study period

Figure 6. Initiation of water fluoridation compared with low/non-fluoridated water: change in proportion of caries-free children (permanent teeth)



Change in dmft/dmfs

Nine studies, with data from 44,268 participants, provided data for dmft (Adriasola 1959; Arnold 1956; Beal 1971; Beal 1981; Blinkhorn (unpublished); DHSS England 1969; DHSS Wales 1969; Guo 1984; Kunzel 1997). We judged all studies to be at high risk of bias and only two (22%) studies were conducted post-1975. Data collection following initiation of water fluoridation ranged from two to 12 years. Data did not allow for an evaluation of effect by duration of exposure to fluoridated water.

The mean difference in change in dmft was 1.81 (95% CI 1.31 to 2.31; P value < 0.00001; Figure 3). At final assessment, the dmft means for the control groups ranged from 1.21 to 7.8, with a median of 5.1. A mean reduction of 1.81 indicates a 35% reduction in dmft in the water fluoridation groups over and above that for the control groups. Although there was considerable heterogeneity (P value < 0.00001; I^2 = 91%), we decided to pool the data as all the mean difference estimates were in the same direction. Some of the heterogeneity is expected due to the large size of the studies ensuring narrow confidence intervals.

Sensitivity analysis, excluding studies with imputed standard deviations gave rise to a similar effect estimate, mean difference in change score 1.83 (95% CI 0.68 to 2.98; 5 studies).

There were no data for dmfs.

Change in DMFT/DMFS

Ten studies, with data from 78,764 participants, provided data for DMFT (Arnold 1956; Beal 1981; Blinkhorn (unpublished); Brown 1965; DHSS England 1969; DHSS Wales 1969; Guo 1984; Hardwick 1982; Kunzel 1997; Tessier 1987). We judged all the studies to be at high risk of bias and only three studies (30%) were conducted post-1975. Data collection following initiation of water fluoridation ranged from two to 11 years. Data did not allow for an evaluation of effect by duration of exposure to fluoridated water.

The mean difference in change in DMFT was 1.16 (95% CI 0.72 to 1.61; P value < 0.00001;Figure 4). At final assessment, the DMFT means for the control groups ranged from 0.71 to 5.5, with a median of 4.4. A mean reduction of 1.16 indicates a 26% reduction in DMFT in the water fluoridation groups over and above that for the control groups. It should be noted that in Guo 1984 the before mean DMFT values for both the control and water fluoridation groups were low at 0.8, and this increased in both groups, however the increase was greater for the control group. This explains why the changes are both negative. The data for Hardwick 1982 are mean DMFT increment data for both groups from the paper, following the same children over time. A lower increment was observed for the water fluoridation group and, as they are caries increments, they have been entered as negative values.

Although there was considerable heterogeneity (P value < 0.00001; I^2 = 97%), once again we decided to pool the data as all but one of the mean difference estimates were in the same direction (ranging from -0.14 to 2.51). Some of the heterogeneity is expected due to the large numbers in the studies ensuring narrow confidence intervals.

Sensitivity analysis in which we excluded studies with imputed standard deviations gave rise to a slightly larger effect estimate; mean difference in change score 1.32 (95% CI 0.53 to 2.11; 4 studies).

Only one study, with data from 343 participants, presented data on DMFS (Hardwick 1982). The study presented increment data

for both groups, with a lower increment being observed for the water fluoridation group; mean difference 2.46 (95% CI 1.11 to 3.81).

Change in proportion of children caries free: deciduous dentition

Ten studies, with data from 39,966 children, provided data for the proportion of caries-free children for deciduous dentition (Adriasola 1959; Ast 1951; Beal 1971; Beal 1981; Blinkhorn (unpublished); DHSS England 1969; DHSS Wales 1969; Gray 2001; Guo 1984; Kunzel 1997). We judged all studies to be at high risk of bias. Three studies (30%) were published post-1975. For all studies combined, there was a 0.15 absolute increase in the proportion of caries-free children in fluoridated areas with mean difference 0.15 (95% CI 0.11 to 0.19; Figure 5). At final assessment, the proportion of caries-free children in the low/non-fluoridated areas ranged from 0.06 to 0.67, with a median of 0.22; an increase of 0.15 in the proportion of caries-free children could be considered substantial. There was considerable heterogeneity (P value < 0.00001; I^2 = 84%), but the value of Tau^2 from the random-effects analysis was low (< 0.001; mean differences ranged from 0.05 to 0.25). Therefore we decided to pool the data.

Change in proportion of children caries free: permanent dentition

Eight studies, with data from 53,538 participants, provided data for the proportion of caries-free children for permanent dentition (Adriasola 1959; Beal 1981; Blinkhorn (unpublished); Brown 1965; DHSS England 1969; DHSS Wales 1969; Guo 1984; Kunzel 1997). We judged all studies to be at high risk of bias and only two (25%) were conducted post-1975. There was a 0.14 absolute increase in the proportion of caries-free children in fluoridated areas with mean difference 0.14 (95% CI 0.05 to 0.23; Figure 6). At final assessment, the proportion of caries-free children in the low/non-fluoridated areas ranged from 0.01 to 0.67, with a median of 0.14; the increase of 0.14 doubles this. There was considerable heterogeneity (P value < 0.00001; I^2 = 98%), but the value of Tau from the random-effects analysis was low at 0.02 (mean differences ranged from -0.03 to 0.30). Therefore we decided to pool the data.

Other caries measures

We did not include four studies that met the inclusion criteria in the quantitative analysis (Backer-Dirks 1961; DHSS Scotland 1969; Loh 1996; Pot 1974). We judged all studies to be at high risk of bias and excluded them from the analysis due to insufficient data (e.g. no data on number of participants evaluated) or different measures of caries, or both. The Backer-Dirks 1961 study reported dentinal approximal lesions as the caries measure, while Pot 1974 reported the percentage with false teeth. The other two studies did not report on the number of participants (DHSS Scotland 1969; Loh 1996). Three of the studies assessing children between the ages of four and 15 years showed a reduction in caries following the initiation of water fluoridation (Backer-Dirks 1961; DHSS Scotland 1969; Loh 1996). Pot 1974 assessed participants between five and 55 years of age and showed an increase in percentage with dentures following fluoridation.

Cessation of water fluoridation

Change in DMFT/DMFS

Only one study, at high risk of bias, presented data on DMFS: the Maupome 2001 fluoride cessation study was conducted over three years. The study was conducted in a population with "generally low caries experience, living in an affluent setting with widely accessible dental services". The results did not demonstrate an increase in caries in the children in the fluoride-ended group compared with the still-fluoridated group, in fact there was a statistically significant decrease in caries severity (including incipient and cavitated lesions) for the fluoride-ended group, which was not found in the still-fluoridated group, for both of the age groups examined. A complex pattern of disease was found when different caries indices were examined.

No studies that met the inclusion criteria reported on change in dmft or proportion of caries-free children (deciduous/permanent dentition) following the cessation of water fluoridation.

Disparities across social class

Three included studies' reported on the effect of water fluoridation on disparities in caries across social class (Beal 1971; Gray 2001; Holdcroft 1999; Table 6). The number of participants was reported in only two of the studies (Beal 1971; Gray 2001). The total number of participants measured for caries in these studies was 35,399. The studies focused on the initiation of water fluoridation in study areas that were reasonably comparable. Measures of caries reported in the studies were dmft, deft and percentage caries-free subjects. All three studies were judged to be at high risk of bias.

Beal 1971 studied three areas, in two of which water fluoridation was initiated (one classed as 'poor' and the other 'industrial'). The control group was classed as 'industrial'. Given the lack of a validated measure of deprivation, and without knowing the composition of the groups under comparison, it is not possible to draw conclusions from this study.

Holdcroft 1999 and Gray 2001 both used the Jarman score (an index to measure socioeconomic variation across small geographical areas, originally developed as a measure of General Practice workload; a positive score equates to deprivation). The Holdcroft 1999 study contained insufficient information about fluoride levels at baseline or follow-up and the number of participants measured at

each time point was unclear. In both studies the Jarman scores at baseline for the control (non-fluoridated areas) were all less than zero. The Jarman scores at baseline in the fluoridated areas ranged from -7.85 to 15.03 in the Holdcroft 1999 study, and from -23.09 to 21.57 in the Gray 2001 study.

Given the reasons above we are unable to draw robust conclusions about the initiation of water fluoridation and its effect on disparities in caries across social class.

Dental fluorosis

Aesthetic concern

Fluoride levels of 5 ppm or less

We included 40 studies, at high risk of bias, that reported data from 59,630 participants in the analysis of dental fluorosis of aesthetic concern. The reported fluoride exposure ranged from 0 to 4.9 ppm with a mean of 0.80 ppm (SD 0.90).

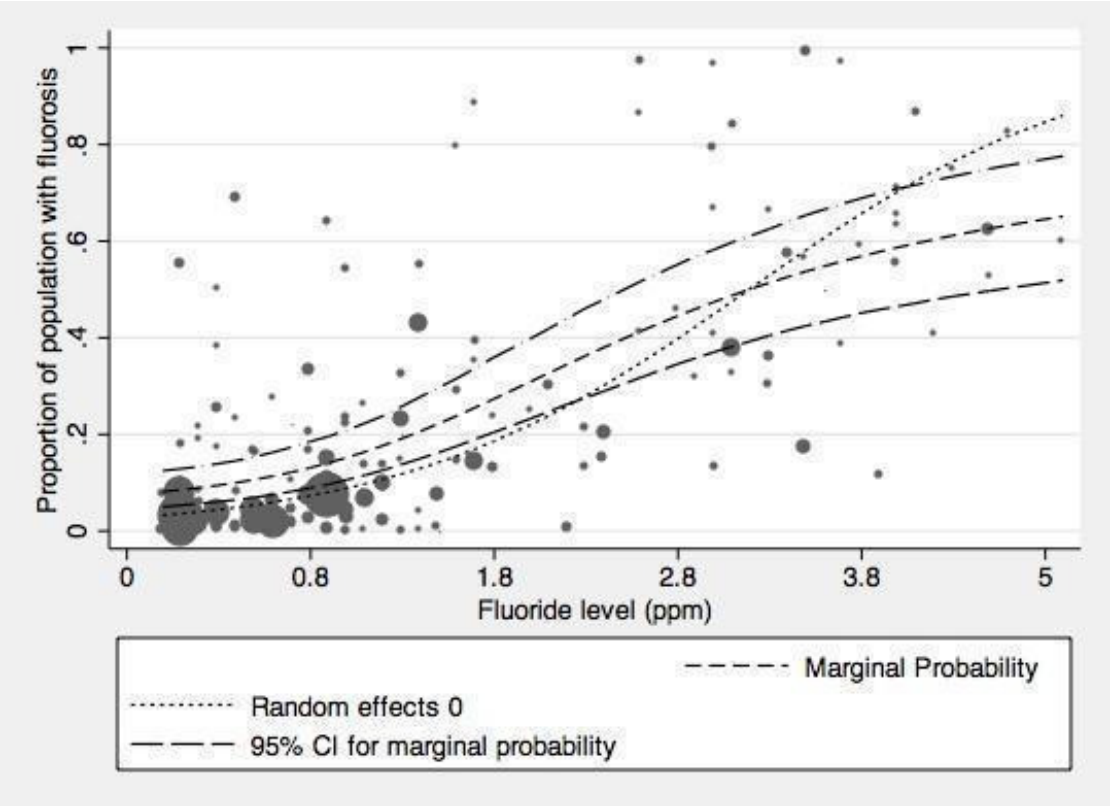
In order to assess the assumption of linearity we plotted the log odds of the prevalence of dental fluorosis with fluoride level and with log of fluoride level (not shown). A positive linear relationship could be assumed in both cases, indicating that as fluoride levels increase so does the prevalence of dental fluorosis. The reported fluoride level was used as a predictor rather than the log of reported fluoride exposure. This was then centred by taking away the grand mean (0.80) from the reported fluoride level.

Caterpillar plots (not shown) of the residuals for slope and intercept indicated that many of the studies differed significantly from the average (random effects at zero) at the 0.05 level of significance. The effect of fluoride exposure was positive and statistically significant; a higher prevalence of dental fluorosis is associated with increased fluoride exposure (OR 2.90, 95% CI 2.05 to 4.10). When controlling for study effects, we would expect the odds of dental fluorosis to increase by a factor of 2.90 for each one unit increase in fluoride exposure.

The random intercept and random slope model indicated that the effect of fluoride exposure differed across studies. The statistically significant negative covariance of -0.82 implies that studies with a higher than average probability of dental fluorosis tend to have a more shallow slope.

The results presented so far have been based on study-specific values. This is indicated in the following graphic, where the random effects of intercept and slope are set to zero, in effect the plotted prevalence of dental fluorosis in an 'average' study. An alternative approach is to calculate the prevalence of dental fluorosis in all studies combined, to obtain the marginal probability of dental fluorosis. The study-specific values indicate the probability of dental fluorosis in terms of 'any given participant' whereas the marginal probabilities indicate the probability of dental fluorosis 'among the participants' (Figure 7).

Figure 7. Proportion of the population with dental fluorosis of aesthetic concern by water fluoride level together with 95% confidence limits for the proportion (studies reporting up to and including 5ppm).



The marginal probabilities of dental fluorosis of aesthetic concern at different fluoride levels are given below.

Fluoride exposure (ppm)	Probability of dental fluorosis of aesthetic concern (95% CI)
0.1	0.08 (0.05 to 0.12)
0.2	0.09 (0.06 to 0.13)
0.4	0.10 (0.06 to 0.15)
0.7	0.12 (0.08 to 0.17)
1	0.15 (0.11 to 0.21)
1.2	0.18 (0.13 to 0.24)
2	0.31 (0.23 to 0.40)
4	0.59 (0.46 to 0.71)

All fluoride levels

The analysis of dental fluorosis of aesthetic concern at all reported fluoride exposure was based on 60,030 observations from 40 studies. The reported fluoride levels ranged from 0 to 7.6 ppm with a mean of 0.85 ppm (SD 1.03).There was very little difference in the results from the analysis restricted to 5 ppm or less. The effect of fluoride exposure is positive and statistically significant; a higher prevalence of dental fluorosis is associated with increased fluoride exposure (OR 2.84, 95% CI 2.00 to 4.03). When controlling for study effects, we would expect the odds of dental fluorosis to increase by a factor of 2.84 for each one unit increase in fluoride level (1 ppm F).

Any dental fluorosis

Fluoride levels of 5 ppm or less

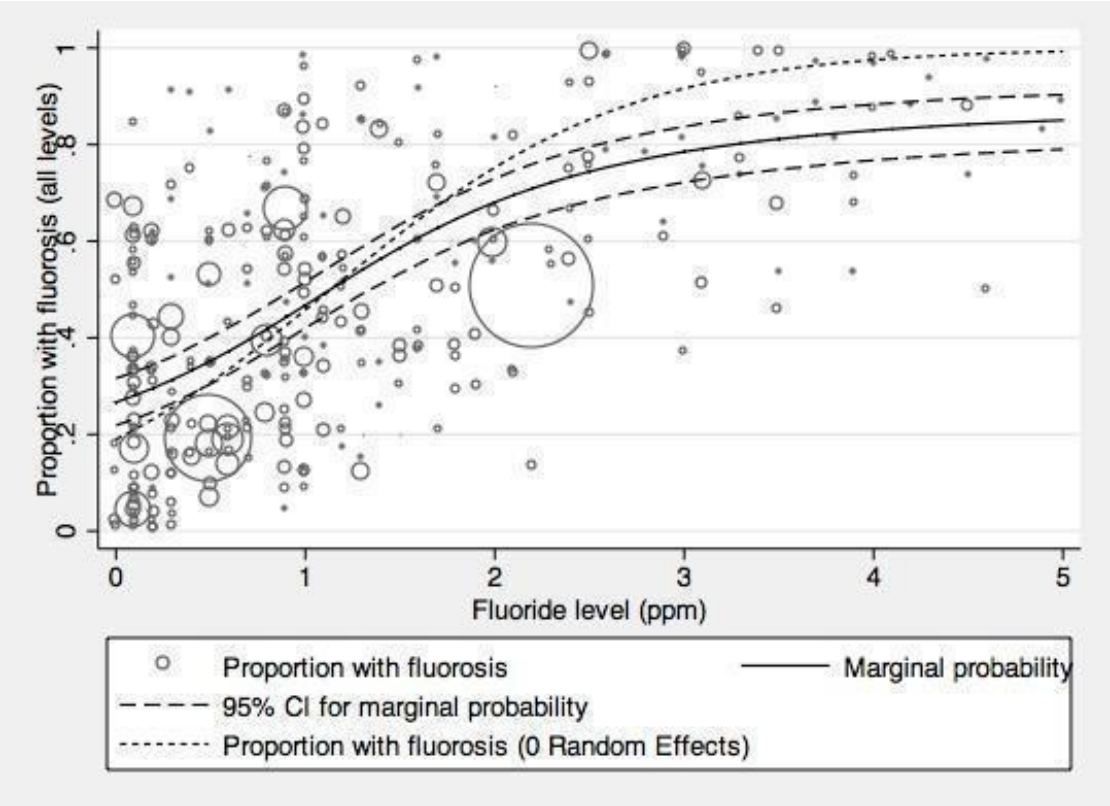
We included 90 studies, at high risk of bias, that reported data from 180,530 participants in this analysis. The reported fluoride levels in the studies ranged from 0 to 5 ppm, with a mean of 1.22 ppm (SD 0.92). When restricted to studies reporting fluoride exposure of 5 ppm or less, there is a clearer positive relationship between the proportion of children with dental fluorosis and fluoride level. The relationship between the log odds of dental fluorosis and fluoride level and log fluoride level were both approximately linear. Consequently the reported fluoride exposure was used as a predictor rather than the log of reported fluoride exposure. This was then centred by taking away the grand mean (1.22) from the reported fluoride exposure level.

The effect of fluoride exposure is positive and statistically significant; a higher prevalence of dental fluorosis is associated with increased fluoride exposure (OR 3.60, 95% CI 2.86 to 4.53). Controlling for study effects, we would expect the odds of dental fluorosis to increase by a factor of 3.60 for each one unit increase in fluoride exposure (1 ppm F).

The random intercept and random slope model indicated that the effect of fluoride exposure differed across studies. The statistically significant negative covariance of -1.05 implies that studies with a higher than average probability of dental fluorosis tend to have a more shallow slope.

The results presented so far have been based on study-specific values. This is indicated in the following graph, where the random effects of intercept and slope are set to zero, in effect the plotted prevalence of dental fluorosis in an 'average' study (Figure 8).

Figure 8. Proportion of the population with dental fluorosis of any level by water fluoride level together with 95% confidence limits for the proportion (studies reporting up to and including 5ppm F)



The marginal probabilities of any dental fluorosis are presented in the table below.

Fluoride exposure (ppm)	Probability of any dental fluorosis (95% CI)
0.1	0.28 (0.23 to 0.33)
0.2	0.30 (0.25 to 0.34)
0.4	0.33 (0.28 to 0.38)
0.7	0.40 (0.35 to 0.44)
1	0.47 (0.42 to 0.52)
1.2	0.52 (0.47 to 0.56)
2	0.68 (0.62 to 0.73)
4	0.83 (0.77 to 0.88)

All fluoride levels

We included 90 studies that reported data from 182,233 participants in this analysis. The reported fluoride levels ranged from 0 to 14 ppm with a mean fluoride level of 1.28 ppm (SD 1.11). There was little change in the pooled estimates when all fluoride levels were included in the analysis. The effect of fluoride exposure is positive and statistically significant; a higher prevalence of dental fluorosis is associated with increased fluoride exposure (OR 3.13, 95% CI 2.55 to 3.85). When controlling for study effects, we would expect the odds of dental fluorosis to increase by a factor of 3.13 for each one unit increase in fluoride exposure (1 ppm F). The statistically significant negative covariance of -0.87 implies that studies with a higher than average probability of dental fluorosis tend to have a shallower slope. The between study variance increases as fluoride level increases.

Post hoc analysis

We used a multivariate analysis to investigate possible sources of heterogeneity in the model. We explored the effects of source of fluoride and its interaction with fluoride concentration by including them as fixed covariates in the models above. Source of fluoride was classed as natural or artificial. We excluded studies that reported mixed sources of fluoridation, or where the source of fluoridation was not reported, from the analysis. This analysis was carried out separately for the outcomes of fluorosis and fluorosis of aesthetic concern, and for studies reporting fluoride concentrations at any level and restricted to 5 ppm or less.

The results from the models with the additional covariates and the ones containing fluoride concentration only as a covariate are not directly comparable, as the additional covariate analyses included fewer studies due to missing data (source of fluoride). For fluorosis of aesthetic concern at all concentrations, fluoride concentration and source of fluoride explain a proportion of the variation between estimates, whereas the interaction between these estimates does not (the OR for fluorosis due to fluoridation becomes 3.16 (95% CI 2.12 to 4.71) when controlling for source of fluoride (OR 0.25, 95% CI 0.09 to 0.70) and interaction (OR 1.89, 95% CI 0.74 to 4.82). The conclusions are the same for fluorosis of aesthetic concern at fluoride concentrations of 5 ppm or less (the OR for fluorosis due to fluoridation becomes 3.22 (95% CI 2.16 to 4.79) when controlling for source of fluoride (OR 0.25, 95% CI 0.10 to 0.70) and interaction (OR 1.82, 95% CI 0.71 to 4.62)).

For the outcome of fluorosis at all levels, the additional covariates do not contribute significantly to the model.

Other dental fluorosis studies

Approximately one third of the dental fluorosis studies that met the review's inclusion criteria did not report data in a way that allowed for further analysis (Appendix 11).

Other adverse effects reported in the included studies

Five studies that reported on dental fluorosis also presented data on the association of water fluoridation with skeletal fluorosis (Chen 1993; Jolly 1971; Wang 2012), bone fracture (Alarcon-Herrera 2001), and skeletal maturity (Wenzel 1982), in participants between the ages of six and over 66 years. Four of the studies included a total of 596,410 participants (Alarcon-Herrera 2001; Chen 1993; Wang 2012; Wenzel 1982), and fluoride concentration in all four studies ranged from less than 0.2 ppm to 14 ppm. The studies were all at high risk of bias and we did not analyse their results further (Table 5).

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Cessation of water fluoridation compared with fluoridated water for the prevention of dental caries

Patient or population: people of all ages
Settings: community setting
Intervention: cessation of water fluoridation
Comparison: fluoridated water

Outcomes	No of participants (studies)	Quality of the evidence (GRADE)	Comments
Caries in permanent teeth (DMFS)[1] Follow-up: 3 years	9249[2] (1 observational study)	⊕◯◯◯ [3]	Insufficient evidence to determine the effect of the cessation of water fluoridation on caries
Caries in deciduous teeth (dmft/dmfs)[4]			No evidence to determine the effect of the cessation of water fluoridation on caries
Change in proportion of caries-free children (deciduous or permanent teeth)			No evidence to determine the effect of the cessation of water fluoridation on caries
Disparities in caries by socioeconomic status (SES)[5]			No evidence to determine the effect of the cessation of water fluoridation on disparities
Adverse effects			No evidence to determine whether cessation of a water fluoridation programme is associated with any harms

⊕⊕⊕⊕: We are very confident that the true effect lies close to that of the estimate of the effect. Further research is very unlikely to change the estimate of effect.
⊕⊕⊕◯: We are moderately confident in the effect estimate. Further research may change the estimate.
⊕⊕◯◯: Our confidence in the effect estimate is limited. Further research is likely to change the estimate.
⊕◯◯◯: We are very uncertain about the estimate.

1. DMFS - decayed missing and filled surfaces in permanent teeth
2. Total number of participants measured
3. Study at high risk of bias; quality of evidence downgraded
4. dmft/dmfs - decayed, missing and filled deciduous teeth/surfaces
5. SES - socioeconomic status

DISCUSSION

Summary of main results

Of the 155 studies that met the inclusion criteria, 107 studies provided sufficient data for quantitative synthesis. Fourteen studies provided adequate data for the assessment of the effect of the initiation of a water fluoridation programme on dental caries, one study focused on the effect of the cessation of water fluoridation. Although three studies evaluated disparities in dental caries across social class, no data were suitable for further analysis. Ninety studies provided sufficient data for inclusion in the analysis of dental fluorosis of any level (40 in the analysis of dental fluorosis of aesthetic concern).

Our confidence in the size of the effect estimates obtained for the prevention of caries is limited (see Quality of the evidence and Summary of findings for the main comparison; Summary of findings 2).

The results from the caries severity data indicate that the initiation of water fluoridation results in reductions in the order of 1.8 dmft and 1.2 DMFT for deciduous and permanent dentitions. This translates to reductions of 35% and 26% compared to the median control group mean values. In addition, there was an increase in the percentage of children who were caries free (15% increase when evaluating deciduous dentition and 14% in the permanent dentition).

There is insufficient information to determine whether initiation of a water fluoridation programme results in a change in disparities in caries levels across SES.

There is insufficient information to determine the effect of stopping water fluoridation programmes on caries levels.

There were no studies that met the review's inclusion criteria that investigated the effectiveness of water fluoridation for preventing caries in adults.

With regard to dental fluorosis, the percentage of participants with dental fluorosis of aesthetic concern was estimated to be approximately 12% for a fluoride level of 0.7 ppm. This increases to 40% when considering dental fluorosis of any level, however, this includes fluorosis that can only be detected under very controlled, clinical conditions and other enamel defects.

Adverse effects, other than dental fluorosis, were rarely reported in the included studies.

Overall completeness and applicability of evidence

The applicability of the evidence on water fluoridation to today's societies is unclear and highly likely to vary according to setting.

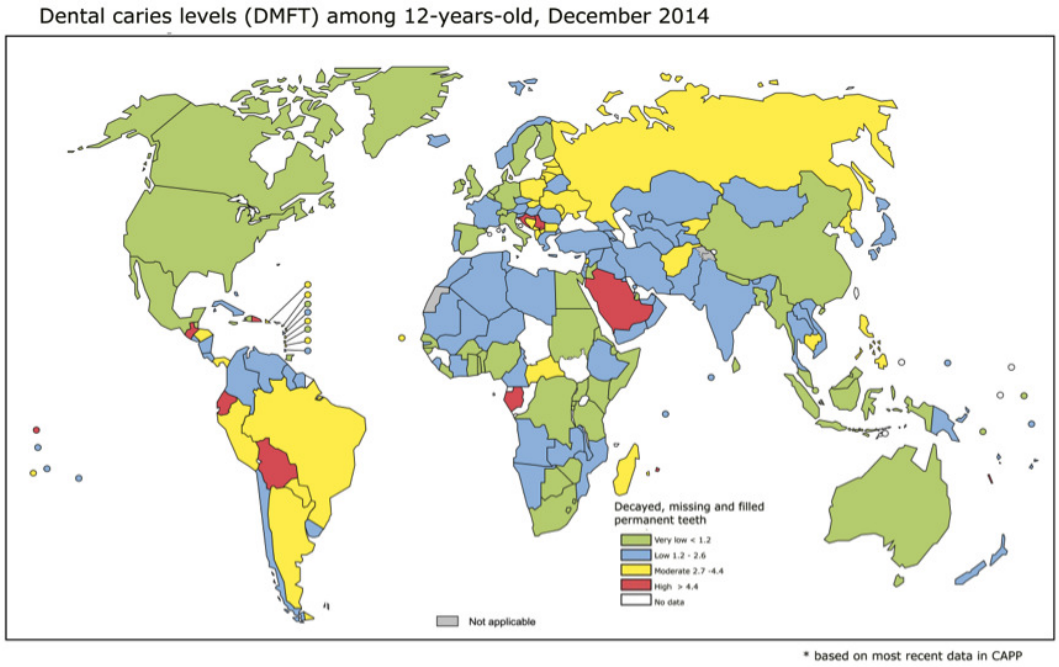
The evidence included in the review pertains to caries in children only. Only one study, that met the review's inclusion criteria, examined the effect of water fluoridation on adults (Pot 1974); the reported outcome for this study was the percentage of participants with dentures. There are no data to determine the effect of water fluoridation on caries levels in adults. Research, utilising data from 26 countries, indicates that dental caries levels in permanent dentition in adults are significantly higher than in children (Bernabe 2014). It has been suggested that greater attention needs to be directed at preventing caries at all stages of life, not just childhood.

Approximately 71% of the included caries studies that evaluated the initiation of water fluoridation were conducted prior to 1975. In developed countries, the widespread use of fluoride toothpastes from the mid to late 1970s, along with increased access to other caries-preventive strategies of proven effectiveness, such as fluoride varnishes (Marinho 2013), and dental sealants (Ahovuo-Saloranta 2013), may mean that the benefit of water fluoridation is reduced in such populations. However, the Marinho 2003a review evaluated the effect of topical fluorides for preventing dental caries in children and adolescents, and found no evidence that the effect of topical fluoride was dependent on background exposure to other fluoride sources. The reviewers did find evidence that the relative effect of topical fluoride may be greater in those who have higher baseline levels of caries.

Globally, caries levels have been reducing. In 1980 the global DMFT for 12 year olds was estimated to be 2.43 (Leclercq 1987). In 2011, this global estimate had reduced to 1.67 DMFT (although there is variation by World Health Organisation region; Table 7). Within the studies included in the review, the mean values for DMFT at follow-up in the non-fluoridated areas were higher, ranging from 0.7 to 5.5.

Figure 9 shows global dental caries levels (DMFT) among 12 year olds. Out of the 189 countries that provided data, 148 (78%) have a DMFT of 3 or less. Areas where a large percentage of the population (more than 60%) receive fluoridated water (either natural or artificial fluoridation) include: North America, Australasia, parts of South America (namely Brazil, Columbia and Chile), the Republic of Ireland, and Malaysia. Whilst these areas tend to have low to very low DMFT (Figure 9), there are many other parts of the world where fluoridated water is not widespread that also have low caries levels. Equally, there are areas with relatively high distribution of water fluoridation and moderate caries levels (e.g. Brazil).

Figure 9. Source:CAPP database, 2015



The applicability of the evidence around water fluoridation has to be considered in the context of reductions in caries levels over time, the uptake of other strategies proven to prevent caries, and global changes in patterns of food consumption (Kearney 2010). Annual sugar consumption, specifically, has risen dramatically since the start of the 20^{th} century when it was approximately 5.1 kg per capita. The consumption of sugar continues to rise with the average sugar consumption now estimated at 23 kg per capita; the greatest rates of growth are currently seen in Asia, the Middle East and Africa (SucDen 2015). In addition, in many parts of the world more industrially processed foods are consumed, with less food being prepared and cooked in the home using locally sourced water (Slimani 2009). Variation in fluoride concentrations in water across regions and countries, and the increase in processed foods and beverages and their transportation, make it difficult to assess dietary fluoride intake. Such changes may mean that, although the tap water is fluoridated in a particular area, some members of the population do not consume a sufficient volume, either through beverages or foods prepared with tap water, to provide a benefit to their oral health.

Ten of the 14 studies used in the analysis of water fluoridation initiation schemes included lifetime residents only. Whilst this is a valid approach it evaluates the absolute effect rather than the benefit to the whole population. The effect size shown in the review may, therefore, be larger than that found in the population, depending on population movement/migration.

There was limited reporting of adverse effects, other than dental fluorosis, in the included studies. The broader literature speculates about harms associated with higher levels of fluoride in water (e.g. cancer, lowered intelligence, endocrine dysfunction), however, there has been insufficient evidence to draw conclusions (MRC 2002).

Quality of the evidence

The GRADE approach was used to assess the quality of the evidence within the review. GRADE has developed over recent years as an internationally recognised framework for systematically evaluating the quality of evidence within both systematic reviews and guidelines. It aims to overcome the confusion that arises from having multiple systems for grading evidence and recommendations, and, because of this key aim, the GRADE working group discourages the use of modified GRADE approaches. However, there has been much debate around the appropriateness of GRADE

when applied to public health interventions, particularly for research questions where evidence from randomised controlled trials is never going to be available due to the unfeasibility of conducting such trials. Community water fluoridation is one such area.

When applying GRADE to non-randomised studies, the quality of the evidence automatically starts at 'low', as opposed to 'high' for RCTs. There has been some criticism of GRADE with regard to its inability to discriminate between stronger and weaker observational designs (Rehfuess 2013). It has been proposed that certain designs, such as quasi-experimental designs and interrupted-time-series studies should begin at 'moderate' quality. Indeed, WHO have previously employed such a modified approach (Bruce 2014). Others suggest that starting non-randomised studies at 'low' simply acknowledges our reduced certainty that observed effects are actually due to the intervention itself. With regard to the current review, using a modified approach to differentiate between stronger and weaker study designs would have no impact on the overall quality assessment as the study designs would still not merit commencing at 'moderate'.

Another concern about applying GRADE is the limited possibilities for 'upgrading' the quality of evidence from observational studies. Modified approaches to GRADE have incorporated the option to upgrade for consistency in findings (Bruce 2014). Within the current review, it was not felt appropriate to upgrade for consistency as there was statistically significant heterogeneity present in all four caries analyses. However, given that the direction of effect was the same for all but one of the outcomes in one of the studies, we have not downgraded with regard to inconsistency.

In our review protocol we stated that we would produce a 'Summary of findings' table, applying the GRADE criteria. We have attempted to be transparent in our decisions regarding the downgrading/upgrading of the quality of the evidence, and feel our decisions are justified. The quality of the evidence, when GRADE criteria are applied, is judged to be low. However, we accept that the terminology of 'low quality' for evidence may appear too judgmental. We acknowledge that studies on water fluoridation, as for many public health interventions, are complex to undertake and that researchers are often constrained in their study design by practical considerations. For many public health interventions, the GRADE framework will always result in a rating of low or very low quality. Decision makers need to recognise that for some areas of research, the quality of the evidence will never be 'high' and that, as for any intervention, the recommendation for its use depends not just upon the quality of the evidence but also on factors such as acceptability and cost-effectiveness (Burford 2012). In order to overcome some of the concerns around the use of GRADE within this review, a decision was made to omit the GRADE terminology of 'low quality' and discuss the findings in terms of our confidence in the results.

With regard to the caries outcomes, all included studies were observational and our confidence in the effect estimate is limited. We downgraded the quality of the evidence due to an overall high risk of bias in the included studies (excluding domains associated with randomisation, allocation concealment, blinding of participants). The main areas of concern were confounding and lack of blind outcome assessment. The evidence was additionally downgraded for indirectness due to the fact that about 71% of the caries studies that evaluated the initiation of water fluoridation were conducted prior to 1975 (Overall completeness and applicability of evidence). Present day reductions in caries may be of a smaller magnitude in developed countries. Also, there were no included studies evaluating caries levels in adults. There was statistically significant heterogeneity present in all four caries analyses (Analysis 1.1; Analysis 1.2; Analysis 1.3; Analysis 1.4), with I^2 statistics of 84% or more. However, given that the direction of effect was the same for all but one of the outcomes in one of the studies, we have not downgraded with regard to inconsistency. The study showing an effect in the opposite direction was the most recently conducted study, with low baseline caries levels, and, as yet, the shortest duration of follow-up (Blinkhorn (unpublished)); both these factors could influence the effect estimate. It is also possible, given the widespread coverage of fluoridated water in Australia, that the low baseline caries reflects diffusion of fluoride from other areas through commercial foods and beverages.

With regard to dental fluorosis, again, all studies were observational and we downgraded the quality of the evidence due to an overall high risk of bias and inconsistency due to substantial between-study variation. Our confidence in the effect estimate is limited.

Potential biases in the review process

Within the review, water with a fluoride concentration of 0.4 ppm or less was classified as non-fluoridated. This cut-off was arbitrary, based on a priori clinical judgement. It is acknowledged that that this cut-off might be high for equivalence of non-fluoridation in hot climates. In practice, only one of the 15 studies that provided sufficient data for analysis of caries levels following a change in fluoridation status had a fluoride concentration greater than 0.2 ppm in the non-fluoridated area.

We imputed the standard deviation for four studies included in the analysis of water fluoridation for preventing caries (dmft and DMFT). This was not prespecified in the protocol. The equation for imputing the standard deviations was estimated from available data where the standard deviations were given (Appendix 10). Sensitivity analysis, excluding those studies for which the standard deviation had been imputed gave similar results.

An arbitrary cut-off date of 1975 was used as an indication of when fluoridated toothpaste use became widespread in industrialised countries. There is no indication in the included studies of the extent to which this is true.

We only reported on dmft in children eight years old and younger. This decision was based on clinical judgement, but was not prespecified in the protocol. The cut-off is unlikely to alter the re-

view's findings as very little data was excluded due to this cut-off. When analysing the dental fluorosis data, our primary analysis focused on fluoride concentrations of 5 ppm or less. Again, this was an arbitrary cut-off; there was little difference in the results obtained when all fluoride concentrations were examined.

Agreements and disagreements with other studies or reviews

The most widely recognised systematic review of water fluoridation was published in 2000 (McDonagh 2000). Our review aimed to update this review, but has adopted different methods in certain areas. Importantly, these included changes to the evaluation of the cessation of water fluoridation programmes and the evaluation of disparities in caries levels.

The McDonagh 2000 review included 26 studies that looked at the effect of water fluoridation on oral health. No pooling of data was undertaken. The mean difference in change in dmft/DMFT and increase in proportion of caries-free children were presented for selected ages/age groups. The range of mean reduction in dmft/DMFT score was from 0.5 to 4.4, with a median of 2.25 dmft/DMFT. In our review, we did undertake statistical pooling, imputing standard deviations where necessary. Rather than selecting specific ages from the data provided in the included studies, we undertook the analyses by dentition, utilising all data for deciduous teeth for children aged eight years and younger, and all available data for permanent teeth. The analyses showed mean reductions of 1.81 in dmft and 1.16 in DMFT, due to water fluoridation.

In terms of the proportion of caries-free children following water fluoridation, the McDonagh 2000 review reported a range of mean differences from -0.05 to an increase of 0.64, with a median of 0.15. The pooled estimate obtained in our review demonstrates an increase in proportion of caries-free children in the areas with water fluoridation of 0.15 for deciduous teeth and 0.14 for permanent teeth.

With regard to the cessation of water fluoridation programmes, the McDonagh 2000 review included eight studies, whereas our review included only one (Maupome 2001). This difference is due to the inappropriate choice of control group in the cessation studies. In a controlled before-and-after study, the groups should be comparable at baseline. Therefore, in the water fluoridation cessation studies, the two groups should both be fluoridated areas, one of which (the 'intervention' group) subsequently has the fluoride removed from the water. The area that remains fluoridated acts as the control. In the majority of the cessation studies, a non-fluoridated area was used as the control at baseline. The intervention and control groups, therefore, were not comparable at the start of the study. Whilst the McDonagh 2000 review suggested that caries prevalence increases following the withdrawal of water fluoridation, this result was not confirmed in the study included in our review.

Neither the McDonagh 2000 review nor our review included studies that evaluated the effectiveness of water fluoridation for preventing caries in adults. However, Griffin 2007 undertook a comprehensive systematic review evaluating the effectiveness of fluoride in preventing caries in adults, including nine studies that examined the effectiveness of water fluoridation. The studies included fell outside the scope of both the McDonagh 2000 review and our review. One of the nine studies they included was a prospective cohort trial, and the remaining eight were cross-sectional studies, with single time-point data. In our review, we only included studies that reported caries data if they had a concurrent control, with at least two points in time evaluated. In the analyses, Griffin 2007 demonstrated a prevented fraction of 34.6% (95% CI 12.6% to 51.0%), when pooling data from seven studies of lifelong residents of control or fluoridated-water communities (5409 participants). When the analysis was limited to studies published after 1979 the prevented fraction was 27.2% (95% CI 19.4% to 34.3%; 5 studies; 2530 participants). The most recent of these post-1979 papers was published in 1992. The fluoride concentration evaluated in these more recent studies was not reported in two studies and was above what is considered the 'optimal level' in a further two studies. Griffin and colleagues acknowledge that the paucity of studies and the quality of the included studies limits their review.

A more recent evaluation of the effects of fluoridated drinking water on dental caries in adults has been conducted in Australia (Slade 2013). A comparison in caries levels was made between a cohort of adults born before the widespread implementation of fluoridation (before 1960; n = 2270) and a cohort born after widespread implementation (n = 1509). Greater lifetime exposure to water fluoridation was associated with lower levels of caries experience in both cohorts. In the study, 31% of participants were excluded from the complete-case analysis due to missing data. The authors report that imputation to account for missing data "did not markedly alter estimated associations between fluoride exposure and caries experience" (Slade 2013).

When addressing the issue of whether water fluoridation results in a reduction in disparities in caries levels across different groups of people, the McDonagh 2000 review included 15 studies, all except two of which were cross-sectional surveys. The authors concluded that, based on a small number of low quality, heterogeneous studies, there was "some evidence that water fluoridation reduces the inequalities in dental health across social classes in five and 12 year-olds, using the dmft/DMFT measure. This effect was not seen in the proportion of caries-free children among five year-olds. The data for the effects in children of other ages did not show an effect." They suggested caution in interpreting these results due to the small number of studies and their low quality rating (McDonagh 2000). There were no data for disparities in caries levels amongst adults.

The cross-sectional studies, whilst able to provide information on whether water fluoridation is associated with a reduction in disparities, are not able to address the question of whether water

fluoridation results in a reduction in disparities in caries levels. There were insufficient data to determine whether initiation of a water fluoridation programme results in a change in disparities in caries levels across different groups of people.

In the past 20 years, the majority of research evaluating the effectiveness of water fluoridation for the prevention of dental caries has been undertaken using cross-sectional studies with concurrent control, with improved statistical handling of confounding factors (Rugg-Gunn 2012). We acknowledge that there may be concerns regarding the exclusion of these studies from the current review. A previous review of these cross-sectional studies has shown a smaller measured effect in studies post-1990 than was seen in earlier studies, although the effect remains significant. It is suggested that this reduction in size of effect may be due to the diffusion effect (Rugg-Gunn 2012); this is likely to only occur in areas where a high proportion of the population already receive fluoridated water. The authors of the review conclude that "There is need for further thought to strengthen study design" (Rugg-Gunn 2012).

The results from our review of the dental fluorosis data are fairly comparable with those of the McDonagh 2000 review. The McDonagh 2000 review fluorosis analysis excluded areas with natural fluoride levels above 5 ppm. It was acknowledged that this is significantly above the level recommended for artificial fluoridation, however the range of concentration of 0 ppm to 5 ppm allowed exploration of a dose-response relationship. In the current review, we also conducted analyses of studies of fluoride concentrations of 5 ppm or lower, in addition to an analyses of all studies irrespective of fluoride concentrations. In the McDonagh 2000 review, the estimated percentage of the population with dental fluorosis of aesthetic concern at a fluoride concentration of 0.7 ppm was 9% (95% CI 4% to 17%; based on studies with fluoride concentration of 5 ppm or lower); in our review this was slightly higher at 12% (95% CI 8% to 17%). There was little change in the pooled estimates when all fluoride levels were included in the analysis.

The broader literature speculates about harms associated with higher levels of fluoride in water (e.g. cancer, lowered intelligence, endocrine dysfunction). These harms have not been systematically evaluated in this review, however, previous reviews suggest there is insufficient evidence to draw conclusions about them (MRC 2002; NHMRC 2007).

AUTHORS' CONCLUSIONS

Implications for practice

There is very little contemporary evidence, meeting the review's inclusion criteria, evaluating the effectiveness of water fluoridation for the prevention of caries.

The data come predominantly from studies conducted prior to 1975, and indicate that water fluoridation is effective at reducing caries levels in both the deciduous and permanent dentition in children. Our confidence in the size of the effect estimates is limited by the observational nature of the study designs, the high risk of bias within the studies, and, importantly, the applicability of the evidence to current lifestyles. The decision to implement a water fluoridation programme relies upon an understanding of the population's oral health behaviours (e.g. use of fluoride toothpaste), the availability and uptake of other caries-prevention strategies, diet and consumption of tap water, and the movement/migration of the population. There is insufficient evidence to determine whether water fluoridation results in a change in disparities in caries levels across socioeconomic status. There are no studies that met the review's inclusion criteria, from which to determine the effectiveness of water fluoridation for preventing caries in adults.

There is insufficient information to determine the effect of stopping water fluoridation programmes on caries levels.

There is a significant association between dental fluorosis (of aesthetic concern or all levels of dental fluorosis) and fluoride level. The evidence is limited due to high risk of bias within the studies and substantial between-study variation.

The studies that have examined dental fluorosis as an outcome are generally more recent than those that have examined caries and, consequently, may be influenced by other sources of fluoride. These additional sources are seldom reported.

Implications for research

More contemporary studies, evaluating the effectiveness of water fluoridation for the prevention of caries, are needed. These studies should include a concurrent control with comparable caries levels at baseline. Caries data should therefore be measured at at least two time points (i.e baseline and follow-up).

Since all the included studies examined the effectiveness of water fluoridation in children, research on effectiveness among adults is needed.

Standardised diagnostic criteria and reporting techniques for caries and dental fluorosis would improve comparability of results across studies.

More research is also needed to understand the contribution of fluoride from sources other than water; the consumption of tap water within a population; the effect of water fluoridation over and above other caries preventive measures, namely dental sealants and fluoride varnishes; the impact of water fluoridation on disparities in oral health; and adverse effects associated with fluoridated water (particularly in areas with naturally high levels of fluoride).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Acharya 2005

Methods	**FLUOROSIS STUDY** Country of study: India Geographic location: Davangere-Nallur, Naganur, Doddabathi, Kundawada and Holesirigere Year of study: not stated Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: school children aged 12-15 years; lifetime residency Exclusion criteria: absence on the day of the survey Other sources of fluoride: not stated Social class: socioeconomic position was similar in all villages Ethnicity: not stated Residential history: lifetime residents Other confounding factors: not stated
Interventions	All natural fluoridation Group 1: 0.43 ppm Group 2: 0.72 ppm Group 3: 1.1 ppm Group 4: 1.22 ppm Group 5: 3.41 ppm
Outcomes	Dental fluorosis (Dean's Index) Age at assessment: 12-15 years
Funding	Not stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Unclear risk	5 villages were selected out of a possible 90. There was insufficient detail reported to determine how selection took place
Confounding	High risk	Did not account for use of other fluoride sources
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information

Acharya 2005 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	Low risk	Outcome of interest reported
Other bias	Low risk	No other apparent bias

Adair 1999

Methods	**FLUOROSIS STUDY** Country of study: USA Geographic location: Warren County, Georgia Year of study: not stated Year of change in fluoridation status: not stated Study design: cross-sectional
Participants	Inclusion criteria: children attending sole elementary and middle schools in study area Exclusion criteria: children whose homes were served with well-water Other sources of fluoride: parents completed questionnaire regarding dentifrice use, home water source and current use of systemic fluoride supplements; all subjects received school water fluoridated at 0.5 ppm Other sources of fluoride: not stated Social class: not stated Ethnicity: not stated Residential history: not considered Other confounding factors: not stated
Interventions	Group 1: 0.5-1.2 ppm (both natural and artifical fluoridation) Group 2: < 0.1 ppm (natural fluoridation)
Outcomes	Dental fluorosis (Dean's Index); caries data collected but not presented in this review due to study design Age at assessment: 8-10 and 11-13 years
Funding	NIDR Grant DE-06113
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Unclear risk	Participants were children attending the sole elementary and middle/high schools in Warren county. There was insufficient detail reported to determine how selection took place

Adair 1999 (*Continued*)

Confounding	High risk	SES was not accounted for
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data for over 80% of participants were reported
Selective reporting (reporting bias)	High risk	Outcome of interest reported. However, data were not presented clearly enough to be considered reliable
Other bias	High risk	Exposure to fluoride water could not be controlled for. Some children had fluoride water at school across groups. Some had non-fluoridated well-water at home

Adriasola 1959

Methods	**CARIES STUDY** Country of study: Chile Geographic location: Curico (F); San Fernando (non-F) Year study started: 1953 Year study ended: 1956 Year of change in fluoridation status: 1953 Study design: CBA
Participants	Inclusion criteria: children aged 3-15; children from 2 primary schools in the study areas Exclusion criteria: none stated Other sources of fluoride: not stated Social class: based on knowledge of their demographics, culture and social economy, it was assumed that the study areas were comparable Ethnicity: not stated Residential history: not stated Other confounding factors: none stated
Interventions	**Initiation of water fluoridation** Group 1: low fluoride content (ppm not reported; natural fluoridation) Group 2: low fluoride content (ppm not reported; natural fluoridation)
Outcomes	% caries-free participants Age at baseline measure: 3-8 years and 11, 12 and 15 years (unclear if deciduous or permanent dentition) Age at final measure: 3-8 years and 11, 12 and 15 years (unclear if deciduous or permanent dentition)
Funding	In collaboration with members of the committee Pro-Fluoridation

Adriasola 1959 (*Continued*)

Notes	Data extracted from Adriasola 1959 differs from that presented in CRD review (additional data extracted) Paper translated from Spanish

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Unclear risk	Following on from the 1953 survey, the authors re-established contact with local authorities, teachers and health educators in 1956 and in a period of 2 months examined children in Curicco and San Fernando attending private and public technical schools, kindergartens, primary and secondary schools. There was insufficient detail reported to determine how selection took place
Confounding	High risk	Study groups assumed comparable for SES. No details were reported on the use of fluoride from other sources or on the dietary habits of the children
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Different children examined at before and after time points. Unclear if all eligible children examined at each time point
Selective reporting (reporting bias)	High risk	Baseline data for proportion of children caries free incomplete for ages 6, 7, 11 and 15 years
Other bias	Low risk	No other apparent bias

Al-Alousi 1975

Methods	**FLUOROSIS STUDY** Country of study: England Geographic location: Anglesey (F); Leeds (non-F) Year of study: 1973 Year of change in fluoridation status: 1955 Study design: cross-sectional
Participants	Inclusion criteria: lifetime residents of study areas; children aged 12-16 years Exclusion criteria: missing, fractured or crowned teeth; refusal to participate (1 school in Leeds) Other sources of fluoride: not stated Social class: not stated Ethnicity: not stated Residential history: lifetime residents Other confounding factors: not stated
Interventions	Group 1: 0.9 ppm (artificial fluoridation) Group 2: < 0.01 ppm (natural fluoridation)
Outcomes	Dental fluorosis Age at assessment: 12-16 years
Funding	Not stated
Notes	Data extracted from Al-Alousi 1975 differs from that presented in CRD review

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Unclear risk	Children were selected from schools in Leeds in a quasi-random way whereby every nth child (n = total children in school/ 20) from the register was selected. Eligible children in Anglesea were selected from schools randomly
Confounding	High risk	Did not account for use of other fluoride sources or SES
Blinding of outcome assessment (detection bias) All outcomes	High risk	A clinical investigation and double-blinded photographic examination were conducted. However, the results reported are those of the unblinded clinical investigation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants

Al-Alousi 1975 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Outcome of interest reported
Other bias	High risk	Diagnoses had to be "agreed" on by the two examiners and there was no mention of any sort of calibration of the examiners. This may have resulted in measurement bias

Alarcon-Herrera 2001

Methods	**FLUOROSIS STUDY** Country of study: Mexico Geographic location: Durango Year of study: not stated Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: children aged 6-12 years who had established permanent residence in the area Exclusion criteria: not stated Other sources of fluoride: not stated Social class: not stated Ethnicity: not stated Residential history: permanent residents Other confounding factors: not stated
Interventions	All natural fluoridation Group 1: non-detectable-1.5 ppm Group 2: 1.51-4.99 ppm Group 3: 5.0-8.49 ppm Group 4: 8.5-11.9 ppm Group 5: > 12 ppm
Outcomes	Dental fluorosis (Dean's Index) Age at assessment: 6-12 years
Funding	Project grant from the Mexican National Council of Science and Technology Conacyt-Sivilla, Project 9502160
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Low risk	Through a polystage conglomerate random sampling, 380 families were selected and prorated into 77-80 families per concentra-

Alarcon-Herrera 2001 (*Continued*)

		tion area zone. The division yielded a total of 1437 individuals from the five different areas
Confounding	High risk	Did not account for use of other fluoride sources or SES
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	Low risk	Outcome of interest reported
Other bias	Unclear risk	No information examiner calibration with regard to detection of the outcome variable

Albrecht 2004

Methods	**FLUOROSIS STUDY** Country of study: Hungary Geographic location: Bár and Dunaszekcsö Year of study: 2004 Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: healthy schoolchildren, aged 6-18 years; lifelong residents in the communities Bár or Dunaszekcsö ; only permanent teeth were investigated Exclusion criteria: any systemic disease Other sources of fluoride: not stated Social class: not stated Ethnicity: not stated Residential history: lifetime residents Other confounding factors: not stated
Interventions	All natural fluoridation Group 1: 1.7 ppm Group 2: 2 ppm
Outcomes	Dental fluorosis (Dean's Index and TSIF) Age at assessment: 6-18 years
Funding	Not stated
Notes	Paper translated from Hungarian

Albrecht 2004 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Sampling	Unclear risk	There was insufficient detail reported to determine how selection took place
Confounding	High risk	Did not account for use of other fluoride sources or SES
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	Low risk	Outcome of interest reported
Other bias	Low risk	No other apparent bias

AlDosari 2010

Methods	**FLUOROSIS STUDY** Country of study: Saudi Arabia Geographic location: Riyadh Year of study: 2010 Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria:Saudi nationality; lifetime residence in the area Exclusion criteria: non-Saudi nationality; absence from school on the day of dental examination Other sources of fluoride: not stated Social class: both schools from urban and rural areas were included in the sample frame Ethnicity: Saudi nationals, no further details Residential history: lifetime residents Other confounding factors: not stated
Interventions	All natural fluoridation Group 1: 0-0.3 ppm Group 2: 0.31-0.6 ppm Group 3: 0.61-1 ppm Group 4: 1.01-1.5 ppm Group 5: 1.51-2 ppm Group 6: 2.01-2.5 ppm Group 7: ≥ 2.51 ppm

AlDosari 2010 (*Continued*)

Outcomes	Dental fluorosis (TF Index) Age at assessment: 6-18 years	
Funding	Supported by a grant from King Abdulaziz City for Science and Technology, Riyadh, Saudi Arabia	
Notes		

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Unclear risk	A list of zones was considered as the sampling frame for the schools, and municipalities were randomly chosen from each zone to represent the urban area. Additionally, rural areas in the municipality with at least one school were surveyed. However there was insufficient detail reported to determine how selection of schools and children within those schools took place
Confounding	High risk	Did not account for use of other fluoride sources
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	High risk	Over 95% of the subjects sampled were examined. However, it is not clear why fluorosis was not scored in permanent teeth of the 6- to 7-year olds
Selective reporting (reporting bias)	High risk	The authors did not report or justify not presenting fluorosis data for the age group 15-18 years
Other bias	Unclear risk	Clinical examination was carried out by 2 dentists, but no information on whether the examiners were calibrated with regard to detection of the outcome variable was given

Angelillo 1999

Methods	**FLUOROSIS STUDY** Country of study: Italy Geographic location: areas around Naples (F); Catanzaro (non-F) Year of study: 1997 Year of change in fluoridation status: NA Study design: cross sectional
Participants	Inclusion criteria: lifetime residents of study areas (children only); children aged 12 years; used community water supply as main sources of drinking water Exclusion criteria: partially erupted teeth; orthodontic banding Other sources of fluoride: tooth brushing habits (frequency of tooth brushing); fluoride tablets; fluoride dentifrices Social class: parents' employment status Ethnicity: not stated Residential history: lifetime residents Other confounding factors: sweet consumption; climate
Interventions	All natural fluoridation Group 1: ≥ 2.5 ppm Group 2: ≤ 0.3 ppm
Outcomes	Dental fluorosis; caries data evaluated in study but not included in review due to study design Age at assessment: 12 years
Funding	Partially supported by a grant of Acquedotto Vesu- viano S.p.A
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Low risk	Schools were selected at random, as were classes with the schools. All eligible children within the selected class were recruited to the study
Confounding	High risk	There was a reported imbalance between groups in the use of fluoride supplements, toothbrushing behaviour and in SES
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data for the majority of participants presented

Angelillo 1999 (*Continued*)

Selective reporting (reporting bias)	Low risk	Outcome of interest reported
Other bias	Unclear risk	The 2 examiners involved had previously been trained and calibrated, but details not presented

Arif 2013

Methods	**FLUOROSIS STUDY** Country of study: India Geographic location: Nagaur district Year of study: 2013 Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: only villages where the mean fluoride concentration was > 1.0 mg/L were selected for the dental fluorosis survey. No other information provided for participants Exclusion criteria: not stated Other sources of fluoride: not stated Social class: not stated Ethnicity: not stated Residential history: not stated Other confounding factors: not stated
Interventions	54 villages receiving water with different natural fluoride concentrations ranging from 0.9 5.8 ppm
Outcomes	Dental fluorosis (Dean's Index) Age at assessment: not stated
Funding	Not stated
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Unclear risk	Only villages where the mean fluoride concentration was > 1.0 ppm were selected. There was insufficient detail reported to determine how selection took place
Confounding	High risk	Did not account for use of other fluoride sources or SES

Arif 2013 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to determine whether data presented for all participants as study details were poorly reported
Selective reporting (reporting bias)	Low risk	Outcome of interest not reported in paper, but made available by authors via email
Other bias	High risk	Fluoride concentration for the different villages overlapped making the data impossible to interpret

Arnold 1956

Methods	**CARIES STUDY** Country of study: USA Geographic location: Grand Rapids (F); Muskegon (non-F) Year study started: 1944 Year study ended: 1951 (after which time the control group became fluoridated; evaluated until 1954) Year of change in fluoridation status: 1945 Study design: CBA
Participants	Inclusion criteria: children aged 4-16 years; used city water supplies since birth Exclusion criteria: children who lived outside study areas for more than 3 months of any 1 year Other sources of fluoride: author stated that there were no concerted efforts to commence special caries control programmes e.g. topical fluoride programmes, in either of the cities since the study began Social class: not stated Ethnicity: not stated Residential history: lifetime residents Other confounding factors: not stated
Interventions	I**nitiation of water fluoridation** Group 1: 1 ppm (artificial fluoridation) Group 2: < 0.2 ppm (natural fluoridation)
Outcomes	DMFT; deft Age at baseline measure: 5-13 years (deciduous dentition); 6-16 years (permanent dentition) Age at final measure: 5-13 years (deciduous dentition); 6-16 years (permanent dentition)
Funding	Not stated

Arnold 1956 (*Continued*)

Notes	Data extracted from Arnold 1956 differed from that presented in CRD review (additional data extracted)

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Low risk	Children were selected through schools. Almost all eligible children in the areas of study were examined
Confounding	High risk	No efforts were made to stop topical fluoride application in either control or test group. However it is not known if the areas differed in terms of the programmes/ services on offer. No details on the dietary habits of the children were reported
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "samples consist of all available children in certain grades (or in sections of the grades)" Number of children examined each year presented, however, numbers varied across each age group and each year (not a continuous study sample)
Selective reporting (reporting bias)	High risk	It is noted in the results that fluorosis observations had been made, but no details were given for the methods and data (just % increase). Also, standard deviation not reported
Other bias	High risk	Calibration of examiners not mentioned

Ast 1951

Methods	**CARIES STUDY** Country of study: USA Geographic location: Newburgh (F); Kingston (non-F) Year study started: 1945 Year study ended: 1952 Year of change in fluoridation status: 1945 Study design: CBA
Participants	Inclusion criteria: all 5- to 12-year-old children present at school on days of examination; lifetime residents of study areas Exclusion criteria: none stated Other sources of fluoride: not stated Social class: not stated Ethnicity: not stated Residential history: lifetime residents Other confounding factors: not stated
Interventions	**Initiation of water fluoridation** Group 1 baseline: < 0.1 ppm (natural fluoridation) Group 1 post intervention: 1-1.2 ppm (artificial fluoridation) Group 2: < 0.1 ppm (natural fluoridation)
Outcomes	DMFT rate per 100 erupted permanent teeth; % caries-free children (deciduous dentition) Age at baseline measure: 5 years (deciduous dentition); 6-12 years (permanent dentition) Age at final measure: 5 years (deciduous dentition); 6-12 years (permanent dentition)
Funding	Not stated
Notes	Data extracted from Ast 1951 differs from that presented in CRD review (additional data extracted)

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Low risk	All 5- to 12-year-old school children present in the schools within the study areas on the days of examination were included in the study
Confounding	High risk	Did not account for SES, the use of other fluoride sources, or the dietary habits of the children
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information

Ast 1951 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	The number of participants for whom outcome data was reported (F = 3054; non-F = 2812) varied from the number of participants reported to have been included in the study (F = 3200; non-F = 3100)
Selective reporting (reporting bias)	High risk	Baseline dates of children in the intervention (1944-45) and control (1945-46) groups varied, which would result in incomparability of data from both study groups
Other bias	High risk	There was no mention of examiner calibration

Awadia 2000

Methods	**FLUOROSIS STUDY** Country of study: Tanzania Geographic location: Arusha and Moshi Year of study: 1996 Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: age 9-14 years; lifelong residence in respective towns or villages Exclusion criteria: not stated Other fluoride sources: toothpaste use: Arusha = 94%; Arusha Meru = 100%; Moshi = 97.1% and Kibosho = 40%Magadi use: Arusha = 31(47%); Arusha Meru = 1(2.9%); Moshi = 41 (58.6%); Kibosho = 83(97.6%) Social class: peasant mothers: Arusha = 1 (1.5%); Arusah Meru = NR; Moshi = 7 (10%); Kibosho = 33 (38.8%); other: Arusha = 65 (98.5%); Arusha Meru = 35 (100%); Moshi = 63 (90%); Kibosho = 52 (61.2%) Ethnicity: Arusha area (Arusha and Arusha Meru) - mainly ethnic Asians; Kilimanjaro region (Moshi and Kibosho) - Africans Residential history: lifetime residents Other confounding factors: not stated
Interventions	All natural fluoridation Group 1: 0.2 ppm Group 2: 0.3 ppm Group 3: 3.6 ppm
Outcomes	Dental fluorosis (TF Index) Age at assessment: 9-14 years
Funding	Supported by the Norwegian State Educational Loan fund, NUFU project 61/96, and the committee for Research and Postgraduate Training, Faculty of Dentistry, University of Bergen, Norway

Awadia 2000 (*Continued*)

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Low risk	Schools in all villages (except in Arusha Meru) as well as participants were randomly selected. For schools where participants were not randomly selected, including the school in Arusha Meru, all the registered school children were chosen to participate
Confounding	High risk	There was a reported imbalance between groups in terms of SES and use of fluoride from other sources
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	High risk	Outcome of interest not fully reported, rather presented as a median score
Other bias	High risk	Only one examiner was involved; no testing for intra-rater reliability with regard to detection of the outcome variable

Azcurra 1995

Methods	**FLUOROSIS STUDY** Country of study: Argentina Geographic location: Sampacho (F); Porteña (non-F) in the Cordoba province Year of study: 1993 Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: children aged 6-7 years (1^{st} grade) and 12-13 years (7^{th} grade) at primary school Exclusion criteria: none stated Other sources of fluoride: frequency of tooth brushing. Group 1 (aged 6-7): 56% brushed at least once a day (28/50) Group 1 (aged 12-13): 74% brushed at least once a day (37/50) Group 2 (aged 6-7): 46% brushed at least once a day (23/50)

Azcurra 1995 (*Continued*)

	Group 2 (aged 12-13): 50% brushed at least once a day (25/50) Social class: determined by occupation and highest attained level of schooling attained by main breadwinner in familyClassified as high, medium, and low social class Group 1 (aged 6-7): 80% low SES (40/50) Group 1 (aged 12-13): 82% low SES (41/50) Control (aged 6-7): 74% low SES (37/50) Control (aged 12-13) 80% low SES (40/50) Residential history: not stated Other confounding factors: not stated
Interventions	All natural fluoridation Group 1: 9.05 ppm Group 2: 0.19 ppm
Outcomes	Dental fluorosis (Dean's Index); caries data evaluated in study but not included in review due to study design Age at assessment: 6-7 years and 12-13 years
Funding	Part of this work was subsidised by the Ministry of Science and Technology (SeCyT) of the National University of Córdoba , Córdoba, Argentina
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Low risk	Stratified random selection was used. Following stratification by age, gender and SES,100 school children were randomly selected from each village
Confounding	High risk	Although SES was considered during sampling, it was not controlled for within the analysis. No details were reported on the use of fluoride from other sources
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding not stated, however the two calibrated operators, as authors of the study, were likely to have knowledge of the study areas
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	Low risk	Outcome of interest was fully reported on and balanced across both groups

Azcurra 1995 (*Continued*)

Other bias	Low risk	No other apparent biases

Backer-Dirks 1961

Methods	**CARIES STUDY** Country of study: Holland Geographic location: Tiel (F); Culemborg (non-F) Year study started: 1952 Year study ended: 1959 Year of change in fluoridation status: 1953 Study design: CBA
Participants	Inclusion criteria: children aged 11-15; lifelong residents of the study areas; used the piped water supply; 100 children of each age examined Exclusion criteria: not stated Other fluoride sources: not stated Social class: areas similar in social class structure and proportional numbers of subjects selected from each school type Ethnicity: not stated Residential history: lifetime residents Other confounding factors: not stated
Interventions	**Initiation of water fluoridation** Group 1: 1.1 ppm (artificial fluoridation) Group 2: 0.1 ppm (natural fluoridation)
Outcomes	Average number of all approximal lesions; average number of approximal dental lesions Age at baseline measure: 11-15 years (permanent dentition) Age at final measure: 11-15 years (permanent dentition)
Funding	Not stated
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Low risk	A proportion of children were chosen at random from different types of schools (public school, Roman Catholic, Protestant)
Confounding	High risk	No details were reported on the use of fluoride from other sources or on the dietary habits of the children

Backer-Dirks 1961 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The radiographs made in Tiel and Culemborg were put into unlabelled envelopes, and examined at random". Each examiner evaluated the same number of radiographs without knowledge of the origin of the films
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It is not clear whether the outcome data were reported for all participants
Selective reporting (reporting bias)	High risk	Outcome of interest reported, however, data not in useable format
Other bias	Low risk	No other bias apparent

Bao 2007

Methods	**FLUOROSIS STUDY** Country of study: China Geographic location: 3 cities (Harbin, Mudanjiang, Zhaodong) and 3 rural areas (Zhaoyuan, Shuangcheng, Linkou) in the Heilongjiang province Year of study: not stated Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: 12-year-old children in Heilongjiang Exclusion criteria: not reported. Other sources of fluoride: not reported Social class: 396 (198 male; 198 female) from cities; 396 (198 male; 198 female) from rural areas Ethnicity: Chinese Residential history: not reported Other confounding factors: not reported
Interventions	All natural fluoridation Group 1 (Linkou): 0.29 ppm Group 2 (Mudanjiang): 0.40 ppm Group 3 (Shuangcheng): 0.68 ppm Group 4 (Harbin): 0.77 ppm Group 5 (Zhaoyuan): 0.80 ppm Group 6 (Zhaodong): 1.14 ppm
Outcomes	Dental fluorosis (CFI); caries data evaluated in study, but excluded from review due to study design Age at assessment: 12 years
Funding	Research Fund of Bureau of Health of Heilongjiang Province (grant no.2005[122])

Bao 2007 (*Continued*)

Notes	Translation from Chinese	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Sampling	Low risk	Quote: "Representative samples were selected by multi-stage, stratified and random sampling" "For each site, 66 12-year-old boys and 66 12-year-old girls were randomly chosen"
Confounding	High risk	3 groups were from cities and 3 groups were from rural areas. The authors did not record/report or adjust for other confounding factors (e.g. other fluoride sources, diet, residential history)
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The authors did not report any information on loss of follow-up or exclusion of participants. Judging by the number of people they chose randomly (792), and the number of people (792) with results of caries examination, there was no loss of follow-up or exclusion of participants
Selective reporting (reporting bias)	High risk	Data not presented in a format that allowed for further evaluation Quote: "Dean's Index was used to classify fluorosis." The authors did not report the number of affected people for each Dean's Index category. They did not report the prevalence fluorosis (number of affected people/number of people examined)
Other bias	Low risk	No other apparent bias

Baskaradoss 2008

Methods	**FLUOROSIS STUDY** Country of study: India Geographic location: 9 villages (Munchirai, Thovalai, Melpuram, Rajakkamangalam, Kurunthencode, Thiruvattar, Agasteeswaram, Thuckalay, Killiyoor) in Kanyakumari district Year of study: 2006 Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: not stated Exclusion criteria: not stated Other sources of fluoride: brushing patter (toothbrush) = 84.6%; toothpaste (Colgate) = 92.2%; frequency (once daily) = 80.7%; age of starting to brush (< 2 years) = 69.2% Social class: low SES (46.1%); urban residence (44.2%) Ethnicity: not stated Residential history: not stated Other confounding factors: Information was collected on diet, seafood intake and tea
Interventions	All natural fluoridation Groups 1-9: specific ppm not presented. Groups listed according to number of Panchayats in the various Blocks of Kanyakumari district with water fluoride level more than 1. 5 and 1.7 ppm
Outcomes	Dental fluorosis (Dean's Index) Age at assessment: 10-15 years
Funding	Not stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Low risk	A stratified cluster sampling method was used to select the samples. 2 schools from each block were selected at random from a list of higher secondary schools. After examining an entire class, only the first 20 were taken until sample size was achieved
Confounding	High risk	Participants had different oral hygiene habits and there was no mention of duration of residency
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information

Baskaradoss 2008 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data for all participants reported
Selective reporting (reporting bias)	High risk	Data not in suitable format for analysis
Other bias	Unclear risk	No mention of calibration

Beal 1971

Methods	**CARIES STUDY** Country of study: England Geographic location: Balsall Heath and Northfield, Birmingham (F); Dudley (non-F) Year study started: 1967 Year study ended: 1970 Year of change in fluoridation status: 1964 Study design: CBA
Participants	Inclusion criteria: children aged 5 attending schools that participated in each year of the study Exclusion criteria: none stated Other sources of fluoride: not stated Social class: Quote: "The socio-economic composition of the districts has been described previously ... ". Balsall Heath is a poor area of the city with high proportion of immigrants; Northfield and Dudley are both industrial areas with comparable populations, but there were more immigrants in Dudley Ethnicity: all areas have some proportion of immigrants Residential history: no attempt was made to select continuously resident children from the samples Other confounding factors: not stated
Interventions	Initiation of water fluoridation Group 1 and Group 2: 1 ppm (artificial fluoridation) Group 3: < 0.1 ppm (natural fluoridation)
Outcomes	dmft; % caries-free children Age at baseline measure: 5 years (deciduous dentition) Age at final measure: 5 years (deciduous dentition)
Funding	MRC grant funded trial
Notes	Quote: "The children, who were 5 years old in 1967, were aged about 3 years when the fluoride in their drinking water reached the recommended level; they had erupted all their deciduous, and these would be expected to have derived only slight benefit at this time. These children do not represent a true baseline; any dental advantage that this group had received, compared with the true but unexamined baseline before fluoride was added would have the effect of decreasing the observed reduction, if any, over subsequent years."

Beal 1971 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Sampling	Unclear risk	There was insufficient detail reported to determine how selection took place
Confounding	High risk	No details were reported on the use of fluoride from other sources or on the dietary habits of the children
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Different children examined at before and after time points. Unclear if all eligible children examined at each time point
Selective reporting (reporting bias)	Low risk	Reporting of outcome of interest balanced across groups
Other bias	High risk	No detail of who performed examinations, their training/consistency

Beal 1981

Methods	**CARIES STUDY** Country of study: England Geographic location: Scunthorpe (F); Corby (non-F) Year study started: 1969 Year study ended: 1975 Year of change in fluoridation status: 1968 Study design: CBA
Participants	Inclusion criteria: lifetime residents in study areas; children aged 5, 8 and 12 Exclusion criteria: teeth extracted for orthodontic purposes Other sources of fluoride: not stated Social class: both areas had iron/steel as main industry-socioeconomic; composition of the 2 areas was similar Ethnicity: not stated Residential history: lifetime residents Other confounding factors: not stated
Interventions	**Fluoride initiation** Group 1: 0.9 ppm (artificial fluoridation) Group 2: 0.35 ppm (natural fluoridation)

Beal 1981 (*Continued*)

Outcomes	dmft; DMFT; % caries-free subjects (deciduous teeth); % caries-free subjects (permanent teeth) Age at baseline measure: 5, 8 and 12 years Age at final measure: 5, 8 and 12 years
Funding	Not stated
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Low risk	Schools were chosen by random selection and every child of eligible age in these schools was examined
Confounding	High risk	No details were reported on the use of fluoride from other sources or on the dietary habits of the children
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data for all participants appears to be presented
Selective reporting (reporting bias)	Low risk	Outcome of interest reported
Other bias	Low risk	The authors reported that was no difference in level of reproducibility of the examiners

Beltran-Aguilar 2002

Methods	**FLUOROSIS STUDY** Country of study: USA Geographic location: not stated Year of study: 1986 Year study ended: 1987 Year of change in fluoridation status: not stated Study design: cross-sectional
Participants	Inclusion criteria: aged 12-14 years; availability of data on type of water system and fluorosis; having residences served by the same type of public water system with respect to fluoride status; determinable date of public water system fluoridation initiation and residence at area before initiation of water fluoridation; availability of continuous residence history if more than 1 residence; fewer than 5 residences; ascertainable exposure

Beltran-Aguilar 2002 (*Continued*)

	to fluoride drops or tables; served by public water systems with ascertainable fluoride status in residences Other fluoride sources: tablets = 623 (14.9%); drops = 627 (14.5%); tablets and drops = 317 (8.4%) Suboptimal fluoride: drops only = 507 (23.0); tablets only = 512 (22.5); tablets and drops = 279 (13.2) Optimal fluoride:drops only = 103 (6.8); tablets only = 98 (6.0); tablets and drops = 32 (2.2) Natural fluoride: drops only = 13 (5.5); tablets only = 17 (7.5);tablets and drops = 6 (2.5) Exclusion criteria: any criterion in discord with the inclusion criteria Social class: not stated Ethnicity: not stated Residential history: all the children were continuous residents of areas with the reported water systems Other confounding factors: not stated
Interventions	Group 1: < 0.7 ppm (natural fluoridation) Group 2: 0.7-1.2 ppm (artificial fluoridation) Group 3: 0.7-4 ppm (natural fluoridation)
Outcomes	Dental fluorosis (Dean's Index) Age at assessment: 12-14 years
Funding	Not stated
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Low risk	The sampling frame was specified and the sample represented 41 percent of all 12- to 14-year olds and more than 4 million schools children, there is no evidence that any eligible children were excluded
Confounding	High risk	The use of other fluoride sources was similar in those that consumed water with optimal and natural fluoride, but very different from those in the suboptimal fluoride group. Did not account for SES
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information

Beltran-Aguilar 2002 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Children with missing outcome data were excluded. It is not clear whether there was an imbalance across groups in excluded children
Selective reporting (reporting bias)	Low risk	Outcome of interest reported
Other bias	High risk	There is an overlap in fluoride concentration between the exposure groups (0.7-1. 2 ppm and 0.7-4.0 ppm) which is likely to dilute the observable effect of exposure to intervention across groups. It is unclear whether the examiners were calibrated as the paper provides insufficient information and we were unable to access associated reports which may have contained examination protocols

Berndt 2010

Methods	**FLUOROSIS STUDY** Country of study: Namibia Geographic location: Ombili, Ondera, Vryheid, Kakuse Year of study: October 2004 Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: aged 8-21 years Other fluoride sources: 47 (39.3%) reported oral hygiene practice with fluoridated toothpaste (1400 ppm); 8 (6.7%) used traditional 'natural' toothbrush. Different ethnic groups differed markedly in their oral hygiene behaviour (P value 0.02) Exclusion criteria: not stated Social class: not stated Ethnicity: !Kung (45%); Heikum (35%); Damara (13%); Bantu (7%) Residential history: residents of Ombili had been resident since 1991 and the residents of the other farms were lifetime residents Other confounding factors: not stated
Interventions	All natural fluoridation Group 1: 0.28 ppm Group 2: 0.38 ppm Group 3: 1.06 ppm Group 4: 1.43 ppm
Outcomes	Dental fluorosis (Dean's Index; CFI) Age at assessment: 8-21 years
Funding	Not stated

Berndt 2010 (*Continued*)

Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Sampling	Unclear risk	Children selected from Ombill Primary School and divided into groups according into place of birth and ethnicity
Confounding	High risk	Imbalance in oral health behaviour and duration of residency between ethnic groups
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for in analysis
Selective reporting (reporting bias)	Low risk	Outcome data fully reported
Other bias	Low risk	No other apparent bias

Birkeland 2005

Methods	**FLUOROSIS STUDY** Country of study: Sudan Geographic location: Triet el Biga, Abu Delaig and Abu Groon Year of study: not stated Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: residence in the village from the age of 1 year Exclusion criteria: not stated Other fluoride sources: not stated Social class: similar socioeconomic conditions Ethnicity: similar ethnicity Residential history: lifetime residents Other confounding factors: not stated
Interventions	All natural fluoridation Group 1: 0.3-1.4 ppm Group 2: 0.8-2.2 ppm Group 3: 2-4.2 ppm

Birkeland 2005 (*Continued*)

Outcomes	Dental fluorosis (TF Index) Age at assessment: 11-13 years	
Funding	Not stated	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Sampling	Unclear risk	The schools were selected from an unspecified sampling frame and insufficient detail was reported to determine how selection of schools took place. However children were selected at random from the schools
Confounding	High risk	No details were reported on the use of fluoride from other sources
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	Low risk	Outcome of interest reported
Other bias	High risk	There is inconsistency in the number of water samples tested (Triet el Biga = 6, Abu Delaig = 11, Abu Groon = 8) and an overlap in range of fluoride concentrations between the 3 study areas. Also examinations were done by a dental assistant and it is not clear whether reliability testing was carried out

Blinkhorn (unpublished)

Methods	**CARIES STUDY** Country of study: Australia Geographic location: Gosford city (newly-F); Wyong Shire (F); Ballina and Byron (non-F) Year study started: 2008 Year study ended: 2012 Year of change in fluoridation status: 2008 Study design: ITS
Participants	Inclusion criteria: children aged 5-7 years (data for 10- to 12-year olds also provided) Exclusion criteria: not stated Other fluoride sources: information on toothbrushing habit was collected, but not reported in details Social class: Shires of Ballina and Byron were more rural and less industrialised than Wyong Shire and Gosford CityInformation on parent's educational attainment and cardholder status was recorded, but not reported in details Ethnicity: aboriginal status was recorded, but not reported in details Residential history: not stated Other confounding factors: information on sugary drink was collected, but not reported in details
Interventions	Group 1: fluoridated (data not included in review) Group 2: newly fluoridated Group 3: non-fluoridated
Outcomes	dmft; DMFT; % caries free (deciduous dentition); % caries free (permanent dentition) Age at baseline measure: 5-7 years Age at final measure: 5-7 years
Funding	Centre for Oral Health Strategy, New South Wales Health, the Australian Dental Association (New South Wales Branch) and Northern Sydney and Central Coast Local Health Service
Notes	All data unpublished

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Low risk	Children were drawn from Catholic and state schools in the 3 areas and schools were randomly selected from a master list until the individual school rolls for primary school children aged 5-7 years added up to around 900
Confounding	High risk	Multivariate analysis of dmft was done taking educational attainment of parents, toothbrushing behaviour and sugary drink

Blinkhorn (unpublished) (*Continued*)

		consumption into account, however this was done by year, not by study area, and there was insufficient information to determine whether these confounding factors were balanced across study groups
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Though response rate was unbalanced across groups, data were presented for all examined participants
Selective reporting (reporting bias)	High risk	Standard deviation not reported
Other bias	Low risk	No other apparent bias

Booth 1991

Methods	**FLUOROSIS STUDY** Country of study: England Geographic location: Huddersfield (F); Dewsbury (non-F) Year of study: 1989 Year of change in fluoridation status: 1989 Study design: cross-sectional
Participants	Inclusion criteria: all 3-year-old white children; lifetime residents of study areas; positive informed consent Exclusion criteria: children who had moved out of the area; children who were ill; children taking fluoride tablets Other sources of fluoride: children taking fluoride tablets excluded from study Social class: areas matched using socioeconomic data from the 1981 census and recent unemployment data; parents asked about occupation of head of household during interview Ethnicity: white children only Residential history: lifetime residents Other confounding factors: not stated
Interventions	Group 1: 1 ppm (artificial fluoridation) Group 2: < 0.3 ppm (natural fluoridation)
Outcomes	Dental fluorosis (modified developmental defects of enamel index), caries data evaluated in study but excluded from review due to study design Age at assessment: 3 years
Funding	North Western Regional Health Authority

Booth 1991 (*Continued*)

Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Sampling	Low risk	Eligible children were identified from a list of all children in the health district and were randomly sampled from each population. The numbers required were based on a pilot study (no reference provided). No further details reported
Confounding	Low risk	Fluoride from other sources was controlled for using inclusion/exclusion criteria and there was no significant difference in SES between the groups
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were presented for the majority of those recruited (attending appointments)
Selective reporting (reporting bias)	Low risk	All expected data reported
Other bias	Low risk	No other apparent bias

Brothwell 1999

Methods	**FLUOROSIS STUDY** Country of study: Canada Geographic location: Wellington and Dufferin (neighbouring counties), South-Western Ontario Year of study: 1996-1997 (academic year) Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: children resident in Wellington-Dufferin-Guelph Health Unit area; parental consent; children aged 7-8 years Exclusion criteria: children with non-erupted or insufficiently erupted central incisors; children absent on day of examination Other sources of fluoride: amount of toothpaste usually used ("48.9% use > pea sized amount, 365/747"); fluoride supplements ("14.5% take supplements, 107/740"); age started brushing; use of mouthwash ("4% routinely use fluoridated mouthwash, 30/752"); breast/bottle fed; whether toothpaste used when brushing Social class: household income; highest level of education received. "It is likely that re-

Brothwell 1999 (*Continued*)

	spondents under-represented the disadvantaged segment of the population. How the low response rate in this subgroup affects the estimates of prevalence is unknown; however, it is unlikely to be a major source of bias. " Ethnicity: not stated Residential history: "The questionnaire assessed … years at current residence", 39% lifelong residents (293/752); 64.8% (487/752 resided at tested source from before the age of 3 (fluorosis-sensitive period - multivariate analysis restricted to these 487 participants) Other confounding factors: breast-feeding duration
Interventions	Group 1: ≥ 0.7 ppm (natural fluoridation) Group 2: < 0.7 ppm (natural fluoridation)
Outcomes	Dental fluorosis (TSIF score > 1) Age at assessment: 7-8 years
Funding	Not stated
Notes	Data extracted from Brothwell 1999 differs from that presented in CRD review

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Unclear risk	Children were selected via schools, however insufficient detail was reported regarding sampling
Confounding	High risk	Bivariate analysis showed that fluoridated mouthwash use and professional fluoride treatments were significantly associated with fluorosis prevalence, however, the data were not reported/presented in a manner which demonstrated adjustment for imbalance at baseline occurred, or was measured well and controlled for
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Testing of water samples for fluoridation level was conducted after screening examination (at the University of Toronto); examinations conducted by a single dental hygienist (in school clinics). It does not appear that, despite the lack of any attempt to blind being reported, that blinding would have had any effect on reducing bias
Incomplete outcome data (attrition bias) All outcomes	High risk	Significant missing data (e.g. 34 participants from the water sample)

Brothwell 1999 (*Continued*)

Selective reporting (reporting bias)	High risk	Comment: there is much that is either not reported in a sufficient manner to be able to glean the necessary information from (i. e. TSIF scores against fluoridation levels of water samples), or has significant missing data (e.g. 34 participants from the water sample) and so is difficult to draw the conclusions required for this review. No evidence of protocol in advance of obtaining data/undertaking analysis
Other bias	Low risk	Reporting dental fluorosis as TSIF score > 1 rather than ≥ 1 puts the results at risk of misclassification bias

Brown 1965

Methods	**CARIES STUDY** Country of study: Canada Geographic location: Brantford (F); Stratford (natural F); Sarnia (non-F), Ontario Year study started: 1948 Year study ended: 1959 Year of change in fluoridation status: 1945 Study design: CBA
Participants	Inclusion criteria: children aged 9-14 years; lifetime residents (absence of < 6 weeks since birth); all primary and secondary schools in study areas Exclusion criteria: none stated Other sources of fluoride: not stated Social class: not stated Ethnicity: not stated Residential history: lifetime residents Other confounding factors: not stated
Interventions	**Initiation of water fluoridation** Group 1: artifical fluoridation - ppm not stated Group 2: natural fluoridation - ppm not stated Group 3: 'negligible' - ppm not stated (natural fluoridation)
Outcomes	DMFT, % caries-free subjects (permanent teeth) Age at baseline measure: 9-11 years and 12-14 years Age at final measure: 9-11 years and 12-14 years
Funding	Not stated
Notes	
Risk of bias	

Brown 1965 (*Continued*)

Bias	Authors' judgement	Support for judgement
Sampling	Low risk	The study sample was selected by random sampling (by school and grade) described in "A Suggested Methodology for Fluoridation Surveys in Canada" (Department of National Health and Welfare 1952)
Confounding	High risk	Did not account for use of other fluoride sources or SES
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	High risk	Children 6-8 years were sampled and initially examined up until 1957, but were no longer included after 1957 as no significant differences were found to exist in that age group
Selective reporting (reporting bias)	Low risk	Outcome of interest reported
Other bias	Unclear risk	Inorder to maintain a uniform scale of observation, all examinations were done by the same examiner and intra-examiner, reproducibility not reported

Budipramana 2002

Methods	**FLUOROSIS STUDY** Country of study: Indonesia Geographic location: 10 villages in Asembagus subdistrict Year of study: 1999 Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: school children aged 6-12 years who were lifetime residents Exclusion criteria: not stated Other sources of fluoride: not stated Social class: the villages all had identical SES Ethnicity: the villages all had identical ethnic profiles Residential history: lifetime residents Other confounding factors: not stated
Interventions	All natural fluoridation Group 1: 0.51 ppm Group 2: 0.81 ppm

Budipramana 2002 (*Continued*)

	Group 3: 2.25 ppm Group 4: 3.16 ppm
Outcomes	Dental fluorosis (Dean's Index); caries data evaluated in study, but excluded from review due to study design Age at assessment: 6-12 years
Funding	Not stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Low risk	The authors reported that participants were chosen randomly from 1 selected primary school in each of the 10 villages. However, it is not clear why only 1 school was selected in each village and if the resulting sample was representative
Confounding	High risk	The use of other fluoride sources was not considered
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data for all participants was reported
Selective reporting (reporting bias)	Low risk	All expected outcome were reported
Other bias	High risk	No mention of examiner calibration

Butler 1985

Methods	**FLUOROSIS STUDY** Country of study: USA Geographic location: 16 Texas communities (selected to reflect a wide range of fluoride levels in drinking water) Year of study: 1980 Year study ended: 1981 Year of change in fluoridation status: unclear if natural or artifical fluoridation Study design: cross-sectional
Participants	Inclusion criteria: lifetime residents of study areas; enrolled in grades 2-6 (aged 7-13 years) and 9-12 (aged 14-19 years) in public schools Exclusion criteria: none stated Other sources of fluoride: fluoride toothpaste, fluoride drops, number of fluoride treatments Social class: mother's education Ethnicity: white/Spanish/black (ethnicity judged by surname?) Residential history: lifetime residents Other confounding factors: home air-conditioning; air temperature; number of months breastfed; children in the family; mother's age at child's birth; total dissolved solids in drinking water and zinc in drinking water; age
Interventions	Unclear as to whether the fluoridation was natural in all areas Group 1: 0.2 ppm Group 2: 0.2 ppm Group 3: 0.3 ppm Group 4: 0.7 ppm Group 5: 1.0 ppm Group 6: 1.0 ppm Group 7: 1.1 ppm Group 8: 1.8 ppm Group 9: 1.9 ppm Group 10: 1.9 ppm Group 11: 2.1 ppm Group 12: 2.1 ppm Group 13: 2.3 ppm Group 14: 2.3 ppm Group 15: 2.4 ppm Group 16: 3.3 ppm
Outcomes	Dental fluorosis (CFI score; prevalence of observed mottling (moderate)) Age at assessment: 7-19 years
Funding	Supported by grants from the US Environmental Protection Agency
Notes	Data extracted from Butler 1985 differs from that presented in CRD review

Risk of bias

Bias	Authors' judgement	Support for judgement

Butler 1985 (*Continued*)

Sampling	Low risk	All eligible children were invited to participate
Confounding	Unclear risk	While some confounders were measured well and some controlled for in the analysis, it is not clear whether the necessary adjustment was done to the data relevant to this review
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	High risk	Comment: reporting balanced across all groups; however not all data presented in a form that can be interrogated. Despite collecting data on the CFI's 6 categories of severity of mottling, only data for moderate mottling was presented independently of the overall CFI score for each group. Furthermore, identified confounders were not presented for each group, but for the portion of the study sample as a whole (despite being possible from authors having collected the data)
Other bias	High risk	Each child received a dental examination performed by one of the authors, however, calibration was not mentioned

Chandrashekar 2004

Methods	**FLUOROSIS STUDY** Country of study: India Geographic location: Davangere district Year of study: 2002 Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: lifetime residency; age 12-15 years Exclusion criteria: not stated Other fluoride sources: not stated Social class: similar socioeconomic conditions Ethnicity: not stated Residential history: lifetime residents

Chandrashekar 2004 (*Continued*)

	Other confounding factors: not stated
Interventions	All natural fluoridation Group 1: 0.22 ppm Group 2: 0.43 ppm Group 3: 0.74 ppm Group 4 0.93 ppm Group 5: 1.1 ppm Group 6: 1.22 ppm Group 7: 1.63 ppm Group 8: 2.08 ppm Group 9: 2.33 ppm Group 10: 2.64 ppm Group 11: 2.91 ppm group 12: 3.41 ppm
Outcomes	Dental fluorosis (TF Index) Age at assessment: 12-15 years
Funding	Not stated
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Unclear risk	Villages satisfying eligibility criteria were selected randomly and children were accessed via schools. It is not clear, however, how the children within the schools were selected
Confounding	High risk	No details were reported on the use of fluoride from other sources
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The number of participants analysed was not reported
Selective reporting (reporting bias)	High risk	Dean's fluorosis index was measured but not reported
Other bias	Low risk	No other apparent bias

Chen 1989

Methods	**FLUOROSIS STUDY** Country of study: Taiwan Geographic location: Shenkang Hsiang, Changwa Year of study: 1987-1988 Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: children aged 6-16 years; lifetime residents of study areas; always used water wells as primary source of drinking water Exclusion criteria: not stated Other fluoride sources: not stated Social class: not stated Ethnicity: not stated Residential history: lifetime residents Other confounding factors: author states that project communities had approximately the same location, climate, diet, food habits and customs, mean average daily temp = 25 ^{o}C, range = 13 ^{o}C-37 ^{o}C
Interventions	All natural fluoridation Group 1: 4.2-4.9 ppm Group 2: 2.1-2.8 ppm Group 3: 1.4-2.1 ppm Group 4: 0.7-1.4 ppm Group 5: 0.4-0.7 ppm Group 6: < 0.4 ppm
Outcomes	Dental fluorosis prevalence (Dean's Index); caries data evaluated in study but not included in review due to study design Age at assessment: 6-16 years
Funding	National Science Council, Taiwan, ROC (NSC-77-0412-B-039-05)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Low risk	All eligible participants in the were included in the study
Confounding	High risk	Did not account for use of other fluoride sources or SES
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information

Chen 1989 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	5172 children recruited and examined, however, data presented for 5072 participants. Unclear if missing data balanced across groups
Selective reporting (reporting bias)	Low risk	Outcome of interest reported
Other bias	Unclear risk	Examiners were calibrated before actual assessments of caries and fluorosis were initiated, however, kappa values were not reported

Chen 1993

Methods	**FLUOROSIS STUDY** Country of study: China Geographic location: Anquan village (low F); Hubei village (high F), Fenshun county, Guangdong Province Year of study: 1984 Year study ended: 1991 Year of change in fluoridation status: 1984 Hubei, 1986 Anquan Study design: before-and-after
Participants	Inclusion criteria: native born children aged 8-12 years for dental fluorosis Exclusion criteria: not stated Other sources of fluoride: not stated Social class: author stated that economic and living habits were similar in all study areas Ethnicity: not stated. Residential history: only native born children were assessed Other confounding factors: not stated
Interventions	Water source from wells changed to river water Group 1: Hubei 4.1 mg/l (1984 pre-intervention - natural from wells); 0.8 mg/l (1984 at point of intervention - natural from river); 3.1 mg/l*(1991, 7 years post-intervention - natural from river) * Increase due to damaged walls of well at bottom of river bed allowing hot spring water with high fluoride content to amalgamate. No regular monitoring took place after changing water supply and therefore unclear when water fluoride content increased in Hubei Group 2: Anquan 12.5 mg/l (1984 pre-intervention - natural from wells); 0.3 mg/l (1986 at point of intervention - natural from river); 0.4 mg/l (1991, 5 years post-intervention - natural from river)
Outcomes	Dental fluorosis (Dean's Index); skeletal fluorosis Age at baseline measure: 8-12 years (dental fluorosis) and 16-65 years (skeletal fluorosis) Age at final measure: 8-12 years (dental fluorosis) and 16-65 years (skeletal fluorosis)

Chen 1993 (*Continued*)

Funding	Not stated	
Notes	Data extracted from Chen 1993 differs from that presented in CRD review Discrepancies between text and table with regard to fluoride concentration	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Sampling	Low risk	All eligible children were included in the study examined for dental fluorosis and for skeletal fluorosis, adults aged 16-65 years were randomly sampled to have roentgenograms taken in pelvis
Confounding	High risk	Did not account for use of other fluoride sources
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	High risk	For both study areas, n = 800 (Anquan) and n = 1331 (Hubei), however, data not reported for all participants
Selective reporting (reporting bias)	Low risk	Outcome of interest reported
Other bias	High risk	No mention of examiner calibration. Also, quote: "by investigation, it was found that the walls of the well for storing water at the bottom of river bed and water pipe were damaged, the hot spring water with high fluoride content gushed into the well and pipe. Because there was no regular monitoring on the water fluoride after changing water sources, it was unclear when the water fluoride content increased in Hubei"

Clark 1993

Methods	**FLUOROSIS STUDY** Country of study: Canada Geographic location: Kelowna (F); Vernon (non-F), British Columbia Year of study: not stated Year of change in fluoridation status: 1954 Study design: cross-sectional
Participants	Inclusion criteria: children in selected schools Exclusion criteria: children with fixed orthodontic appliances; missing anterior teeth Other sources of fluoride: not stated Social class: 2 communities selected because of regional and socioeconomic similarities Ethnicity: not stated Residential history: information recorded in questionnaire and verified by telephone, but doesn't appear to have been prohibitive for inclusion in study Other confounding factors: 274 participants had been exposed to fluoride supplements
Interventions	Group 1: 1.2 ppm (artificial fluoridation) Group 2: < 0.1 ppm (natural fluoridation)
Outcomes	Dental fluorosis (TSIF) Age at assessment: school age
Funding	Supported by the British Columbia Health Research Foundation
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Low risk	Primary schools were stratified into low, medium and high SES categories from a specified sampling frame. Schools were then randomly selected and all eligible children within the selected schools were included in the studies
Confounding	High risk	Did not account for use of other fluoride sources
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	Low risk	Outcome of interest reported

Clark 1993 (*Continued*)

Other bias	High risk	Kappa value of 0.44 suggests a moderate degree of inter-examiner agreement

Clarkson 1989

Methods	**FLUOROSIS STUDY** Country of study: Ireland and England Geographic location: Cork (low and high F; 2 separate areas) and Manchester (low F) Year of study: not stated Year of change in fluoridation status: not stated Study design: cross-sectional
Participants	Inclusion criteria: children aged 8 and 15 years Exclusion criteria: not stated Other sources of fluoride: not stated Social class: not stated Ethnicity: not stated Residential history: not stated Other confounding factors: not stated
Interventions	Group 1: 'optimal' level - ppm not stated (artificial fluoridation) Group 2: 'low' level - ppm not stated (natural fluoridation) Gruop 3: 'low' level - ppm not stated (natural fluoridation)
Outcomes	Enamel defects (DDE) Age at assessment: 8 and 15 years
Funding	Not stated
Notes	Data extracted from Clarkson 1989 differs from that presented in CRD review

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Low risk	Sampling was by stratified random selection of eligible children in the study areas. Stratification based on school size and gender
Confounding	High risk	Did not account for the use of other fluoride sources
Blinding of outcome assessment (detection bias) All outcomes	High risk	To assess reproducibility, 46 children were examined twice without the examiner's knowledge, however, there is no indication of the examiner being blind to fluoridation

Clarkson 1989 (*Continued*)

		status of participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	Low risk	Outcome of interest was fully reported and balanced across groups
Other bias	Low risk	No other apparent bias

Clarkson 1992

Methods	**FLUOROSIS STUDY** Country of study: Ireland Geographic location: Ireland Year of study: 1984 Year of change in fluoridation status: 1964 Study design: cross-sectional
Participants	Inclusion criteria: children aged 8 and 15 years Exclusion criteria: none stated Other sources of fluoride: increase in use of fluoride-containing toothpaste and infant formula made with fluoridated water Social class: not stated Ethnicity: not stated Residential history: not stated Other confounding factors: problems of consistent levels in the fluoridated supply during the 1960s and early 1970s
Interventions	Group 1: 'optimal' level - ppm not stated (artificial fluoridation) Group 2: 'low' level - ppm not stated (natural fluoridation)
Outcomes	Dental fluorosis (Deans Index); enamel defects (DDE) Age at assessment: 8 and 15 years
Funding	Not stated
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Low risk	A stratified proportional random sampling procedure was used with size of school with fluoridation status and sex as stratifying factors

Clarkson 1992 (*Continued*)

Confounding	High risk	Did not account for the use of other fluoride sources or SES
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The number of participants recruited was not reported and there was a variation in the number of children examined for enamel defects and children interviewed on perception of defects. It is not clear whether data were presented for all recruited participants
Selective reporting (reporting bias)	High risk	Data not in suitable format for analysis
Other bias	Low risk	No other apparent bias

Cochran 2004a

Methods	**FLUOROSIS STUDY** Country of study: Ireland, England, Greece, Netherlands, Finland, Iceland, and Portugal Geographic location: Cork, Haalem, Athens, Reykjavik, Oulu, Knowsley, Almada/Setubal Year of study: 1997-1998 Year of change in fluoridation status: varies Study design: cross-sectional
Participants	Inclusion criteria: not stated Exclusion criteria: not stated Other sources of fluoride: information about use of fluoride supplements, age at which toothpaste was first used and the amount and type of toothpaste used were collected but not reported Social class: the sampling ensured a wide socioeconomic spread of participants Ethnicity: not stated Residential history: parents were given questionnaires to supply information on history of living a fluoridated area. No further details reported Other confounding factors: not stated
Interventions	Group 1: < 0.01 ppm (natural fluoridation) Group 2: 0.05 ppm (natural fluoridation) Group 3: 0.08 ppm (natural fluoridation) Group 4: < 0.1 ppm (natural fluoridation) Group 5: 0.13 ppm (natural fluoridation) Group 6: 1 ppm (artificial fluoridation)
Outcomes	Dental fluorosis (TF Index); enamel defects (DDE) Age at assessment: 8 years

Cochran 2004a (*Continued*)

Funding	Not stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Unclear risk	The sampling frame was specified, but the eligibility criteria were not stated. It is not clear whether the number of children photographed as a percentage of the total population of children in the age group (12-23%) is representative
Confounding	High risk	Data were collected on the use of fluoride from other sources but not reported on
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Fluorosis was assessed using photographs and was done without reference to the area from which they were collected
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "A total of 5250 transparencies was taken, of which 114 (2.2%) were not suitable for analysis" Unlikely to influence results
Selective reporting (reporting bias)	Unclear risk	Outcome of interest fully reported, however data relating to confounding variables was collected but not reported
Other bias	Unclear risk	Reliability testing was carried out. The Kappa statistic from all the study sites showed substantial to excellent agreement with the 'gold standard', except for one study site that showed moderate agreement (0.49; Cochran 2004b). It is not clear what effect this moderate agreement would have on the results given that agreement at the other study sites was substantial to excellent

Colquhoun 1984

Methods	**FLUOROSIS STUDY** Country of study: New Zealand Geographic location: Auckland Year of study: 1983 Year of change in fluoridation status: 1953 Study design: cross-sectional
Participants	Inclusion criteria: school children aged 7-12 years Exclusion criteria: children with mottling who were known to have grown up in areas with different fluoridation status from the place in which they were examined Other sources of fluoride: fluoride toothpaste use accounted for 76% of toothpaste sales in New Zealand in 1980. Though there had been a marked increase in fluoride toothpaste use since 1970, there was no trend toward a greater severity of dental fluorosis among younger children Social class: results stratified on social class - incidence of advanced dental fluorosis inversely related to social class but prevalence of dental fluorosis slightly higher in lower social class Ethnicity: ethnic composition of study areas was similar except for higher proportion of Maori and Pacific Island people in the lower socioeconomic areas Residential history: proportion of children at each clinic who were not life-long residents of the suburb was not ascertained, but there was no reason to suppose that proportions differed between areas Other confounding factors: not stated
Interventions	Group 1: 1 ppm (artificial fluoridation) Group 2: 'low' level - ppm not stated (natural fluoridation)
Outcomes	Dental fluorosis (diffuse opacities) Age at baseline measure: 7-12 years
Funding	Not stated
Notes	Data extracted from Colquhoun 1984 differs from that presented in CRD review

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Unclear risk	A population of 458 school children in the fluoridated area had initially been investigated, so the author made further observations on school children of the same age in 6 additional dental clinics chosen at random. An additional 342 children of same age were examined from the non-fluoridated area, but how they were selected was not reported

Colquhoun 1984 (*Continued*)

Confounding	High risk	Some children had used fluoride tablets, but were not excluded from the analysis. The fluoridated area had participants that were of low, middle and high SES while the non-fluoridated area had only participants of low SES
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	High risk	Data not in suitable format for analysis
Other bias	High risk	Intra- and inter-examiner reliability not mentioned

Correia Sampaio 1999

Methods	**FLUOROSIS STUDY** Country of study: Brazil Geographic location: rural areas of Paraiba Year of study: 1997 Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: lifetime residents of study areas; children attending public schools (aged 6-11 years) Exclusion criteria: children who refused to be examined; those without permanent teeth; undetermined place of birth Other sources of fluoride: no topical or systemic fluoride programme implemented in schools; children interviewed about oral health habits and use of toothpaste Social class: all study areas were of low socioeconomic status Ethnicity: not stated Residential history: lifetime residents Other confounding factors: nutritional status
Interventions	Group 1: > 1.0 ppm (natural fluoridation) Group 2: 0.7-1.0 ppm (natural fluoridation) Control: < 0.7 ppm (natural fluoridation)
Outcomes	Dental fluorosis (TF Index) Age at assessment: 6-11 years
Funding	Brazilian Ministry of Education CAPES (1666/95-4)

Correia Sampaio 1999 (*Continued*)

Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Sampling	Low risk	All eligible children attending schools in the study area were included
Confounding	Unclear risk	It was reported that the areas of study were generally low SES. Data were collected on the use of fluoride toothpaste and brushing habits, but showed that those brushing their teeth less frequently had higher levels of fluorosis. It was also reported that the levels of fluorosis in the area had not changed since the introduction of fluoride toothpastes
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	Low risk	Outcome of interest was fully reported and balanced across groups
Other bias	Low risk	No other apparent biases

Cutress 1985

Methods	**FLUOROSIS STUDY** Country of study: New Zealand Geographic location: Auckland, Frankton and Rodney Year of study: not stated Year of change in fluoridation: 1953 Study design: cross-sectional
Participants	Inclusion criteria: children returning parental consent forms and completed questionnaires; lifetime residents of study areas; children aged 9 Exclusion criteria: none stated Other sources of fluoride: ingestion of fluoride tablets Social class: not stated Ethnicity: European (80% F; 84% non F); Polynesian (16%F; 11% non-F); Asian (2% F; 1% Non-F); Mixed (2% F; 4% non-F) Residential history: lifetime residents

Cutress 1985 (*Continued*)

	Other confounding factors: not stated
Interventions	Group 1: 1.0 ppm (artificial fluoridation) Group 2: < 0.3 ppm (natural fluoridation)
Outcomes	Any enamel defect Age at assessment: 9 years
Funding	Not stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Unclear risk	Schools in the fluoridated area were randomly selected. All schools in the control area were selected. No details were reported about how the children were selected for the study
Confounding	High risk	There was an imbalance in lifetime residents using fluoride tables in the fluoridated area compared to the non-fluoridated area. SES was not accounted for
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Children were taken to the examination centre by bus to prevent the examiner from identifying residence or fluoridation status
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	Low risk	Outcome of interest was fully reported on and balanced across groups
Other bias	Low risk	No other apparent bias

Cypriano 2003

Methods	**FLUOROSIS STUDY** Country of study: Brazil Geographic location: Porto Feliz, Ipero, Itaoca and Barra do Chapeu (F); Bom Sucesso do Itarare and Itapirapua Paulista (non-F) Year of study: 2003 Year of change in fluoridation status: 1981 Study design: cross-sectional
Participants	Inclusion criteria: pre-school children aged 5-6 years and students aged 7-12 years Exclusion criteria: individuals outside the 5-12 years age bracket Other sources of fluoride: not stated Social class: not stated Ethnicity: not stated Residential history: not stated Other confounding factors: not stated
Interventions	Group 1: 'optimal' level - ppm not stated (artificial fluoridation) Group 2: 'low' level - ppm not stated (natural fluoridation)
Outcomes	Dental fluorosis (Community Fluorosis Index) Age at assessment: 5-12 years
Funding	Not stated
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Low risk	7 out of 48 counties were randomly selected by raffle, based on size and the presence or absence of fluoridated water. Children were then randomly selected from schools
Confounding	High risk	Did not account for the use of other fluoride sources or SES
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data for all participants appears to be presented
Selective reporting (reporting bias)	High risk	Fluorosis data were not reported for children between 5 and 6 years and no explanations were provided

Cypriano 2003 (*Continued*)

Other bias	Low risk	No other apparent bias

de Crousaz 1982

Methods	**FLUOROSIS STUDY** Country of study: Switzerland Geographic location: Bale-Ville (F); Friburg and Neuchatel (non-F) Year of study: 1979 Year of change in fluoridation status: 1961 Study design: cross-sectional
Participants	Inclusion criteria: not stated for control areas, for fluoride area only Exclusion criteria: children born outside Switzerland Other sources of fluoride: not stated Social class: not stated Ethnicity: not stated Residential history: lifetime residents Other confounding factors: not stated
Interventions	Group 1: 1 ppm (artificial fluoridation) Group 2: 'low' level - ppm not stated (natural fluoridation)
Outcomes	Dental fluorosis (TFI) Age at assessment: 6-13 years
Funding	Subsidy from SSO research funds
Notes	Data extracted from de Crousaz 1982 differs from that presented in CRD review

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Unclear risk	The children were accessed via schools, however the sampling frame was unspecified
Confounding	High risk	Did not account for the use of other fluoride sources or SES
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Examiners worked independently without knowledge of the origin of the children
Incomplete outcome data (attrition bias) All outcomes	High risk	Data were not presented for all participants and missing outcome data varied greatly across study groups

de Crousaz 1982 (*Continued*)

Selective reporting (reporting bias)	High risk	Data not in suitable format for analysis
Other bias	High risk	Examiners were calibrated and trained but kappa values for reliability not reported. The authors assume that a combination of clinical and photographic examination are sufficient for the verification of intra-and inter-examiner reproducibility, so kappa values may not have been calculated

DHSS England 1969

Methods	**FLUOROSIS STUDY** Country of study: England Geographic location: Watford (F); Sutton (non-F) Year of study: 1956 Year study ended: 1967 Year of change in fluoridation status: 1956 Study design: CBA
Participants	Inclusion criteria: lifetime residents of study areas; consumed piped water at home and at school Exclusion criteria: children that were not continuous residents Other sources of fluoride: none stated Social class: none stated, however, study areas and associated control area had be situated near to each other and be of the same character (e.g. industrial, semi-industrial, rural or residential) Ethnicity: none stated Residential history: lifetime residents Other confounding factors: information on oral hygiene was recorded
Interventions	**Initiation of water fluoridation** Group 1 at baseline: 'low' level - ppm not stated (natural fluoridation) Group 1 post intervention: 0.89-0.99 ppm (artificial fluoridation) Group 2: 'low level' - ppm not stated (natural fluoridation)
Outcomes	dmft, DMFT, % caries-free subjects (deciduous teeth), % caries-free subjects (permanent teeth) Age at baseline measure: 3-14 years Age at final measure: 3-14 years
Funding	Not stated
Notes	Data extracted from DHSS England 1969 differs from that presented in CRD review (additional data extracted)

Risk of bias

DHSS England 1969 (*Continued*)

Bias	Authors' judgement	Support for judgement
Sampling	Low risk	Representative groups of children of all ages included in the study were examined in each area and as far as possible the same standards of examination were maintained in the pairs of areas for which the dental findings were to be compared (HMSO 1962)
Confounding	High risk	No details were reported on the use of fluoride from other sources or on the dietary habits of the children
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data for all participants appears to have been presented
Selective reporting (reporting bias)	High risk	Enamel defects, white or stained, which might be confused with fluoride mottling were also noted but not presented in the report; standard deviation not reported
Other bias	High risk	No mention of calibration and reliability testing of the examiners

DHSS Scotland 1969

Methods	**CARIES STUDY** Country of study: Scotland Geographic location: Kilmarnock (F); Ayr (non-F) Year study started: 1961 Year study ended: 1968 Year of change in fluoridation status: 1956 Study design: cBA
Participants	Inclusion criteria: lifetime residents of study areas; consumed piped water at home and at school Exclusion criteria: not stated Other sources of fluoride: not stated Social class: not stated Ethnicity: not stated Residential history: continuous residents Other confounding factors: not stated

DHSS Scotland 1969 (*Continued*)

Interventions	**Initiation of fluoridation** Group 1: 1 ppm (artificial fluoridation) Group 2: 'low' level - ppm not reported (natural fluoridation)
Outcomes	dmft, % caries-free subjects (primary teeth) Age at baseline measure: 5 years Age at final measure: 5 years
Funding	Not stated
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Low risk	Representative groups of children of all ages included in the study were examined in each area and as far as possible the same standards of examination were maintained in the pairs of areas for which the dental findings were to be compared (HMSO 1962)
Confounding	High risk	The effect of sugary diet consumption and use of fluoride from other sources were not taken into account
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blind outcome assessment not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	A cross-section of children were examined each year, together with some children in nurseries and nursery schools, but findings for the later were not presented
Selective reporting (reporting bias)	High risk	Enamel defects, white or stained, which might be confused with fluoride mottling were also noted but not presented in the report; standard deviation not reported
Other bias	High risk	No mention of calibration of examiners and reliability testing

DHSS Wales 1969

Methods	**CARIES STUDY** Country of study: Wales Geographic location: Gwalchmai zone (F); Holyhead (mainly F - gets most of water from Gwalchmai, but occasionally also receives water from Bodafon); and Bodafon zone (non-F) Year study started: 1956 Year study ended: 1965 Year of change in fluoridation status: 1955 Study design: CBA
Participants	Inclusion criteria: continuous residents of study areas; consumed piped water both at home and school; up to 15 years (Gwalchmai and Bodafon); up to 11 years (Holyhead) Exclusion criteria: not stated Other sources of fluoride: not stated Social class: none stated, however, study areas and associated control area had be situated near to each other and be of the same character (e.g. industrial, semi-industrial, rural or residential) Ethnicity: not stated Residential history: continuous residents Other confounding factors: information on oral hygiene was recorded
Interventions	**Initiation of water fluoridation** Group 1 baseline: 'low' level - ppm not stated (natural fluoridation) Group 1 post intervention: 0.8-0.9 ppm (artificial fluoridation) Group 2 baseline: 'low' level - ppm not stated (natural fluoridation) Group 2 post intervention: 0.8-0.9 ppm (artificial fluoridation) Group 3: 'low' level - ppm not stated (natural fluoridation)
Outcomes	dmft, DMFT, % caries-free subjects (deciduous teeth), % caries-free subjects (permanent teeth) Age at baseline measure: 3-14 years Age at final measure: 3-14 years
Funding	Not stated
Notes	Data extracted from DHSS Wales 1969 differs from that presented in CRD review (additional data extracted)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Unclear risk	Pre-school children examined were a reasonably good cross-section of Anglesey children of that age, however, different age criteria were used for school children in different study areas (up to 15 years in Gwalchmai and Bodafon; up to 11 years in Holyhead). The reason for this was not

DHSS Wales 1969 (*Continued*)

		reported. (HMSO 1962)
Confounding	High risk	No details were reported on the use of fluoride from other sources or on the dietary habits of the children
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data for all participants appears to be presented
Selective reporting (reporting bias)	High risk	Enamel defects, white or stained, which might be confused with fluoride mottling were also noted but not presented in the report
Other bias	High risk	No mention of calibration and reliability testing of examiners

Downer 1994

Methods	**FLUOROSIS STUDY** Country of study: England, Scotland and Ireland Geographic location: Dublin (F); north London, Edinburgh and Glasgow (non-F) Year of study: not stated Year of change in fluoridation status: 1965 Study design: cross-sectional
Participants	Inclusion criteria: children aged 12 years; lifetime residents of study areas Exclusion criteria: not stated Other sources of fluoride: not stated Social class: not stated, however, sampling in the fluoridated areas was done to achieve a mix of participants from different SES Ethnicity: not stated Residential history: lifetime residents Other confounding factors: not stated
Interventions	Group 1: 0.9 ppm (artificial fluoridation) Group 2: 'low' level - ppm not stated (natural fluoridation) Group 3: 'low' level - ppm not stated (natural fluoridation) Group 4: 'low' level - ppm not stated (natural fluoridation)
Outcomes	Enamel defects (DDE); caries data also evaluated within the study but excluded from review due to study design Age at assessment: 12 years

Downer 1994 (*Continued*)

Funding	Not stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Unclear risk	25% of the secondary schools in Glasgow and Dublinwere randomly selected to participate, and participants were selected at random. Sampling in London was aimed at examining all 12-year-old children in secondary schools in 3 districts and 14 out of 19 schools. The reason for non-participation of 5 out of the 19 eligible schools in the non-fluoridated area was logistical and the authors state that this was (Quote:) *"unlikely to have caused sampling bias"*. In Edinburgh a random selection of 20% of children in 20 out of 50 eligible schools, drawn at random, formed the sample
Confounding	High risk	No details were reported on the use of fluoride from other sources
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	High risk	Data not in suitable format for analysis
Other bias	Low risk	No other apparent bias

Driscoll 1983

Methods	**FLUOROSIS STUDY** Country of study: USA Geographic location: 7 rural Illinois communities within 75 miles of each other Year of study: 1980 Year of change in fluoridation status: NA Study design: cross-sectional

Driscoll 1983 (*Continued*)

Participants	Inclusion criteria: children in grades 3-10 (age 8-16 years); lifetime residents of study areas; consumed public water Parental consent Exclusion criteria: not stated Other sources of fluoride: not stated Social class: relatively small, rural communities chosen because they shared several similar characteristics Ethnicity: < 5% non white Residential history: lifetime residents Other confounding factors: same climatic zone
Interventions	Group 1: 3.84-4.07 ppm (natural fluoridation) Group 2: 2.84-3.77 ppm (natural fluoridation) Group 3: 2.08 ppm (natural fluoridation) Group 4: 1.06 ppm (natural fluoridation)
Outcomes	Dental fluorosis (Dean's Index; CFI; TSIF was also used but reported in a later paper); caries data were measured but excluded from this review due to study design Age at assessment: 8-16 years
Funding	Not stated
Notes	None of the communities had made any change in its water source that was likely to alter the fluoride concentration during the period relevant to the study

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Unclear risk	There was insufficient detail reported to determine how selection took place
Confounding	High risk	Did not account for the use of other fluoride sources or SES
Blinding of outcome assessment (detection bias) All outcomes	High risk	Different examiners carried out measurements in order to avoid bias, however, this may not have been sufficient to avoid detection bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	All findings were based only on those children assessed for both fluorosis and majority of the children fall under this category. Also, the higher-than-optimal study area had considerably fewer children compared to the other areas due to small size of the communities and other similar communities in same geographic area were not available. This was not considered sufficient to

Driscoll 1983 (*Continued*)

		introduce bias
Selective reporting (reporting bias)	High risk	Data not in suitable format for analysis
Other bias	Low risk	No other apparent bias

Ekanayake 2002

Methods	**FLUOROSIS STUDY** Country of study: Sri Lanka Geographic location: Uda Walawe Year of study: 2001 Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: completion of the 14th but not the 15th birthday; availability in school on the day of the examination Exclusion criteria: not stated Other sources of fluoride: not stated Social class: almost all belonged to the low socioeconomic group Ethnicity: not stated Residential history: resident at present address since birth Other confounding factors: no details reported; nearly 75% of the subjects had used fluoride toothpaste from the age of about 9-12 months (discussion section)
Interventions	All natural fluoridation Group 1: $\leq$ 0.3 ppm Group 2: 0.31-0.49 ppm Group 3: 0.5-0.7 ppm Group 4: > 0.7 ppm
Outcomes	Enamel defect (DDE) Age at assessment: 14 years
Funding	Not stated
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Low risk	6 schools were selected on the basis of being sufficiently large for study. All eligible children present on day of study were examined

Ekanayake 2002 (*Continued*)

Confounding	High risk	While it is stated in the paper that "Less than 75% of the participants started teeth brushing with fluoride toothpaste from 9-12 months of age", the use of other fluoride sources was not controlled for, neither was it reported by fluoridation status
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	6.25% of the children examined were not included in the analysis. The authors did not report their fluoride exposure, and it is not clear whether their exclusion may have introduced bias
Selective reporting (reporting bias)	Low risk	Outcome of interest reported
Other bias	Low risk	No other apparent bias

Eklund 1987

Methods	**FLUOROSIS STUDY** Country of study: USA Geographic location: Lordsburg (high-F); Deming (lower-F), New Mexico Year of study: not stated Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: resident in study areas for the first 6 years of life; subjects aged approximately 30-60 years old; consumed city water supplies Exclusion criteria: not stated Other sources of fluoride: not stated Social class: areas similar for education and income level; number of years of education similar between areas Ethnicity: Lordsburg: 89.6% = Hispanic; Deming: 74.2% = Hispanic Residential history: residence for the first 6 years of life Other confounding factors: not stated
Interventions	All natural fluoridation Group 1: 3.5 ppm Group 2: 0.7 ppm
Outcomes	Dental fluorosis (Dean's Index); caries data also evaluated within the study but excluded from review due to study design Age at assessment: 27-65 years

Eklund 1987 (*Continued*)

Funding	Not stated
Notes	Data extracted from Eklund 1987 differs from that presented in CRD review

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Low risk	Efforts were made to recruit all eligible adults in all the communities and 80%-90% of eligible people consented and participated
Confounding	High risk	No details were reported on the use of fluoride from other sources
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	Low risk	Outcome of interest was fully reported on and balanced across groups
Other bias	Low risk	No other apparent bias

Ellwood 1995

Methods	**FLUOROSIS STUDY** Country of study: Ireland and Wales Geographic location: Chester (non-F); Bala (non-F); Anglesey (F); Cork (F) Year of study: 1991 Year study ended: not reported Year of change in fluoridation status: NA Study design: cross-sectional study
Participants	Inclusion criteria: lifetime residents of study areas (children only); agreement to participate Exclusion criteria: fixed orthodontic appliances Other sources of fluoride: tooth brushing behaviour - age started brushing; weekly tooth brushing frequency Social class: children from all 3 groups were from schools with a similar social profile Ethnicity: not stated Residential history: lifetime residents Other confounding factors: not stated

Ellwood 1995 (*Continued*)

Interventions	Group 1: 0.7 ppm (artificial fluoridation) Group 2: 0.9 ppm (artificial fluoridation) Group 3: < 0.1 ppm (natural fluoridation)
Outcomes	Enamel defect (DDE) Age at assessment: 14 years
Funding	Not stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Unclear risk	There was insufficient detail reported to determine how selection took place
Confounding	Low risk	SES and reported tooth brushing frequency were similar across groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Photographs were taken, identified randomly and examined without reference to subject details
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	Low risk	Outcome of interest was fully reported on and balanced across groups
Other bias	Low risk	No other apparent bias

Ellwood 1996

Methods	**FLUOROSIS STUDY** Country of study: England and Wales Geographic location: Anglesey (F); Chester and Bala (non-F) Year of study: 1991 Year of change in fluoridation status: 1955 Study design: cross sectional
Participants	Inclusion criteria: children in their 3rd year of secondary education; lifelong residents of study areas Exclusion criteria: children with fixed orthodontic appliances; absence at the time of examination Other sources of fluoride: not stated

Ellwood 1996 (*Continued*)

	Social class: not stated, however, the schools in the non-fluoridated areas had similar catchment areas to those from the fluoridated area. No further details reported Ethnicity: not stated Residential history: lifetime residents Other confounding factors: not stated
Interventions	Group 1: 0.7 (artificial fluoridation) Control: < 0.1 (natural fluoridation)
Outcomes	Dental fluorosis (TF Index); caries data also evaluated within the study but excluded from review due to study design Age at assessment: 14 years
Funding	Not stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Unclear risk	3 schools from Anglesey were selected and for the control group, schools with catchment areas as similar as possible to those from Anglesey were chosen from Chester and Bala using national census statistics. There was no random selection of schools in Anglesey, and it is not clear whether the selected schools were a representative sample
Confounding	High risk	Did not account for the use of other fluoride sources or SES
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Photographs were taken, randomly mixed and scored without reference to subject details
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	Low risk	Outcome of interest was fully reported on and balanced across groups
Other bias	Low risk	No other apparent bias

Ermis 2003

Methods	**FLUOROSIS STUDY** Country of study: Turkey Geographic location: Izmir and Isparta Year of study: not stated Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: lifelong residence; use of the public water supply continuously as source of drinking water; absence of nutrition deficiency Exclusion criteria: not stated Other sources of fluoride: not stated Social class: the selected schools were public secondary schools Ethnicity: not stated Residential history: lifetime residents Other confounding factors: toothbrushing frequency: did not brush = 22 (7.9%); irregularly = 49 (17.6%); once a day = 115 (41.4%); more than once = 92 (33.1%)
Interventions	All natural fluoridation Group 1: 0.3-0.4 ppm Group 2: 1.42-1.54 ppm Group 3: 1.55-1.66 ppm
Outcomes	Dental fluorosis prevalence (TSIF); caries data also evaluated within the study but excluded from review due to study design due to study design Age at assessment: 12-14 years
Funding	Not stated
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Low risk	4 schools were selected using a random sampling technique from a list of all public secondary schools. Within these schools eligible children were selected randomly
Confounding	Unclear risk	Toothbrushing habits differed between participants, however it is not clear whether they varied across study groups
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants

Ermis 2003 (*Continued*)

Selective reporting (reporting bias)	High risk	Fluorosis prevalence was measured, but only reported for the high fluoride areas and not for the low fluoride area
Other bias	Low risk	No other apparent bias

Firempong 2013

Methods	**FLUOROSIS STUDY** Country of study: Ghana Geographic location: Bongo district (Zone A: Atampiisi, Soeboko and Aliba; Zone B: Nayire, Boyrigo, Anabisa, Amagre and Tigre; Zone C: Soe, Kuyeligo, and Kunduo; Zone D: Yakanzanway, Gurigo, Ababorobiisi, Zaasi, and Anafobiisi) Year of study: 2008-2009 Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: lived in the area for the first 7 years of childhood; using water from a constant source that could still be traced Exclusion criteria: medically confirmed dental problem different from dental fluorosis; history of tobacco or kola use Other sources of fluoride: information on frequency of toothbrushing (P value 0.101) and type of oral health product (P value 0.179) were collected and there was no difference between the 4 zones Social class: the children had similar educational backgrounds Ethnicity: not stated Residential history: lifetime residents for first 7 years of childhood Other confounding factors: not stated
Interventions	All natural fluoridation Group 1: 0.95 ppm Group 2: 1 ppm Group 3: 1.86 ppm Group 4: 2.36 ppm
Outcomes	Dental fluorosis (Dean's Index) Age at assessment: 7-18 years
Funding	Supported by the Regional Laboratory of the Ghana Water Company/Aqua Viten Rands Limited in Tamale, Ghana
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Firempong 2013 (*Continued*)

Sampling	Unclear risk	Stated that eligible children were randomly selected, but insufficient detail provided to make a clear judgement
Confounding	High risk	While there appears to be little difference in the use of oral hygiene habits across groups, did not account for SES
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	Low risk	Outcome of interest reported
Other bias	High risk	Quote: "A professional examiner was engaged to carry out all the testing measurements ..." Comment: intra-examiner reliability test not reported and may not have been conducted

Forrest 1956

Methods	**FLUOROSIS STUDY** Country of study: England Geographic location: West Mersey (5.8 ppm); Burnham-on-Crouch (3.5 ppm); Harwich (2/1.6 ppm); Slough (0.9 ppm) Saffron Walden and District (non-F); Stoneleigh and Malden West (non-F) Year of study: 1954 Year of change in fluoridation status: NA Study design: cross sectional
Participants	Inclusion criteria: lifetime residents of study areas; children aged 12-14 years Exclusion criteria: not stated Other sources of fluoride: not stated Social class: not stated Ethnicity: not stated Residential history: lifetime residents Other confounding factors: not stated
Interventions	All natural fluoridation Group 1: 5.8 ppm Group 2: 3.5 ppm Group 3: 2.0 ppm Group 4: 0.9 ppm

Forrest 1956 (*Continued*)

	Group 5: 0.1-0.2 ppm Group 6: 0.1 ppm
Outcomes	Dental fluorosis (Dean's Index); caries data also evaluated within the study but excluded from review due to study design due to study design Age at assessment: 12-14 years
Funding	Not stated
Notes	Data extracted from Forrest 1956 differs from that presented in CRD review

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Unclear risk	Areas were selected opportunistically. Entire populations of children in some areas were selected for study but insufficient detail is given on how they were accessed
Confounding	High risk	SES and the use of other fluoride sources was not sufficiently reported and controlled for
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	High risk	Results are presented for the majority of participants. However, while the results are presented in full for 4 of the 5 areas the area of highest F ppm appears to have 10% of participants missing from results
Selective reporting (reporting bias)	High risk	Data not in suitable format for analysis
Other bias	High risk	There is risk of measurement bias as examiner calibration was not mentioned

Forrest 1965

Methods	**FLUOROSIS STUDY** Country of study: Wales Geographic location: Gwalchmai (F); Bodafon (non-F), Anglesey Year of study: 1963 Year of change in fluoridation status: 1955 Study design: cross-sectional
Participants	Inclusion criteria: children aged 8 years from a selection of schools Exclusion criteria: schools in Holyhead; schools in Llangefni and Beaumaris, as changed supply from fluoridated to non-fluoridated in 1961 Other sources of fluoride: not stated Social class: not stated Ethnicity: not stated Residential history: not clearly stated, however, the participants were chosen for being the only ones who had had fluoride for most of their lives Other confounding factors: not stated
Interventions	Group 1: 1 ppm (artificial fluoridation) Group 2: ≤ 0.2 ppm (natural fluoridation)
Outcomes	Outcome: enamel defects Age at assessment: 8 years
Funding	Not stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Unclear risk	Schools were selected for study and then children within these schools, however it is not clear how the children were examined
Confounding	High risk	SES and the use of fluoride from other sources were not reported on
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The examiners were unaware of the children's fluoridation status since they all resided in the same county
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	Low risk	Outcome of interest was fully reported on and balanced across groups

Forrest 1965 (*Continued*)

Other bias	Low risk	No other apparent bias

Franzolin 2008

Methods	**FLUOROSIS STUDY** Country of study: Brazil Geographic location: Sao Paulo Year of study: not stated Year of change in fluoridation status: 1975 Study design: cross-sectional
Participants	Inclusion criteria: residence in the same geographical area as the school since birth Exclusion criteria: not stated Social class: homogenous population comprising entirely of public school students Ethnicity: white = 243 (67.5%); black = 41 (11.4%); admixture = 73 (20.3%); Asian = 3 (0.8%) Residential history: lifetime residents Other confounding factors: not stated
Interventions	Group 1: 'optimal' level - ppm not stated (artificial fluoridation via water treatment station) Group 2: 'optimal' level - ppm not stated (artificial fluoridation via direct fluoridation in well) Group 3: 'low' level - ppm not stated (natural fluoridation)
Outcomes	Dental fluorosis (TF Index); caries data collected, however, excluded from the review due to study design Age at assessment: 12 years
Funding	Not stated
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Low risk	Multi-stage random sampling was used whereby schools were selected randomly and the children within them
Confounding	High risk	Did not account for the use of other fluoride sources or SES
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The examiner and recorder were reported to have been blinded to the type of water supply of the schools

Franzolin 2008 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	High risk	Data not in suitable format for analysis
Other bias	Unclear risk	Examinations carried out by a single, previously calibrated examiner, however, kappa score not reported

Garcia-Perez 2013

Methods	**FLUOROSIS STUDY** Country of study: Mexico Geographic location: Morelos Year of study: 2013 Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: children who had been born in the community, lived in the community from 1 year of age onwards, or had not moved in or out of the community for more than 6 months Exclusion criteria: systemic diseases requiring premedication; absence on the days of the oral examination; children who had brackets Other sources of fluoride: bottled water often containing 0.3-0.6 ppm fluoride levels; dentifrice use; number of times brushing teeth per day Social class: both communities had a low socioeconomic level Ethnicity: not stated Residential history: lifetime residents Other confounding factors: not stated
Interventions	All natural fluoridation Group 1: 0.56-0.76 ppm Group 2: 1.45-1.61 ppm
Outcomes	Dental fluorosis (TF Index); caries data also evaluated within the study but excluded from review due to study design Age at assessment: 12 years
Funding	Partially funded by the Metropolitan Autonomous University, Xochimilco (Universidad Autonoma Metropolitana, UAM-X) and the National Council of Science and Technology (Consejo Nacional de Ciencia y Tecnologia, CONACYT)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Garcia-Perez 2013 (*Continued*)

Sampling	Unclear risk	There was insufficient detail reported to determine how selection took place
Confounding	Low risk	Both villages were of low SES, participants were lifetime residents and there was no difference in toothbrushing frequency or bottled water consumption
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data presented as percentages making it difficult to determine if all participants are accounted for
Selective reporting (reporting bias)	High risk	Fluorosis prevalence was not reported for all severities of dental fluorosis
Other bias	Low risk	No other apparent bias

Gaspar 1995

Methods	**FLUOROSIS STUDY** Country of study: Brazil Geographic location: Piracicaba (F); Iracemapolis (non-F) Year of study: not stated Year of change in fluoridation status: 1974 Study design: cross-sectional
Participants	Inclusion criteria: children aged 10-14; lifetime residents of study areas Exclusion criteria: not stated Other sources of fluoride: not stated Ethnicity: not stated Social class: not stated Residential history: lifetime residents Other confounding factors: not stated
Interventions	Group 1: < 0.2 ppm (natural fluoridation) Group 2: 0.7 ppm (artificial fluoridation)
Outcomes	Dental fluorosis prevalence (TF Index) Age at assessment: 10-14 years
Funding	Not stated
Notes	Data from CRD review (unverified data)

Gaspar 1995 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Sampling	Unclear risk	Unable to make a judgement as study was unavailable
Confounding	High risk	Did not appear to account for the use of other fluoride sources or SES in analysis
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unable to make a judgement as study was unavailable
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unable to make a judgement as study was unavailable
Selective reporting (reporting bias)	Unclear risk	Unable to make a judgement as study was unavailable
Other bias	Unclear risk	Unable to make a judgement as study was unavailable

Goward 1982

Methods	**FLUOROSIS STUDY** Country of study: England Geographic location: 2 adjacent districts of Leeds with different fluoride levels Year of study: 1979 Year of change in fluoridation status: 1968 Study design: cross sectional
Participants	Inclusion criteria: lifetime residents of study areas (children only); children aged 5 Exclusion criteria: not clear, though children using systemic or topical fluoride supplements were excluded from the study Other sources of fluoride: children using systemic or topical fluoride supplements excluded from the study Social class: not stated Ethnicity: not stated Residential history: lifetime residents Other confounding factors: difference in breast fed vs bottle fed children
Interventions	Group 1: 0.9 ppm (artificial fluoridation) Group 2: < 0.1 ppm (natural fluoridation)
Outcomes	Dental fluorosis (defined by Al-Alousi) Age at time of measurement: 5 years

Goward 1982 (*Continued*)

Funding	Not stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Unclear risk	There was insufficient detail reported to determine how selection took place
Confounding	High risk	Did not account for SES
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	Low risk	Outcome of interest reported
Other bias	High risk	No information on calibration of examiners

Gray 2001

Methods	**CARIES STUDY** Country of study: England Geographic location: Dudley (F), Sedgeley and Cosely (F), Halesowen (F), Brierly Hill and Kingswinford (F); Stourbridge (non-F) Year study started: 1988 Year study ended: 1997 Year of change in fluoridation status: 1987 Study design: CBA
Participants	Inclusion criteria: children living in study area since 1988 Exclusion criteria: not stated Other sources of fluoride: not stated Social class: participants were all from state-funded primary schools and might have been socioeconomically similar Ethnicity: not stated Residential history: lifetime residents Other confounding factors: not stated
Interventions	**Initiation of water fluoridation** Group 1: 1 ppm (artificial fluoridation) Group 2: 1 ppm (artificial fluoridation)

Gray 2001 (*Continued*)

	Group 3: 1 ppm (artificial fluoridation) Group 4: 1 ppm (artificial fluoridation) Group 5: 0.3 ppm (natural fluoridation)
Outcomes	% caries free (deciduous teeth) Age at baseline measure: 5 years Age at final measure: 5 years
Funding	Not stated
Notes	Data extracted from Gray 2001 differs from that from Gray 2000 (unpublished) which was originally presented in CRD review

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Low risk	According to Pitts 1997, representative samples were drawn from a whole population of Dudley health authority
Confounding	High risk	No details were reported on the use of fluoride from other sources or on the dietary habits of the children
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "...blinding was not possible"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	Low risk	Outcome was reported
Other bias	High risk	At baseline the fluoridation status of the children was determined by the location of their school

Grimaldo 1995

Methods	**FLUOROSIS STUDY** Country of study: Mexico Geographic location: San Luis Potasi Year of study: not stated Year of change in fluoridation status: NA Study design: cross-sectional

Grimaldo 1995 (*Continued*)

Participants	Inclusion criteria: lifetime residents at same address; children aged 11-13 years in selected schools; parental consent Exclusion criteria: not stated Other sources of fluoride: not stated Social class: not stated Ethnicity: not stated Residential history: lifetime residents Other confounding factors: local diet rich in calcium, reduces fluoride absorption
Interventions	All natural fluoridation Group 1: > 2.0 ppm Group 2: 1.2-2.0 ppm Group 3: 0.7-1.2 ppm Group 4: < 0.7 ppm
Outcomes	Dental fluorosis (Dean's Index) Age at assessment: 11-13 years
Funding	Not stated
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Unclear risk	The authors reported that schools and participants from the study areas were selected at random. No further details reported
Confounding	High risk	Did not account for the use of other fluoride sources or SES
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	High risk	There was a variation in the numbers of children reported to have been examined for dental fluorosis compared to the number of children initially reported to be receiving different water fluoride levels
Selective reporting (reporting bias)	Low risk	Outcome of interest was fully reported on and balanced across groups
Other bias	High risk	No indication that the examiners were calibrated

Grobler 1986

Methods	**FLUOROSIS STUDY** Country of study: South Africa Geographic location: Nourivier (low F); Tweeriviere (high F) in North Western Cape province Year of study: not stated Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: lifetime residents of study areas; children aged 12-13 years Exclusion criteria: not stated Other sources of fluoride: both communities had virtually no dental care or fluoride therapy Social class: similar socioeconomic status in both study areas (reported by authors) Ethnicity: similar ethnicity in both study areas (reported by authors) Residential history: lifetime residents Other confounding factors: areas similar in nutrition and dietary habits (reported by authors); temperature 27 °C-32 °C
Interventions	All natural fluoridation Group 1: 3.7 ppm Grpup 2: 0.62 ppm
Outcomes	Outcome: fluorosis prevalence (Deans Index); caries data collected but not presented in this review due to study design Age at assessment: 12-13 years
Funding	Not stated
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Unclear risk	All available subjects were included in the study population. Insufficent information was reported on the sampling frame
Confounding	Low risk	SES was similar across groups and there was virtually no dental care or fluoride therapy in the population at the time
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information. Examinations were made at the children's schools but no mention of blind assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants

Grobler 1986 (*Continued*)

Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	High risk	Examinations were done by a single examiner but no mention of intra-examiner calibration

Grobler 2001

Methods	**FLUOROSIS STUDY** Country of study: South Africa Geographic location: Leeu Gamka, Kuboes and Sanddrif Year of study: not stated Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: continuous residence since birth; having virtually no dental care or fluoride therapy including the use of fluoride-containing toothpaste; absence of any obvious under-nutrition and no dietary habits that could significantly contribute to the ingestion of fluorine Exclusion criteria: not stated Other sources of fluoride: participants had virtually no dental care or fluoride therapy, including the use of fluoride-containing toothpaste Social class: similarly low socioeconomic status across groups reflected in the fact that they all lived in sub-economic housing units Ethnicity: mixed ethnic origin from Khoi, Caucasian and Negroid roots which over hundreds of years have developed into a homogenous ethnic group Residential history: lifetime residents Other confounding factors: not stated
Interventions	All natural fluoridation Group 1: 0.19 ppm Group 2: 0.48 ppm Group 3: 3 ppm
Outcomes	Outcome: fluorosis prevalence (Deans Index); caries data also evaluated within the study but excluded from review due to study design Age at assessment: 10-15 years
Funding	Not stated
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Low risk	All available children in the specified study areas were examined

Grobler 2001 (*Continued*)

Confounding	Low risk	SES was similar across groups and there was virtually no exposure to fluoride from other sources
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	Low risk	Outcome of interest reported
Other bias	Low risk	No other apparent bias

Guo 1984

Methods	**CARIES STUDY** Country of study: Taiwan Geographic location: Chung-Hsing New Village (F); Tsao-Tun (non-F) Year of study: 1971 Year study ended: 1984 Year of change in fluoridation status: 1971 Study design: CBA
Participants	Inclusion criteria: lifetime residents of study areas Exclusion criteria: children who migrated from other areas during study period Other sources of fluoride: not stated Social class: not stated Ethnicity: not stated Residential history: lifetime residents Other confounding factors: similar climate with mean daily air temperature of 24 °C
Interventions	**Initiation of water fluoridation** Group 1 baseline: 0.07 ppm (natural fluoridation) Group 1 post intervention: 0.6 ppm (artificial fluoridation) Group 2: 0.08 ppm (natural fluoridation)
Outcomes	dmft, DMFT, % caries free (deciduous), % caries free (permanent) Age at baseline measure: 5, 8, 12 and 15 years Age at final measure: 5, 8, 12 and 15 years
Funding	Not stated
Notes	Data extracted from Guo 1984 differs from that presented in CRD review
Risk of bias	

Guo 1984 (*Continued*)

Bias	Authors' judgement	Support for judgement
Sampling	Low risk	All eligible children in the study areas were included in the study
Confounding	High risk	Did not account for the use of other fluoride sources or SES
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	Low risk	Outcome of interest reported
Other bias	High risk	Examinations were carried out by the dentists from the University hospital and recorded on the same type of record forms but there is no mention of examiner calibration

Haavikko 1974

Methods	**FLUOROSIS STUDY** Country of study: Finland Geographic location: Espoo (low F); Elimaki (high F); Hanko (optimal F); Lohja (low F) Year of study: 1969 Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: children who had been resident in study areas for the first 6 years of life; children aged 10-11 years Exclusion criteria: none stated Other sources of fluoride: not stated Social class: not stated Ethnicity: not stated Residential history: continuous residence for the first 6 years Other confounding factors: food sources of fluoride
Interventions	All natural fluoridation Group 1: 1.08 ppm Group 2: 0.41 ppm Group 3: 0.11 ppm Group 4: 0.05 ppm

Haavikko 1974 (*Continued*)

Outcomes	Dental fluorosis (Dean's Index) Age at assessment: 10-11 years
Funding	Not stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Unclear risk	Eligible children were selected at random from the health records. No further details regarding the sampling frame were reported
Confounding	High risk	SES and the use of fluoride from other sources were not reported on
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	Low risk	Outcome of interest was fully reported on and balanced across groups
Other bias	High risk	Both dentists carried out the diagnosis of enamel defects but there was no mention of examiner calibration

Harding 2005

Methods	**FLUOROSIS STUDY** Country of study: Ireland Geographic location: Cork city (F); Cork county (non-F) Year of study: not stated Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: age 5 years; location of the school attended and fluoridation status of water supply Exclusion criteria: absence on the day of examination; too apprehensive to participate or < 5 years; incorrectly received a form; incomplete form; existing medical condition Other sources of fluoride: fluoride prevalence of children with different nutritional and brushing habits were reported: breast-fed = 30 (28%) vs not breast-fed = 38 (21%); brushing before 12 months: F = 47 (22.6%) vs non-F = 19 (22.1%); started brushing

Harding 2005 (*Continued*)

	with toothpaste between 12 and 18 months: F = 79 (38%) vs non-F = 25 (29.1%); started brushing with toothpaste between 19 and 24 months: F = 37 (17.8%) vs non-F = 21 (24.4%); started brushing with toothpaste after 24 months: F = 41 (19.7%) vs non-F = 18 (20.9%) Social class: schools were chosen to provide a socioeconomic spread; 7 urban and 10 rural schools Ethnicity: not stated Residential history: lifetime residents Other confounding factors: food sources of fluoride
Interventions	Group 1: 0.8-1 ppm (artificial fluoridation) Group 2: 'low' level - ppm not stated (natural fluoridation)
Outcomes	Dental fluorosis (TSIF) Age at assessment: 5 years
Funding	Not stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Low risk	A stratified sample for 5-year olds was drawn from study areas on the basis of age, location, school attended and fluoridation status. Schools were chosen to provide a socioeconomic spread
Confounding	Low risk	SES range (by school) was sampled. There were similar levels of toothpaste use across the groups
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of the 311 participants examined, outcome data were not presented for 17 participants due to partial fluoride history; unlikely to influence the results
Selective reporting (reporting bias)	High risk	Data not in suitable format for analysis
Other bias	High risk	Clinical examination was carried out by one examiner trained extensively by a gold standard but no report of calibration nor intra-examiner reliability tests

Hardwick 1982

Methods	**CARIES STUDY** Country of study: England Geographic location: Alsager, Middlewich, Nantwich (F), Northwich (non-F) Year study started: 1974 Year study ended: 1978 Year of change in fluoridation status: 1975 Study design: prospective cohort
Participants	Inclusion criteria: 12-year-old children living in study area. Consent from relevant country authorities and teachers at schools included in the study Exclusion criteria: none stated Other sources of fluoride: Fluoride group (n = 152): 142 (94%) used only fluoride dentifrices; 125 (83%) used at least once a day Control group (n = 194): 185 (95%) used only fluoride dentifrices; 147 (76%) used at least once a day 2 children in fluoride group and 4 children in control had used fluoride tablets Social class: control and experimental groups matched on urban and rural characteristics Ethnicity: not stated Residential history: not stated Other confounding factors: not stated
Interventions	**Initiation of water fluoridation** Group 1 baseline: < 0.1 ppm (natural fluoridation) Group 1 post intervention: 1.0 ppm (artificial fluoridation) Group 2: < 0.1 ppm (natural fluoridation)
Outcomes	DMFT, DMSF Age at baseline measure: 12 years Age at final measure: 16 years
Funding	Not stated
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Low risk	All eligible children were invited to participate
Confounding	High risk	Use of fluoride from other sources was broadly equal between the groups. The groups were matched on SES however, no information was reported on the dietary habits of the children

Hardwick 1982 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The children were transported to a central examination centre in small numbers and were then randomly mixed with children from the other group. Furthermore, the children were requested not to wear school uniform and, in case they forgot, donned a large operating gown to hide their clothes"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	Low risk	Outcome of interest reported
Other bias	Low risk	No other apparent bias

Heifetz 1988

Methods	**FLUOROSIS STUDY** Country of study: USA Geographic location: 7 rural towns within 75 miles of each other in Illinois Year of study: 1980-1985 Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: children aged 8-10 and 13-15 years; continuous residence in study community Exclusion criteria: not stated Other sources of fluoride: food and drinks produced in fluoride areas Social class: study areas shared similar socioeconomic characteristics Ethnicity: not stated Residential history: continuous residence Other confounding factors: not stated
Interventions	All natural fluoridation Group 1: 3.8-4.1 ppm Group 2: 2.8-3.8 ppm Group 3: 2.1 ppm Group 4: 1.1 ppm
Outcomes	Dental fluorosis (TSIF); caries data also evaluated within the study but excluded from review due to study design Age at assessment: 13-15 years
Funding	Not stated
Notes	

Heifetz 1988 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Sampling	Unclear risk	There was insufficient detail reported to determine how selection took place
Confounding	High risk	Participants consumed food and drinks produced in fluoride areas, however, it is not clear whether there was a difference in consumption among different areas. Insufficient detail is provided regarding use of fluoride from other sources
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	High risk	Data not in suitable format for analysis
Other bias	Low risk	No other apparent bias

Heintze 1998

Methods	**FLUOROSIS STUDY** Country of study: Brazil Geographic location: Garca (F); Itrapolis (non-F), Sao Paulo state Year of study: 1995 Year of change in fluoridation status: 1973 and 1975 Study design: cross-sectional
Participants	Inclusion criteria: subjects aged 5-24 years; from all social strata; used tap water; took urine samples from all 3 daytime periods Exclusion criteria: usbjects that used tap water, otherwise not stated Other sources of fluoride: subjects asked about use of toothpaste or mouth rinses containing fluoride. 98% used toothpaste containing fluoride and 16.5% used a fluoride mouth rinse daily or weekly Social class: cities similar in socioeconomic and sociodemographic conditions, subjects from all social strata included Ethnicity: not stated Residential history: not stated Other confounding factors: Garca altitude = 526 m, mean temp = 22 °C, population = 41,351; Itapolis: altitude = 491 m, mean temp = 23 °C, population = 30, 111

Heintze 1998 (*Continued*)

Interventions	Group 1: 0.9 ppm (artificial fluoridation) Group 2: 0.02 ppm (natural fluoridation)
Outcomes	Dental fluorosis (TF Index) Age at assessment: 5-24 years
Funding	Not stated
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Low risk	Participants were accessed via health centres, schools and factories and all eligible participants were included in the study
Confounding	High risk	Study areas were matched for SES. Information was collected on the use of fluoride paste and mouth rinse, however this was not reported according to exposure of water fluoridation
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data presented as percentages making it difficult to determine if all participants are accounted for
Selective reporting (reporting bias)	Low risk	Outcome of interest reported
Other bias	Unclear risk	Dental fluorosis was recorded by a trained and calibrated examiner, however, details of intra-examiner reliability not provided

Heller 1997

Methods	**FLUOROSIS STUDY** Country of study: USA Geographic location: national survey of oral health of US school children Year of study: 1986 Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: lifetime residents of study areas; aged 7-17 years; ompletion of survey by parents Exclusion criteria: none stated Other sources of fluoride: written questionnaire included question regarding child's use of fluoride drops, fluoride tablets, professional topical fluoride treatments and school fluoride rinses Social class: not stated Ethnicity: not stated Residential history: continuous residency Other confounding factors: results standardised to age and sex distribution of US schoolchildren who participated in survey
Interventions	Group 1: > 1.2 ppm (natural fluoridation) Group 2: 0.7-1.2 ppm (artificial fluoridation) Group 3: 0.3-0.7 ppm (natural fluoridation) Group 4: < 0.3 ppm (natural fluoridation)
Outcomes	Dental fluorosis (Dean's Index); caries data also evaluated within the study but excluded from review due to study design Age at assessment: 7-17 years
Funding	Not stated
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Low risk	Stratified sampling was carried out and oral examination was conducted for 78% of all sampled students
Confounding	High risk	Results were not adjusted for SES and the use of fluoride from other sources
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants

Heller 1997 (*Continued*)

Selective reporting (reporting bias)	Low risk	Outcome of interest was fully reported on and balanced across groups
Other bias	Low risk	No other apparent bias

Hernandez-Montoya 2003

Methods	**FLUOROSIS STUDY** Country of study: Mexico Geographic location: not stated Year of study started: 2001 Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: having at least 1 year residence in the study area Exclusion criteria: not stated Other sources of fluoride: not stated Social class: not stated Ethnicity: not stated Residential history: ≥ 1 year residence in study area Other confounding factors: in all study areas, parents reported the use of fluoride toothpaste
Interventions	All natural fluoridation Group 1: 0.74 ppm Group 2: 1.3 ppm Group 3: 3.56 ppm Group 4: 4.07 ppm Group 5: 5.19 ppm Group 6: 5.57 ppm Group 7: 7.59 ppm
Outcomes	Dental fluorosis (Dean's Index); caries data also evaluated within the study but excluded from review due to study design Age at assessment: 9-11 years
Funding	Financial and logistical support from the Health Institute of the State of Aguascalientes, Institute Tecnologico de Aguascalientes and COSNET
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Low risk	Random sampling was performed and considered the total population exposed to flu-

Hernandez-Montoya 2003 (*Continued*)

		oridated water at each study area
Confounding	High risk	Did not account for SES
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Some participants were excluded from the analysis but no reason was provided
Selective reporting (reporting bias)	Low risk	Outcome of interest reported
Other bias	Unclear risk	Outcome was assessed by a working group previously trained and calibrated. Insufficient information on reliability testing

Holdcroft 1999

Methods	**CARIES STUDY** Country of study: England Geographic location: north Birmingham and Sandwell (F), North Staffordshire, Herefordshire and Shropshire (non-F) Year study started: 1985/6 Year of change in fluoridation status: 1986 Study design: CBA
Participants	Inclusion criteria: not stated Exclusion criteria: not stated Other sources of fluoride: not Stated Social class: measured using Jarman scores Ethnicity: not stated Residential history: not stated Other confounding factors: not stated
Interventions	**Initiation of water fluoridation** Group 1: not stated Group 2: not stated
Outcomes	dmft Age at baseline measure: not stated Age at final measure: not stated
Funding	Not stated
Notes	Data from original CRD review (unverified data)
Risk of bias	

Holdcroft 1999 (*Continued*)

Bias	Authors' judgement	Support for judgement
Sampling	Unclear risk	Unable to make a judgement as study was unavailable
Confounding	High risk	Data does not appear to have been controlled for SES and use of fluoride from other sources
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unable to make a judgement as study was unavailable
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unable to make a judgement as study was unavailable
Selective reporting (reporting bias)	Unclear risk	Unable to make a judgement as study was unavailable
Other bias	Unclear risk	Unable to make a judgement as study was unavailable

Hong 1990

Methods	**FLUOROSIS STUDY** Country of study: Taiwan Geographic location: Chung-hsing New village (F) and Tsao-tun (non-F) Year of study: not stated Year of change in fluoridation status: 1978 Study design: cross sectional
Participants	Inclusion criteria: children aged 6-15 years: resident in village since initiation of fluoridation Exclusion criteria: children who migrated from other areas during study period Other sources of fluoride: not stated Social class: 2 communities alike in social and living customs Ethnicity: not stated Residential history: resident since fluoride initiation Other confounding factors: 2 areas have virtually identical climates, only 3 km apart
Interventions	Group 1: 0.6 ppm (artificial fluoridation) Group 2: 0.08 ppm (natural fluoridation)
Outcomes	Dental fluorosis (Dean's Index) Age at assessment: 6-15 years
Funding	Not stated

Hong 1990 (*Continued*)

Notes		

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Unclear risk	The participating sample consisted of children from 6-15 years in the study areas. No other information was provided on sample selection
Confounding	High risk	Did not account for the use of other fluoride sources
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	Low risk	Outcome of interest was fully reported on and balanced across groups
Other bias	Low risk	No other apparent bias

Ibrahim 1995

Methods	**FLUOROSIS STUDY** Country of study: Sudan Geographic location: Abu Gronn (F); Treit El Biga (low F) Year of study: 1992 Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: at least 1 erupted permanent maxillary incisor; lifetime residents of study areas; age 7-16 years Exclusion criteria: not stated Other sources of fluoride: not stated Social class: author stated that areas had more or less the same socioeconomic background Ethnicity: author stated that areas had more or less the same ethnic background Residential history: lifetime residents Other confounding factors: altitude= 300m for both areas; mean temperature = 25-35 °C. In low F area boys had significantly more fluorosis than girls
Interventions	All natural fluoridation Group 1: 2.56 ppm Group 2: 0.25 ppm

Ibrahim 1995 (*Continued*)

Outcomes	Dental fluorosis (Community Fluorosis Index) Age at assessment: 7-16 years
Funding	Norwegian Universities Committee for Development Research and Education
Notes	Data extracted from Ibrahim 1995 differs from that presented in CRD review

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Unclear risk	Insufficient information was reported on sampling; the sampling frame was unspecified
Confounding	High risk	Did not account for the use of fluoride from other sources
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	Low risk	Outcome of interest reported
Other bias	High risk	No mention of calibration of examiners and reliability testing

Indermitte 2007

Methods	**FLUOROSIS STUDY** Country of study: Estonia Geographic location: Tartu city Year of study: not stated Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: 12-year-old children; continuous residence; only districts supplied by definite tube wells of known fluoride concentration were selected Exclusion criteria: not stated Social class: selected districts were of same eco-environmental, ethnic as well as socioeconomic standards Ethnicity: not stated Residential history: lifetime residents Other confounding factors: not stated

Indermitte 2007 (*Continued*)

Interventions	All natural fluoridation Group 1: 0.2 ppm Group 2: 0.3 ppm Group 3: 1.2 ppm Group 4: 1.6 ppm Group 5: 2.4 ppm Group 6 3.9 ppm
Outcomes	Dental fluorosis (index not reported) Age at assessment: 12 years
Funding	The study was supported by the Target Funding Projects no. 0180052s07 and no. 0182648s04 of the Ministry of Education and Science of Estonia and by Estonian Society of Stomatololgy
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Unclear risk	Areas of study were sampled purposively and limited information was reported on the selection of individuals
Confounding	High risk	Did not account for the use of fluoride from other sources
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	Low risk	Outcome of interest reported
Other bias	High risk	Examination carried out by a trained examiner with an assistant, but no mention of calibration and reliability testing

Indermitte 2009

Methods	**FLUOROSIS STUDY** Country of study: Estonia Geographic location: not stated Year of study: not stated Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: not stated Exclusion criteria: not stated Other sources of fluoride: not stated Social class: not stated Ethnicity: not stated Residential history: lifetime residents Other confounding factors: not stated
Interventions	All natural fluoridation Group 1: < 1 ppm Group 2: 1-1.5 ppm Group 3: 1.51-2 ppm Group 4: 2.1-3 ppm Group 5: 3.1-4 ppm Group 6: > 4 ppm
Outcomes	Dental fluorosis (Dean's Index) Age at assessment: 7-15 years
Funding	The study was supported by the Estonian Society of Stomatology and Estonian Science Foundation grant number 7403
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Unclear risk	Sampling was partly based on data from 2 previous studies which provide insufficient sampling information while the sub-sample was selected from town of Tartu, where the fluoride content in drinking water varied significantly between regions
Confounding	High risk	Did not account for the use of fluoride from other sources or SES
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information

Indermitte 2009 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	Low risk	Outcome of interest reported
Other bias	High risk	Clinical examination by a 'trained' dentist. Insufficient information on intra-examiner reliability testing

Ismail 1990

Methods	**FLUOROSIS STUDY** Country of study: Canada Geographic location: public and private schools in Trois Rivieres (F) and Sherbrooke (non-F), Quebec Year of study: 1987 Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: children randomly selected from private and public schools separately; children aged 11-17 years; resident in study areas for first 6 years Exclusion criteria: none stated Other sources of fluoride: fluoride tablet use around 13% in F areas and 67% in non-F area Social class: stratified on school type: private or public (authors state private school likely to have been higher social class) Ethnicity: not stated Residential history: resident from 0-6 years Other confounding factors: not stated
Interventions	All natural fluoridation Group 1: 1.0 ppm Group 2: < 0.1 ppm
Outcomes	Dental fluorosis prevalence (TSIF); caries data collected, however, not presented in this review due to study design Age at assessment: 11-17 years
Funding	National Health Research and Development Program, Health and Welfare (6605-1316-53)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Ismail 1990 (*Continued*)

Sampling	Low risk	A 2-stage stratified sample was selected from each city. In the first stage, private and public schools were randomly selected. In the second stage, students were randomly selected from the private and public schools separately
Confounding	High risk	There was an imbalance of the use of fluoride supplements between groups with more supplements being consumed by those living in the non-fluoridated area
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Examiners were blind to the content of questionnaire" and by implication, fluoridation status of participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data appear to be presented for all participants
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	No other apparent bias

Jackson 1975

Methods	**FLUOROSIS STUDY** Country of study: Wales Geographic location: Anglesey (F); Bangor and Caernarfon (non-F) Year of study: 1974 Year of change in fluoridation status: 1955 Study design: unclear
Participants	Inclusion criteria: lifetime residents of study areas; continuous use of public water supply; school children aged 15 years; parental consent Exclusion criteria: children who had ever received fluoride tablets; left the study area; did not consume piped water supply for entire life; unavailable at time of sampling Other sources of fluoride: children who had received fluoride tablets excluded Social class: not stated Ethnicity: not stated Residential history: lifetime residents Other confounding factors: not stated
Interventions	Group 1: 0.9 ppm (artificial fluoridation) Group 2: < 0.1 ppm (natural fluoridation)
Outcomes	Mottling; caries data collected, however, not presented in this review due to study design Age at assessment: 15 years

Jackson 1975 (*Continued*)

Funding	Not stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Unclear risk	Stated that children were randomly sampled, however information on sampling was insufficient
Confounding	High risk	Children who had received fluoride tablets were excluded, however SES was not taken into account
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants were taken to a central examination centre by taxi and examiners were unaware of the area from which a child came
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data presented for approximately 30% of participants sampled from each study area (Anglesey 28%; Bangor 32%)
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	High risk	Even though the examiners carried out their investigations independently, no sort of calibration seemed to have been carried out

Jackson 1999

Methods	**FLUOROSIS STUDY** Country of study: USA Geographic location: Connersville (non-F); Brownsburg (optimal-F); Lowell (high-F), Indiana Year of study: 1992 Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: lifetime residents of study areas; consumed public water from birth or supply with comparable water level;cChildren aged 7-14; parental and personal consent Exclusion criteria: factors in medical history that would contraindicate a dental examination; full mouth fixed orthodontic appliance Other sources of fluoride: use of fluoride supplements: non-F areas = 58%; optimal-F area = 20%; high-F area = 9%. Also fluoride from mouth rinses, gels, other topical

Jackson 1999 (*Continued*)

	applications Social class: not stated Ethnicity: approximately 2% non-white (stated for baseline survey) Residential history: lifetime residents Other confounding factors: areas all in same climatic zone
Interventions	All natural fluoridation Group 1: 4.0 ppm Group 2: 1.0 ppm Group 3: 0.2 ppm
Outcomes	Dental fluorosis (TSIF) Age at assessment: 7-10 years and 11-14 years
Funding	Not stated
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Unclear risk	There was insufficient detail reported to determine how selection took place
Confounding	High risk	Information on the use of other fluoride sources was collected, however, the results were not adjusted for this factor. Did not account for SES
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The examiner was unaware of the residency status of the participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	Low risk	Outcome of interest reported
Other bias	Low risk	No other apparent bias

Jolly 1971

Methods	**FLUOROSIS STUDY** Country of study: India Geographic location: the Punjab Year of study: not stated Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: school children Exclusion criteria: none stated Other sources of fluoride: not stated Social class: not stated Ethnicity: not stated Residential history: not stated Other confounding factors: not stated
Interventions	All naturally fluoridated Group 1: 0.7 ppm Group 2: 1.4 ppm Group 3: 2.4 ppm Group 4: 2.4 ppm Group 5: 2.5 ppm Group 6: 3.0 ppm Group 7: 3.0 ppm Group 8: 3.3 ppm Group 9: 3.3 ppm Group 10: 3.6 ppm Group 11: 4.3 ppm Group 12: 5.0 ppm Group 13: 5.09 ppm Group 14: 5.49 ppm Group 15: 7.02 ppm Group 16: 8.5 ppm Group 17: 9.5 ppm
Outcomes	Mottled enamel Age at assessment: 5-15 years
Funding	Not stated
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Unclear risk	There was insufficient detail reported to determine how selection took place

Jolly 1971 (*Continued*)

Confounding	High risk	Did not account for the use of fluoride from other sources or SES
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of participants examined was not reported and the outcome was reported as a proportion
Selective reporting (reporting bias)	High risk	The outcome of interest was reported as a proportion; and without absolute numbers or the number of participants examined (n) it is unclear what the proportion represents. Data not in suitable format for analysis
Other bias	High risk	No mention of examiner calibration

Kanagaratnam 2009

Methods	**FLUOROSIS STUDY** Country of study: New Zealand Geographic location: Auckland Year of study: not stated Year of change in fluoridation status: not stated Study design: cross-sectional
Participants	Inclusion criteria: only children who returned signed consent form and questionnaire completed by parents Exclusion criteria: schools with fewer than 5 9-year-old children were excluded because of resource, time and efficiency constraints Other sources of fluoride: data presented on fluoride tablet supplementation, brushing with toothpaste frequency, amount of toothpaste used and toothpaste swallowed, however, the use of other sources of fluoride had no effect on the proportion of children with diffuse opacities Social class: high (deciles 8-10) = 40% (F), 19% (non-F); middle (deciles 4-7) = 141% (F) , 44% (non-F); low (deciles 1-3) = 19% (F), 37% (non-F) (a schools decile indicates the extent to which it includes students from low socioeconomic communities) Ethnicity: more children of European descent and fewer children of Asian descent attended schools within non-fluoridated areas compared with fluoridated areas Residential history: lifetime residents and intermittent residents, however, data on lifetime residents alone presented in this review due to confounding Other confounding factors: not stated
Interventions	Group 1: 0.1-0.3 ppm (natural fluoridation) Group 2: 0.7-1 ppm (artificial fluoridation)

Kanagaratnam 2009 (*Continued*)

Outcomes	Dental fluorosis (Dean's Index); caries data collected, however, not presented in this review due to study design Age at assessment: 7-15 years
Funding	Funded by AUT University, Counties Manukau District Health Board and New Zealand Dental Research Foundation
Notes	Fluoride concentrations were not reported in the study but deduced from discussion section and anecdotal evidence

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Low risk	The number of schools and students from each school were probabilistically sampled to reflect the overall decile and school size distribution representative of Auckland schools yet produce a sample that was balanced between fluoridated and non-fluoridated regions
Confounding	Unclear risk	While the sample included participants from a range of SES, the numbers in these groups were not equal. There were significantly fewer children in high-decile schools in non-fluoridated areas and fewer children in low-decile schools in fluoridated areas
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data appear to be presented for all participants
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	No other apparent bias

Kotecha 2012

Methods	**FLUOROSIS STUDY** Country of study: India Geographic location: not stated Year of study: not stated Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: all age groups Exclusion criteria: those who could not be studied in the second visit Other sources of fluoride: not stated Social class: not stated Ethnicity: not stated Residential history: not stated Other confounding factors: not stated
Interventions	All natural fluoridation Group 1: < 1.5 ppm Group 2: > 1.5 ppm
Outcomes	Dental fluorosis (index not reported); caries data also evaluated within the study but excluded from review due to study design Age at assessment: all age groups
Funding	Not stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Low risk	11 out of 261 villages with high fluoride content in the drinking water and 11 out of 1490 villages with normal fluoride drinking water were randomly selected for water sampling
Confounding	High risk	Did not account for the use of fluoride from other sources or SES
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	High risk	Data for 75% of population of the study areas presented and attrition was not balanced across groups
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported

Kotecha 2012 (*Continued*)

Other bias	High risk	Measurement done by trained tutors and assistant professors, however, it is not clear whether the personnel measuring the outcome were calibrated

Kumar 1999

Methods	**FLUOROSIS STUDY** Country of study: USA Geographic location: Newburgh City (F); Newburgh Town (F 1984); New Windsor (non-F); Kingston (non-F) Year study started: 1986 Year study ended: 1995 Year of change in fluoridation status: 1984 Study design: CBA
Participants	Inclusion criteria: children aged 7-14 years; lifetime residents of study areas Exclusion criteria: not stated Other sources of fluoride: fluoridation plus early brushing or tablet use, fluoride tablet plus early brushing, early brushing, and fluoride tablets all associated with an increased risk of fluorosis scored very mild to severe compared to children exposed to none of these additional sources Social class: not stated Ethnicity: no difference in odds of fluorosis in African-Americans compared to white and other races Residential history: lifetime residents Other confounding factors: not stated
Interventions	Group 1: 1 ppm (artificial fluoridation) Group 2: 1 ppm (artificial fluoridation) Group 3: 'low' level - ppm not stated (natural fluoridation) Group 4: 'low' level - ppm not stated (natural fluoridation) Group 5: 'low' level - ppm not stated (natural fluoridation)
Outcomes	Dental fluorosis (Dean's Index); caries data also evaluated within the study but excluded from review due to study design Age at baseline measure: 7-14 years Age at final measure: 7-14 years
Funding	Supported by a grant from the National Institute of Dental Research (R01 DE 1088801)
Notes	Group 1 (Newburgh City) had been fluoridated since 1945; Group 2 (Newburgh Town) was fluoridated in 1984. Data for 1995 only were available for Group 5 (Ulster)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Kumar 1999 (*Continued*)

Sampling	Unclear risk	Insufficient detail reported to determine how selection took place
Confounding	Unclear risk	While the authors reported that SES was considered, this information was not reported
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	High risk	Data not in suitable format for analysis
Other bias	High risk	There were great methodological differences between the before- and after-study in questionnaire design and examiner and the examiners were not reported to have been calibrated

Kumar 2007

Methods	**FLUOROSIS STUDY** Country of study: India Geographic location: not stated Year study started: 1999-2000 Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: not stated Exclusion criteria: not stated Other sources of fluoride: not stated Social class: not stated Ethnicity: not stated Residential history: not stated Other confounding factors: not stated
Interventions	All natural fluoridation Group 1: 0.6 ppm Group 2: 1.1 ppm Group 3: 1.1 ppm Group 4: 1.1 ppm Group 5: 1.2 ppm Group 6: 1.3 ppm Group 7: 1.7 ppm Group 8: 1.7 ppm

Kumar 2007 (*Continued*)

	Group 9: 1.8 ppm Group 10: 1.9 ppm Group 11: 2.1 ppm Group 12: 2.9 ppm Group 13: 4.6 ppm
Outcomes	Dental fluorosis (Smith's classification) Age at assessment: 5-14 years
Funding	Indian Council of Medical Research
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Low risk	A stratified random sampling procedure was adopted for selection of water sources and villages
Confounding	High risk	Did not account for the use of fluoride from other sources or SES
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	Low risk	Outcome of interested reported
Other bias	High risk	Examiner calibration was not mentioned

Kunzel 1976

Methods	**FLUOROSIS STUDY** Country of study: Cuba Geographic location: La Salud (low F); Mir (medium F); San Augustin and Blanqizal (high F) Year of study: 1973 Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: children resident in study areas. Exclusion criteria: not stated Other sources of fluoride: not stated

Kunzel 1976 (*Continued*)

	Social class: not stated Ethnicity: not stated Residential history: not stated however, most of the children were born in the area Other confounding factors: not stated
Interventions	All natural fluoridation Group 1: 2.3-3.6 ppm Group 2: 1.1-1.6 ppm Group 3: 0.6-0.8 ppm Group 4: 0.1 ppm
Outcomes	Dental fluorosis (Dean's Index); caries data also evaluated within the study but excluded from review due to study design Age at assessment: 9-10 years
Funding	Not stated
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Unclear risk	There was insufficient detail reported to determine how selection took place
Confounding	High risk	Did not account for the use of fluoride from other sources or SES
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The dental examinations were carried out while the fluoride content of the water consumed was unknown"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	Low risk	All expected outcome reported
Other bias	Low risk	No other apparent biases

Kunzel 1997

Methods	**CARIES STUDY** Country of study: Germany Geographic location: Chemnitz (F); Plauen (non-F) Year study started: 1959 Year study ended: 1971 Year of change in fluoridation status: 1959 Study design: CBA
Participants	Inclusion criteria: children born in study areas Exclusion criteria: children who had moved into the 2 study areas; disabled children Other sources of fluoride: number of topical applications of fluoride toothpastes; solutions and gel was low - water fluoridation was the only preventive measure Social class: not stated Ethnicity: not stated Residential history: lifetime residents Other confounding factors: increasing annual sugar consumption in both areas
Interventions	**Initiation of water fluoridation** Group 1 baseline: 0.2 ppm (natural fluoridation) Group 1 post intervention: 1 ppm (artificial fluoridation) Group 2: 0.2 ppm (natural fluoridation)
Outcomes	dmft, DMFT, % caries free (deciduous dentition), % caries free (permanent dentition) Age at baseline measure: 6-15 years Age at final measure: 6-15 years
Funding	Supported by the German Federal Ministry of Education, Science, Research and Technology, grant 01 ZZ 9502
Notes	Data extracted from Kunzel 1997 differs from that presented in CRD review (additional data extracted) Study presents data on both initiation and cessation of water fluoridation, but cessation data excluded from this review due to unsuitable control group

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Unclear risk	Sampling details had previously been published (Kunzel 1980), however, the exclusion of disabled children as stated in this study, puts the representativeness of the sample in doubt
Confounding	High risk	Did not account for SES
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information

Kunzel 1997 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Data appear to be presented for all participants
Selective reporting (reporting bias)	Low risk	Standard deviation was not reported
Other bias	Low risk	No other biases apparent

Leverett 1986

Methods	**FLUOROSIS STUDY** Country of study: USA Geographic location: Rochester, NY and several surrounding towns (F); 4 towns in western New York state (non-F) Year of study: 1981 Year of change in fluoridation status: 1963 Study design: cross sectional
Participants	Inclusion criteria: children resident in study areas; children aged 7-17 years Exclusion criteria: none stated Other sources of fluoride: not stated Social class: not stated Ethnicity: not stated Residential history: children in both non-F and F areas were "not necessarily lifetime residents of their communities" Other confounding factors: none stated
Interventions	Group 1: 1.0 ppm (artificial fluoridation) Group 2: ≤0.3 ppm (natural fluoridation)
Outcomes	Dental fluorosis (Dean's Index) Age at assessment: 7-17 years
Funding	Not stated
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Unclear risk	There was insufficient detail reported to determine how selection of children within schools took place
Confounding	High risk	Did not account for the use of fluoride from other sources or SES

Leverett 1986 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	Low risk	Outcome of interest reported
Other bias	High risk	The examiners do not seem to have been calibrated

Levine 1989

Methods	**FLUOROSIS STUDY** Country of study: England Geographic location: Birmingham (F); Leeds (non-F) Year of study: 1987 Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: lifetime residents of study areas (children only); schools with catchment areas inside study areas; children aged 9-10 years Exclusion criteria: Asian and West Indian children; non-continuous residents; teeth with fractures or restorations; children who had received fluoride supplements at any time Other sources of fluoride: children who had received fluoride supplements at any time excluded Social class: schools selected that served similar socioeconomic populations (social class groups 3,4,5) Ethnicity: Asian and West Indian children excluded Residential history: lifetime residents Other confounding factors: not stated
Interventions	Group 1: 1 ppm (artificial fluoridation) Group 2: < 0.1 ppm (natural fluoridation)
Outcomes	Enamel defect-hypoplasia (TSIF) Age at assessment: 9-10 years
Funding	Not stated
Notes	Data extracted from Levine 1989 differs from that presented in CRD review

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Levine 1989 (*Continued*)

Sampling	Unclear risk	There was insufficient detail reported to determine how selection took place
Confounding	Low risk	Children using fluoride supplements were excluded and sampling ensured that groups were comparable in terms of SES
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Photographic examination was blinded Quote: "The colour transparencies were coded and placed in a random sequence before being projected and viewed"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was balanced across groups as results for 18 (2.9%) and 12 (2.4%) children from the non-F and F area respectively were not available for photographic assessment
Selective reporting (reporting bias)	Unclear risk	There was selective reporting on the central incisor and the reason was not stated
Other bias	Low risk	No other apparent bias

Lin 1991

Methods	**FLUOROSIS STUDY** Country of study: China Geographic location: Xinyuan (F); Langan and Jiayi (non-F) Year of study: not stated Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: school children aged 7-14 years Exclusion criteria: not stated Other sources of fluoride: not stated Social class: low socioeconomic status, mean annual income of about 200 yuan Ethnicity: not stated Residential history: not reported Other confounding factors: not stated
Interventions	All natural fluoridation Group 1: 0.88 ppm Group 2: 0.34 ppm
Outcomes	Dental fluorosis Age at assessment: 7-14 years
Funding	Not stated

Lin 1991 (*Continued*)

Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Sampling	Low risk	Used rRandom stratified sampling
Confounding	High risk	Did not account for the use of fluoride from other sources
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It is unclear whether data presented for all participants assessed for dental fluorosis
Selective reporting (reporting bias)	Low risk	Outcome of interest reported
Other bias	High risk	The examiners do not seem to have been calibrated

Loh 1996

Methods	**CARIES STUDY** Country of study: Singapore and Malacca (West Malaysia) Geographic location: Singapore (F); Malacca (non-F) Year study started: 1957 Year study ended: 1966 Year of change in fluoridation status: 1958 Study design: CBA
Participants	Inclusion criteria: Chinese and Malay children aged 7-9 years Exclusion criteria: not stated Other sources of fluoride: not stated Social class: not stated Ethnicity: Chinese and Malay children - results presented separately Residential history: unclear Other confounding factors: not stated
Interventions	**Initiation of water fluoridation** Group 1: 0.7 ppm (artificial fluoridation) Group 2: 'low' level - ppm not stated (natural fluoridation)
Outcomes	DMFT Age at baseline measure: 7-9 years Age at final measure: 7-9 years

Loh 1996 (*Continued*)

Funding	Not stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Unclear risk	Insufficient detail reported to determine how selection of schools and children within those schools took place
Confounding	High risk	No details were reported on the use of fluoride from other sources, SES or on the dietary habits of the children
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding was not undertaken
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Numbers of children examined at each time point are approximate
Selective reporting (reporting bias)	High risk	The outcomes of interest were not clearly stated a priori and while dental caries was reported (not fully), dental fluorosis appears to have been measured on a different age group, but not reported in useful format
Other bias	Low risk	No other bias detected

Louw 2002

Methods	**FLUOROSIS STUDY** Country of study: South Africa Geographic location: Sanddrif, Williston, Kuboes, Fraserburg, Brandvlei, Kenhardt, and Leeu Gamka Year of study: not stated Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: aged 11-13 years, similar nutrition and dietary habits, similar ethnic and socioeconomic status Exclusion criteria: not stated Other sources of fluoride: no dental care or fluoride therapy, including the use of fluoride containing toothpaste Social class: similarly low SES reflected in living in subeconomic housing units

Louw 2002 (*Continued*)

	Ethnicity: mixed with Khoi, Caucasian and Negroid roots that developed into a homogenous ethnic group Residential history: lifetime residents Other confounding factors: similar nutrition and dietary habits - mostly bread and potatoes with sporadic intake of vegetables and meat, all located in arid rural sections of South Africa
Interventions	All natural fluoridation Group 1: 0.19 ppm Group 2: 0.36 ppm Group 3: 0.48 ppm Group 4: 1 ppm Group 5: 1.66 ppm Group 6: 2.64 ppm Group 7: 3 ppm
Outcomes	Dental fluorosis prevalence (Dean's Index) Age at assessment: 11-13 years
Funding	Not stated
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Unclear risk	Insufficient detail reported to determine how selection took place
Confounding	Low risk	SES was reported as comparable and the participants were not in receipt of dental care, fluoride supplements or toothpaste
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all (99%) participants
Selective reporting (reporting bias)	Low risk	Expected outcome reported
Other bias	Low risk	No other apparent bias

Machiulskiene 2009

Methods	**FLUOROSIS STUDY** Country of study: Lithuania Geographic location: Vilkaviskis and Jonuciai Year of study: 2004 Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: never having taken part in any caries preventive programme; lifetime residency in the area; informed consent to participate Exclusion criteria: 1 school in Vilkaviskis was not eligible to participate in the study as a result of current caries prevention programmes, involving fluoride rinses and fissure sealants; tooth surfaces from which recordings could not be made because of the presence of fixed orthodontic appliances Other sources of fluoride: not stated Social class: children affected by parental unemployment: 1.1 ppm fluoride group = 39%; 0.3ppm fluoride group = 23%. More children in the 1.1 ppm fluoride group reported parental unemployment, however, the 2 towns were initially considered similar from a socioeconomic point of view Ethnicity: not stated Residential history: lifetime residents Other confounding factors: not stated
Interventions	All natural fluoridation Group 1: 0.3 ppm Group 2: 1.1 ppm
Outcomes	Dental fluorosis (TF Index); caries data also evaluated within the study but excluded from review due to study design Age at assessment: 13 years (mean)
Funding	Funded by Unrestricted grant from Colgate Palmolive (USA)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Low risk	All eligible secondary schools and students within them were invited to participate
Confounding	High risk	Did not account for the use of fluoride from other sources
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information. The measurement and recording of outcome were by different personnel, but they were not reported to have been blinded

Machiulskiene 2009 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	Low risk	All expected outcome reported
Other bias	Low risk	No other apparent bias

Mackay 2005

Methods	**FLUOROSIS STUDY** Country of study: New Zealand Geographic location: not stated Year of study: 2002 Year of change in fluoridation status: not stated Study design: cross-sectional
Participants	Inclusion criteria: not stated Exclusion criteria: not stated Other sources of fluoride: ingestion of toothpaste before the age of three = 40%; use of fluoride tablets up to (and including) age three = 49 (11.2%) Ethnicity: not stated Social class: high SES school (deciles 8-10) = 192 (44%); medium SES school (deciles 4-7) = 121 (27.8%); low SES school (deciles 1-3) = 128 (28.2%) Residential history: the study included both continuous and intermittent residents, however, only data from continuous residents included in analysis Other confounding factors: not stated
Interventions	Group 1: 0.1-0.3 ppm (natural fluoridation) Group 2: 0.8 ppm (artificial fluoridation)
Outcomes	Enamel defects (DDE); caries data also evaluated within the study but excluded from review due to study design Age at assessment: 8.7-11.1 years
Funding	New Zealand Dental Research Foundation
Notes	Fluoride concentration deduced from discussion section and anecdotal evidence

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Low risk	A random sample of 600 Year 5 children enrolled with the Southland District Health Board's school dental service was invited to participate in the study

Mackay 2005 (*Continued*)

Confounding	High risk	A statistical model used showed that hypoplastic defects were influenced by ingestion of toothpaste before age four but the results were not adjusted for this factor
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	436 (74.5%) of the 600 children invited to the study were examined
Selective reporting (reporting bias)	Low risk	All expected outcome reported
Other bias	Low risk	No other apparent bias

Macpherson 2007

Methods	**FLUOROSIS STUDY** Country of study: Sweden Geographic location: Kungsbacken (F); Halmsted (non-F) Year of study: 2002-2003 Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: presence of 2 individual anterior labial-view photographs of any upper anterior teeth present; similar date of birth (difference in age due to undertaking fieldwork in study areas a year apart) Exclusion criteria: not stated Other sources of fluoride: Age at which started brushing: 6-12 months vs 12 months (P value 0.99) Frequency of brushing: $\leq$ 1/day vs $\geq$ 2/day (P value 0.42) Toothpaste F < 1000 ppm vs $\geq$ 1000 ppm (P value 0.49) Amount of toothpaste $\leq$ pea size vs > pea size (P value 0.09) Fluoride tablets previously: 'No' vs 'Yes' (P value 0.001) Fluoride tablets now: 'No' vs 'Yes' (P value 0.001) Ethnicity: not stated Social class: low education: F = 47, non-F = 56; high education: F = 64, nonF = 73. Both groups were similar with respect to parents' education attainment (P value 0.87) Residential history: children from Kungsbacka were generally exposed to fluoridated water in early childhood, while those from Halmstad were not exposed to fluoridated water during infancy (discussion section) Other confounding factors: not stated
Interventions	All natural fluoridation Group 1: 0.1 ppm Group 2: 1.3 ppm

Macpherson 2007 (*Continued*)

Outcomes	Dental fluorosis (TF Index; photographic assessment) Age at assessment: 7-10 years	
Funding	Not stated	
Notes		

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Low risk	Cluster random sample of parents of eligible children aged 7-10 years from the same birth cohort
Confounding	High risk	Use of fluoride toothpaste and frequency of brushing was similar across groups, however, current use of fluoride supplements as well as past use was significantly higher in the control group. This information is used to provide adjusted odds ratios however, for the purposes of this review only the raw data has been used which remains subject to confounding factors
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blind to the source area of each slide
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	Unclear risk	Photographic assessment as well as TF Index of dental fluorosis were measured but only photographic assessment reported
Other bias	Low risk	No other apparent bias

Mandinic 2009

Methods	**FLUOROSIS STUDY** Country of study: Serbia Geographic location: Valjevo and Vranjska Banja Year of study: not stated Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: not stated Exclusion criteria: not stated Other sources of fluoride: used the fluoride concentration database and consumption database to determine fluoride exposure Ethnicity: not stated Social class: not stated Residential history: used the fluoride concentration database and consumption database to determine fluoride exposure Other confounding factors: dietary sources of fluoride - potato, beans
Interventions	All natural fluoridation Group 1: 0.1 ppm Group 2: 11 ppm
Outcomes	Dental fluorosis (Dean's Index) Age at assessment: 12 years
Funding	Not stated
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Unclear risk	Insufficient detail reported to determine how selection took place - sampling frame was unspecified
Confounding	High risk	Fluoride exposure and consumption were measured but not reported. Did not account for SES
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	Low risk	Expected outcome reported

Mandinic 2009 (*Continued*)

Other bias	Low risk	No other apparent bias

Mandinic 2010

Methods	**FLUOROSIS STUDY** Country of study: Serbia Geographic location: Valjevo, Veliko Gradiste, Kacarevo and Vranjska Banja Year of study: 2006 Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: healthy 12-year-old school children, both genders, lifetime residents of the same municipality Exclusion criteria: not stated Other sources of fluoride: not stated Social class: not stated Ethnicity: not stated Residential history: lifetime residents Other confounding factors: there were no addition sources of exposure, i.e. industries that could pollute the environment by fluoride emission
Interventions	All natural fluoridation Wells Group 1: 0.79 ppm Group 2: 0.1 ppm Group 3: 0.15 ppm Group 4: 11 ppm Tap water Group 1: 0.17 ppm Group 2: 0.07 ppm Group 3: 0.1 ppm Group 4: 0.15 ppm
Outcomes	Dental fluorosis (Dean's Index) Age at assessment: 12 years
Funding	Ministry of Science and Technological Development of the Republic of Serbia
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Unclear risk	Insufficient information on sampling

Mandinic 2010 (*Continued*)

Confounding	High risk	The use of other fluoride sources and SES were not considered
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data for all participants was reported
Selective reporting (reporting bias)	High risk	Data not in suitable format for analysis
Other bias	Low risk	No other bias apparent

Marya 2010

Methods	**FLUOROSIS STUDY** Country of study: India Geographic location: 30 villages from district Gurgaon and district Hissar Year of study: not stated Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: only continuous residents; selected individuals had to have all their permanent teeth (except third molars) erupted Exclusion criteria: not stated Other sources of fluoride: not stated Ethnicity: not stated Social class: environmental factors such as eating habits, nutritional status, consumption of water**,** living conditions were almost uniform in all 7 groups studied Residential history: continuous residents Other confounding factors: not stated
Interventions	All natural fluoridation Group 1: 0.5 ppm Group 2: 0.87 ppm Group 3: 1.51 ppm Group 4: 2.45 ppm Group 5: 5.27 ppm Group 6: 8.5 ppm
Outcomes	Dental fluorosis (Dean's Index) Age at assessment: 12-16 years
Funding	Not stated
Notes	

Marya 2010 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Sampling	Unclear risk	Insufficient detail reported to determine how selection took place
Confounding	Unclear risk	Environmental factors such as eating habits, nutritional status, consumption of water, and living conditions were almost uniform in all 7 groups studied, however, it was unclear whether this extended to exposure to fluoride from other sources
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	Low risk	Expected outcome reported
Other bias	Low risk	No other apparent bias

Masztalerz 1990

Methods	**FLUOROSIS STUDY** Country of study: Poland Geographic location: Neisse (high-F), Breslau (F), Militsch and Gryfo w (non-F) Year of study: not stated Year of change in fluoridation status: not stated Study design: cross sectional
Participants	Inclusion criteria: none stated Exclusion criteria: children who were not lifetime residents and had those who did not yet have permanent canine teeth Other sources of fluoride: not stated Social class: not stated Ethnicity: not stated Residential history: lifelong residents Other confounding factors: fluoride in the air was high in Greifenberg
Interventions	Appeared to be natural fluoridation, however this was not clear Group 1: 4-7 ppm Group 2: 0.7-0.9 ppm Group 3: < 0.2 ppm

Masztalerz 1990 (*Continued*)

Outcomes	Dental fluorosis (index unclear) Age at time of measurement: 12 years
Funding	Not stated
Notes	Paper translated from German

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Unclear risk	The authors report that all eligible children were to be studies however, the sampling frame was not specified
Confounding	High risk	Did not account for SES or the use of fluoride from other sources (except from air pollution though this is unclear)
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information. No details on blinding were reported, no standard index for measurement of fluorosis appears to have been used
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for 88% of participants
Selective reporting (reporting bias)	Low risk	Data appears present
Other bias	Low risk	No other bias detected

Maupome 2001

Methods	**CARIES STUDY** Country of study: Canada Geographic location: British Columbia Year study started: 1993-1994 Year study ended: 1996-1997 Year of change in fluoridation status: 1992 Study design: CBA
Participants	Inclusion criteria: not stated Exclusion criteria: not stated Other sources of fluoride: data on oral hygiene and exposure to diverse fluoride technologies were collected but not reported. However, the authors stated that British Columbia had relatively homogeneous exposure to fluorides, widespread use of fluoride toothpastes. good adherence to oral hygiene regimens and good access to oral health care

Maupome 2001 (*Continued*)

	Social class: participants showed similar SES at baseline Ethnicity: not stated Residential history: information about the regression analysis suggests that both lifetime and non-lifetime residents might have been included Other confounding factors: not reported
Interventions	**Fluoride cessation** Group 1: 'optimal' level - ppm not stated (artificial fluoridation) to non-fluoridated Group 2: 'optimal' level - ppm not stated (artificial fluoridation)
Outcomes	DMFS Age at baseline: Grades 2, 3, 8 and 9 Age at final measurement: Grades 2, 3, 8 and 9
Funding	NHRDP operating grant 6610-2225-002 supported this study
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Unclear risk	Study was a multi-site study and also both a repeated cross-sectional prevalence survey and a longitudinal investigation. Children were examined in their schools but no other sampling details reported
Confounding	High risk	At baseline data for lifetime and non-lifetime residents were reported; information on diet (snacks) and other fluoride sources were collected but the results were not adjusted for these factors
Blinding of outcome assessment (detection bias) All outcomes	High risk	Used different examiners for different study sites who where not blinded to fluoridation status
Incomplete outcome data (attrition bias) All outcomes	High risk	About 90% of all eligible children were examined at baseline; 64.2% at follow-up with variation across groups
Selective reporting (reporting bias)	Low risk	Expected outcome was presented
Other bias	Unclear risk	Baseline data were collected 14-19 months after cessation of fluoridation. This gap between the actual cessation of fluoridation and the beginning of data collection might be a source of bias, towards the null, since

Maupome 2001 (*Continued*)

		the exposure had been modified from fluoridated to non-fluoridated water

Mazzotti 1939

Methods	**FLUOROSIS STUDY** Country of study: Mexico Geographic location: all areas in Mexico, 11 states, 107 cities Year of study: 1938 Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: not stated Exclusion criteria: not stated Other sources of fluoride: not stated Social class: not stated Ethnicity: not stated Residential history: not stated Other confounding factors: not stated
Interventions	Groups: 0-4 unclear ppm
Outcomes	Dental fluorosis (index unclear) Age at assessment: not stated
Funding	Not stated
Notes	Paper translated from Spanish

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Unclear risk	There was insufficient detail reported to determine how selection took place
Confounding	High risk	No details were reported on SES or fluoride from other sources
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to determine whether there was attrition
Selective reporting (reporting bias)	High risk	Data not in suitable format for analysis

Mazzotti 1939 (*Continued*)

Other bias	Unclear risk	Overall reporting on any information too poor to permit thorough assessment of any risk of bias

McGrady 2012

Methods	**FLUOROSIS STUDY** Country of study: Thailand Geographic location: Chiang Mai Year of study: 2007 Year study ended: not stated Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: life long residency; good general health with both maxillary incisors fully erupted; free from fixed orthodontic appliances Exclusion criteria: non-lifetime residents; unsuitable dentition Other sources of fluoride: • Non-fluorosed breast and formula: 88/305 (28.8%) • Formula only: 14/57 (24.6%) • F content paste: < 1000 ppm = 13/59 (22%); 1000 ppmF = 150/501 (29.9%) • Toothbrushing frequency: once/day = 45/130 (34.6%); twice/day = 99/360 (27.5%); > 3 times/day =19/70 (27.1%) • Age toothbrushing started: 4 years+ = 20/76 (26.3%); 3-4 years = 43/138 (31.2%); 2-3 years = 48/178 (27%); 1-2 years = 35/126 (27.8%); 0-1 year = 8/23 (34.8%) Ethnicity: not stated Social class: not stated Residential history: continuous residents Other confounding factors: not stated
Interventions	All natural fluoridation Group 1: < 0.2 ppm Group 2: 0.2-0.59 ppm Group 3: 0.6 -0.89 ppm Group 4: ≥ 0.9 ppm
Outcomes	Dental fluorosis (TF Index) Age at assessment: 8-13 years
Funding	One author was funded by a Clinician Scientist Award from the National Institute for Health Research (UK). The Colgate Palmolive Dental Health Unit was funded by an unrestricted grant from Colgate Palmolive Possible conflicts of interest: RPE is an employee of a manufacturer of oral care products
Notes	

Risk of bias

McGrady 2012 (*Continued*)

Bias	Authors' judgement	Support for judgement
Sampling	High risk	The study was based on a convenience sample population with varying exposures to fluoride
Confounding	High risk	The data on fluoride from other sources was not presented in a usable format and outcome data were not adjusted for it. Did not account for SES
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The examiners were blinded to the probable fluoride exposure and the images were presented for examination in a randomised order
Incomplete outcome data (attrition bias) All outcomes	High risk	Data for 148 (21%) examined participants not analysed
Selective reporting (reporting bias)	Low risk	Outcome of interest reported
Other bias	Low risk	No other bias apparent

McInnes 1982

Methods	**FLUOROSIS STUDY** Country of study: South Africa Geographic location: Kenhardt (F); Keimoes (non-F); North-western Cape Province Year of study: not stated Year of change in fluoridation status: NA Study design: cross sectional
Participants	Inclusion criteria: lifetime residents of study area; pre-school children aged 1-5 years Exclusion criteria: none stated Other sources of fluoride: majority of babies were breastfed so would not be exposed to fluoride from water used in preparation of infant formula Social class: reported as being the same across groups; experimental and control groups reported as being similar (parents were land or railway labourers) Ethnicity: all children same ethnic origin i.e. European-African-Malay origin Residential history: lifetime residents Other confounding factors: same climatic conditions in both areas
Interventions	All natural fluoridation Group 1: 2.2-4.1 ppm Group 2: 0.2 ppm
Outcomes	Dental fluorosis (Dean's Index) Age at time of measurement: 1-5 years

McInnes 1982 (*Continued*)

Funding	Part funded by South African Sugar Association
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Unclear risk	Insufficient detail reported to determine how selection took place
Confounding	High risk	Malnutrition and SES were reported to be similar across groups but no supporting data provided Did not report any details about other sources of fluoride
Blinding of outcome assessment (detection bias) All outcomes	High risk	Did not undertake blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data appear to be presented for all participants
Selective reporting (reporting bias)	Low risk	All expected data appeared to be present
Other bias	Low risk	No other apparent bias

Mella 1992

Methods	**FLUOROSIS STUDY** Country of study: Chile Geographic location: students attending 2 boarding institutions in Santiago, who lived in areas throughout Chile Year of study: not stated Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: students at boarding institution, exposure estimated from home fluoride level; lived for first 6 years in home town Exclusion criteria: students who could not remember the areas in which they spent the first 6 years of their life Other sources of fluoride: not stated Social class: distribution of subjects by high, moderate, low social class, but no significant differences between fluoride groups Ethnicity: not stated Residential history: first 6 years of life Other confounding factors: years lived in city of birth

Mella 1992 (*Continued*)

Interventions	All natural fluoridation Group 1: > 0.3 ppm Group 2: ≤0.3 ppm
Outcomes	Dental fluorosis (Dean's Index) Age at assessment: 19 years
Funding	Not stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	High risk	All subjects were selected from 2 boarding schools. Insufficient detail reported to determine how sampling took place
Confounding	High risk	Did not account for the use of fluoride from other sources
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	Unclear risk	Unclear why only very mild, mild and moderate severities of dental fluorosis reported for both groups
Other bias	Low risk	No other apparent bias

Mella 1994

Methods	**FLUOROSIS STUDY** Country of study: Chile Geographic location: Iquique (F); Santiago (non-F); Valparaiso-Vina (F); Temuco (low-F) Year of study: 1983 Year of change in fluoridation status: not stated Study design: cross-sectional
Participants	Inclusion criteria: 4 schools in study areas Exclusion criteria: not stated Other sources of fluoride: not stated

Mella 1994 (*Continued*)

	Social class: 2 schools in each area, 1 from low social class, 1 from medium/high social class, results presented separately by social class Ethnicity: not stated Residential history: not stated Other confounding factors: not stated
Interventions	Group 1: 2.2 ppm (natural fluoridation) Group 2: 0.0 ppm (natural fluoridation) Group 3: 1.0 ppm (artificial fluoridation) Group 4: 0.3 ppm (natural fluoridation)
Outcomes	Dental fluorosis (Dean's Index) Age at assessment: 7 and 12 years
Funding	Not stated
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Unclear risk	Insufficient detail reported to determine how selection took place. 4 schools from a list of schools benefiting from school feeding programs were selected from each city, however it was not reported how these were chosen or how the children within the schools were chosen
Confounding	High risk	Did not account for the use of fluoride from other sources
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	Low risk	Outcome of interest reported
Other bias	Low risk	No other apparent bias

Meyer-Lueckel 2006

Methods	**FLUOROSIS STUDY** Country of study: Iran Geographic location: Youssefabad, Seman, Dibaj Year of study: 2003 Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: school children aged 6-9 years who were lifetime residents Exclusion criteria: not stated Other sources of fluoride: not stated Social class: Youssefabad, Semnan were of upper middle and lower middle class, social class of the third community was not mentioned Ethnicity: not stated Residential history: lifetime residents Other confounding factors: not stated
Interventions	All natural fluoridation Group 1: 0.2 ppm Group 2: 0.3 ppm Group 3: 1.3 ppm
Outcomes	Dental fluorosis (TSIF); caries data evaluated in study but excluded from review due to study design Age at assessment: 6-9 years
Funding	Not stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Low risk	2 schools (one boys' and one girls') were randomly selected from 2 of the 3 study areas, and in the third study area the only school (coeducation) was selected and all participants were then examined
Confounding	High risk	2 study areas varied in social class, while there was no information on SES for the third study area; in addition the use of other fluoride sources was not considered
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported

Meyer-Lueckel 2006 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Fluorosis outcome data were reported in bar charts making it difficult to assess whether there were incomplete outcome data or not
Selective reporting (reporting bias)	High risk	Though outcome of interest was reported, fluorosis outcome was not reported for the Youssefabad area
Other bias	Unclear risk	The single examiner involved in the study was calibrated, and though the reliability of caries recording was assessed, it was not done for fluorosis outcome

Milsom 1990

Methods	**FLUOROSIS STUDY** Country of study: England Geographic location: Nantwich (F); Northwich (non-F) Year of study: 1988 Year of change in fluoridation status: 1975 Study design: cross-sectional
Participants	Inclusion criteria: children aged 8 years attending state-maintained schools; lifetime residents of study areas; parental consent Exclusion criteria: parishes not bounded on all sides by parishes with optimally fluoridated water for fluoride areas; exposure to fluoride supplements Other sources of fluoride: age at which tooth brushing first began Social class: measured by parental occupation; social class makeup of study areas almost identical (data presented in paper) Ethnicity: not stated Residential history: lifetime residents Other confounding factors: not stated
Interventions	Group 1: 1 ppm (artificial fluoridation) Group 2: < 0.3 ppm (natural fluoridation)
Outcomes	Enamel defect (DDE) Age at assessment: 8 years
Funding	Financial support from the North Western Regional Health Authority
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Milsom 1990 (*Continued*)

Sampling	Low risk	The study included all eligible children who lived in the non-fluoridated area and those in the fluoridated area were selected by a two-stage random sampling technique
Confounding	Low risk	There was no difference in SES across groups and children with exposure to fluoride supplements were excluded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants were taken to the examination centre by bus, examiner was unaware of the schools in attendance and fluoridation status
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data appear to be presented for all participants
Selective reporting (reporting bias)	Low risk	Outcome of interest appears present
Other bias	Unclear risk	Data were collected on age of commencement of tooth brushing but not reported

Mondal 2012

Methods	**FLUOROSIS STUDY** Country of study: India Geographic location: Nalhati I (Nasipur, Vabanandapur, Deshnabagram) and Rampurhat II (Chalk Atla, Nowapara, Junitpur and Kamdebpur) Year of study: 2003 Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: not stated Exclusion criteria: not stated Other sources of fluoride: not stated Social class: not stated Ethnicity: not stated Residential history: lifetime residents Other confounding factors: not stated
Interventions	All natural fluoridation Group 1: 3.15 ppm Group 2: 3.83 ppm
Outcomes	Dental fluorosis (Dean's Index) Age at assessment: < 10 years to > 50 years

Mondal 2012 (*Continued*)

Funding	Not stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	High risk	"The recruitment of respondents was performed at seven primary schools in the study area with pupils in the age range of 4-10 years and the rest of the age group samples were collected from the respective villages". There was no indication that random sampling was carried out
Confounding	High risk	Participants were lifetime residents, however, SES and the use of other fluoride sources were not considered
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data for all participants reported
Selective reporting (reporting bias)	Low risk	Outcome of interest fully reported
Other bias	Unclear risk	Examination was done by a 'competent dentist', however, there was no mention of calibration

Montero 2007

Methods	**FLUOROSIS STUDY** Country of study: Venezuela Geographic location: Maria May, Roscio and Madre Emilia Year of study: not stated Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: not stated Exclusion criteria: not stated Other sources of fluoride: not stated Ethnicity: not stated Social class: not stated Residential history: not stated

Montero 2007 (*Continued*)

	Other confounding factors: not stated
Interventions	All natural fluoridation Group 1: 0.13 ppm Group 2: 0.31 ppm Group 3: 1.58 ppm
Outcomes	Dental fluorosis (Dean's Index); caries data also evaluated in study but excluded from review due to study design Age at assessment: 8-12 years
Funding	Not stated
Notes	Paper translated from Spanish

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Low risk	Random sampling was used
Confounding	High risk	Did not account for the use of fluoride from other sources or SES
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data appear to be presented for all participants
Selective reporting (reporting bias)	Low risk	All expected outcome presented
Other bias	Low risk	No other apparent bias

Nanda 1974

Methods	**FLUOROSIS STUDY** Country of study: India Geographic location: 23 villages in Lucknow (North Central India) Year of study: not stated Year of change in fluoridation status: NA Study design: cross sectional
Participants	Inclusion criteria: lifetime residents of study areas; children from 103 urban and 66 rural schools; all permanent teeth (excluding third molars) present Exclusion criteria: none stated Other sources of fluoride: dietary fluoride intake

Nanda 1974 (*Continued*)

	Social class: not stated Ethnicity: not stated Residential history: lifelong residents Other confounding factors: climate
Interventions	All natural fluoridation Group 1: > 1.21 ppm Group 2: 0.81-1.2 ppm Group 3: 0.41-0.8 ppm Group 4: 0-0.4 ppm
Outcomes	Dental fluorosis (Dean's Index) Age at time of measurement: 6-17 years
Funding	Supported by PL-480 grants from the Bureau of Health Manpower Education, Division of Dental Health Public Health Service under the aegis of the Indian Council of Medical Research, New Delhi
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Unclear risk	Insufficient detail reported to determine how selection took place
Confounding	High risk	Did not account for SES
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding was not undertaken
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear due to poor reporting of participant numbers and data
Selective reporting (reporting bias)	High risk	Poor reporting of outcome data
Other bias	High risk	No other bias detected

Narbutaite 2007

Methods	**FLUOROSIS STUDY** Country of study: Lithuania Geographic location: Klaipeda and Kaunas Year of study: 1997 Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: not stated Exclusion criteria: not stated Other sources of fluoride: not stated Ethnicity: not stated Social class: Klaipeda and Kaunas said to be the 2 largest cities in Lithuania and to be of a similar size and socioeconomic structure Residential history: lifetime residents Other confounding factors: not stated
Interventions	All natural fluoridation Group 1: 0.22 ppm Group 2: 1.7-2.2 ppm
Outcomes	Dental fluorosis (TF Index); caries data also evaluated within the study but excluded from review due to study design Age at assessment: 12 years
Funding	Not stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Unclear risk	8 out of 23 ordinary secondary schools in Klaipeda (the high-F area) and 8 out of 30 in Kaunas (the low-F area), were selected to cover the regions. However, it is not clear how these schools were selected
Confounding	High risk	No details were reported on the use of fluoride from other sources
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported

Narbutaite 2007 (*Continued*)

Other bias	High risk	All examinations were carried out by 1 examiner who was a specialist with additional training in dental fluorosis diagnosis but no mention of reliability testing; water was taken from 3 sampling sites in the high-F area and 1 in the low-F area, no explanation was provided for the inconsistency

Narwaria 2013

Methods	**FLUOROSIS STUDY** Country of study: India Geographic location: Dumduma, Bangama, Hazinager, Sillarpur, Sirsod, Nichroli, Toda Karera, Toda Rampur, Kali Pahadi and Zuzai in Karera Year of study: not stated Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: primary school children; mostly 5-12 years Exclusion criteria: not stated Other sources of fluoride: not stated Ethnicity: not stated Social class: not stated. Residential history: not stated Other confounding factors: not stated
Interventions	All natural fluoridation Group 1: 1.65 ppm Group 2: 1.84 ppm Group 3: 1.84 ppm Group 4: 1.88 ppm Group 5: 1.91 ppm Group 6: 2.15 ppm Group 7: 2.22 ppm Group 8: 2.53 ppm Group 9: 3.91 ppm
Outcomes	Dental fluorosis (Dean's Index) Age at assessment: 5-12 years
Funding	Funding for travelling and laboratory facilities provided by Special Assistance Program (SAP)-I UGC, New Delhi
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Narwaria 2013 (*Continued*)

Sampling	Low risk	10 villages were selected for study using the eligibility criteria. Within these villages, all government schools were included and children were randomly selected from each class
Confounding	High risk	Did not account for the use of fluoride from other sources or SES
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	Low risk	Outcome of interested reported
Other bias	High risk	Examination was performed by 2 trained dentists. No mention of calibration or of reliability testing

Nunn 1992

Methods	**FLUOROSIS STUDY** Country of study: England Geographic location: Hartlepool, Newcastle and Middlesborough Year of study: 1989 Year of change in fluoridation status: NA Study design: cross-sectional study
Participants	Inclusion criteria: lifetime residents of study areas; children in selected schools aged 15-16 years Exclusion criteria: children with fractured incisor teeth, orthodontic bracket or surface otherwise obscured Other sources of fluoride: not stated Social class: occupation of head of household recorded; participants of low and high SES were recruited when possible Ethnicity: ethnicity recorded but no expansion on variable Residential history: lifetime residents Other confounding factors: not stated
Interventions	Group 1: 1-1.3 ppm Group 2: 1 ppm Group 3: 0.2 ppm
Outcomes	Enamel defect Age at assessment: 12 years

Nunn 1992 (*Continued*)

Funding	Financial assistance from the British Council
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Unclear risk	There was insufficient detail reported to determine how selection took place
Confounding	High risk	Did not account for the use of fluoride from other sources. Balance of SES between groups was unclear
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Photographs of the maxillary central incisors of participants were cut out from the print and identified with a code which would prevent identification by the examiners
Incomplete outcome data (attrition bias) All outcomes	High risk	In England, data for 68% of examined participants were reported due to camera failure in a school of SES
Selective reporting (reporting bias)	Low risk	Expected outcome appeared to be present
Other bias	Low risk	No other apparent bias

Nunn 1994a

Methods	**FLUOROSIS STUDY** Country of study: England Geographic location: north-east England Year of study: 1990-1991 Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: lifetime residents of study areas (England only); children aged 12 years; parental consent (England only) Exclusion criteria: none stated Other sources of fluoride: not stated, but expected higher use of toothpaste in higher SES groups Social class: children divided into high and low social class Ethnicity: not stated Residential history: UK participants were lifetime residents Other confounding factors: not stated

Nunn 1994a (*Continued*)

Interventions	Group 1: 0.1 ppm Group 2: 0.5 ppm Group 3: 1.0 ppm
Outcomes	Enamel defect (DDE) Age at assessment: 12 years
Funding	Not stated
Notes	Two study centres: England Sri Lanka. Different methodology used in England and Sri Lankan study centres, therefore reported under different study ID's (England - Nunn 1994a and Sri Lankan - Nunn 1994b)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Unclear risk	Schools were selected by the district dental officer in order to achieve a target of about 150 eligible 12 year old children in each sub-group. Insufficient information provided regarding how the children were selected within the schools
Confounding	High risk	Higher reported use of toothpaste in the higher SES groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The examiner was largely unaware of fluoride and socioeconomic status of the children
Incomplete outcome data (attrition bias) All outcomes	Low risk	Participants sampled were < 80% in the study areas and not balanced across groups, however, data presented for all recruited participants
Selective reporting (reporting bias)	Low risk	Expected outcome was presented
Other bias	Low risk	No other apparent bias

Nunn 1994b

Methods	**FLUOROSIS STUDY** Country of study: Sri-Lanka Geographic location: Sri Lanka Year of study: 1990-1991 Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: children aged 12. Exclusion criteria: none stated Other sources of fluoride: not stated, but expected higher use of toothpaste in higher SE groups Social class: children divided into high and low social class Ethnicity: not stated Residential history: Sri Lankan populations were non-mobile and confirmed continuous residence when asked at the time of examination Other confounding factors: not stated
Interventions	Group 1: 0.1 ppm Group 2: 0.5 ppm Group 3: 1.0 ppm
Outcomes	Enamel defect (DDE) Age at assessment: 12 years
Funding	Not stated
Notes	Two study centres: England Sri Lanka. Different methodology used in England and Sri Lankan study centres, therefore reported under different study ID's (England - Nunn 1994a and Sri Lankan - Nunn 1994b)

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Unclear risk	Schools were selected by the district dental officer in order to achieve a target of about 150 eligible 12-year-old children in each sub-group. Insufficient information provided regarding how the children within the schools were selected
Confounding	High risk	Imbalance of SES between groups. Two of the three study areas recruited only children of low SES and one area recruited both low and high SES children
Blinding of outcome assessment (detection bias) All outcomes	High risk	The examiner was aware of the fluoride and socioeconomic status of the children

Nunn 1994b (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Participants sampled were < 80% in the study areas and not balanced across groups, however, data presented for all recruited participants
Selective reporting (reporting bias)	Low risk	Expected outcome was presented
Other bias	Low risk	No other apparent bias

Ockerse 1941

Methods	**FLUOROSIS STUDY** Country of study: South Africa Geographic location: Upington, Kenhardt and Pofadder Year of study: 1939 Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: children attending schools in study areas; children aged 6-17 years Exclusion criteria: none stated Other sources of fluoride: not stated Social class: not stated Ethnicity: not stated Residential history: participants were born and lived up to the age of 8 in the study areas Other confounding factors: sStudy areas at same altitude, same climate, similar countryside and vegetation, differences in drinking water composition discussed
Interventions	All natural fluoridation Group 1: 2.46 ppm (average) Group 2: 6.8 ppm Group 3: 0.38 ppm
Outcomes	Mottled enamel; caries data also evaluated within the study but excluded from review due to study design Age at assessment: 6-17 years
Funding	Not stated
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	High risk	Areas thought to be most affected by caries and mottling were selected and visited. Selection of 'at risk' population is likely to

Ockerse 1941 (*Continued*)

		have introduced bias
Confounding	High risk	Did not account for the use of fluoride from other sources or SES
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	High risk	Caries data reporting may have been a post-hoc decision
Other bias	High risk	Data were collected on age of commencement of tooth brushing but not reported. There was no mention of examiner training or calibration

Pontigo-Loyola 2008

Methods	**FLUOROSIS STUDY** Country of study: Mexico Geographic location: urban - Tula Centro and San Marcos; rural - El Llano Year of study: 1999 Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: not stated Exclusion criteria: having fixed orthodontic appliances; metal crowns; refusal to be examined; unavailable for oral examination Other sources of fluoride: not stated Ethnicity: not stated Social class: not stated. Residential history: birth to $\geq$ 6 years Other confounding factors: not stated
Interventions	All natural fluoridation Group 1: 1.38 ppm Group 2: 1.42 ppm Group 3: 3.07 ppm
Outcomes	Dental fluorosis (modified Dean's Index) Age at assessment: 12 and 15 years
Funding	Data collection by the Universidad Autonoma del Estado de Hidalgo and data analysis was partially supported by a grant from the National Council of Science and Technology of Mexico

Pontigo-Loyola 2008 (*Continued*)

Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Sampling	Low risk	All eligible participants were included in the study
Confounding	High risk	Did not account for the use of fluoride from other sources or SES
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Only 66.6% of the included participants were in the final study population. The reason for withdrawal was not reported
Selective reporting (reporting bias)	Low risk	Outcome of interest reported
Other bias	Low risk	No other apparent bias

Pot 1974

Methods	**CARIES STUDY** Country of study: Holland Geographic location: Tiel (F); Culemborg (non-F) Year study started: 1950 Year study ended: 1970 Year of change in fluoridation status: 1953 Study design: CBA
Participants	Inclusion criteria: residents of study areas born between 1896 and 1945; lifelong residents of study areas Exclusion criteria: subjects who left the study areas for more than 3 months after fluoridation was introduced Other sources of fluoride: not stated Social class: not stated Ethnicity: not stated Residential history: lifetime residents Other confounding factors: age: results for final survey presented in 5-year age groups and showed that higher proportion of younger subjects had prosthetic teeth in Culemborg than in Tiel
Interventions	Group 1: 1.1 ppm (artificial fluoridation) Group 2: 0.1 ppm (natural fluoridation)

Pot 1974 (*Continued*)

Outcomes	Outcome: % with false teeth Age at baseline measure: 5-55 Age at final measure: 25-75	
Funding	Not stated	
Notes	Paper translated from Dutch	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Sampling	Low risk	Participants were selected by random sampling from the city population registers
Confounding	High risk	Did not report on SES or the use of other fluoride sources
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data presented for all participants
Selective reporting (reporting bias)	High risk	Study reports on % false teeth; no caries data
Other bias	High risk	There was no mention of examiner calibration or of reliability testing

Ray 1982

Methods	**FLUOROSIS STUDY** Country of study: India Geographic location: Rustampur and Ledhupur, 2 adjacent village in Varanasi District Year of study: not stated Year of change in fluoridation status: NA Study design: cross sectional
Participants	Inclusion criteria: none stated Exclusion criteria: none stated Other sources of fluoride: not stated Social class: study areas similar with respect to demographic and socioeconomic characteristics Ethnicity: not stated Residential history: not stated Other confounding factors: villages similar with respect to geoclimatic characteristics

Ray 1982 (*Continued*)

Interventions	All natural fluoridation Group 1: > 2 ppm Group 2: 1-2 ppm Group 3: < 1 ppm
Outcomes	Dental fluorosis (index not stated) Age at assessment: not stated
Funding	Funded by the Indian Council of Medical Research
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Low risk	All eligible participants were included in the study
Confounding	High risk	Did not report on the use of fluoride from other sources
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of participants recruited not stated
Selective reporting (reporting bias)	Low risk	Outcome of interest reported
Other bias	High risk	No mention of how examination was conducted or whether the examiner was calibrated

Riordan 1991

Methods	**FLUOROSIS STUDY** Country of study: Australia Geographic location: Perth (F); Bunbury (non-F), Western Australia Year of study: 1989 Year of change in fluoridation status: 1968 Study design: cross-sectional
Participants	Inclusion criteria: children born in 1978; children attending government schools in study areas; parental consent Exclusion criteria: subjects with amelogenesis imperfecta or orthodontic banding

Riordan 1991 (*Continued*)

	Other sources of fluoride: questionnaire investigated periods and duration of use of fluoride supplements, use of fluoride toothpaste, included age at which use of toothpaste commenced, whether child swallowed toothpaste Social class: schools assigned socioeconomic score - no significant difference in scores between study areas Ethnicity: not stated Residential history: not stated Other confounding factors: not stated
Interventions	Group 1: 0.8 ppm (artificial fluoridation) Group 2: < 0.2 ppm (natural fluoridation)
Outcomes	Dental fluorosis (TF Index) Age at assessment: 12 years
Funding	Not stated
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Low risk	Random selection of 14 Dental Therapy Centres; selection of 1 class/centre of children born in 1978
Confounding	High risk	Insufficient information to determine whether use of other fluoride sources was balanced across groups
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blind outcome assessment (with regard to residency) was not undertaken
Incomplete outcome data (attrition bias) All outcomes	Low risk	7/376 and 3/338 not available for evaluation; unlikely to influence results
Selective reporting (reporting bias)	Low risk	All relevant outcome data reported
Other bias	Low risk	No other apparent bias

Riordan 2002

Methods	FLUOROSIS STUDY Country of study: Australia Geographic location: Western Australia Year of study: 2000 Year of change in fluoridation status: NA Study design: Cross-sectional
Participants	Inclusion criteria: Children born around 1990 (10 yrs old) who had lived in Australia/ New Zealand for most of their lives (so as to ensure life time exposure to water fluoridation) Exclusion criteria: Migrants from outside Australia and New Zealand, refusal to consent, not present at school at the time of exam Other sources of fluoride: Information was collected on use of infant formula, age at which toothpaste was introduced and the use of fluoride supplements. Fluoride supplement use was almost exclusive to residents of the non-fluoridated areas Social class: Not specified Ethnicity: Not specified Residential history: Participants were categorised as having been exposed to water fluoridation if they had spent more than half their life between the ages of 0-5 in a water fluoridated area Other confounding factors: Not specified
Interventions	Group 1: 0.8ppm (artificial fluoridation) Group 2: 0.2-0.3 ppm (naturally fluoridated)
Outcomes	Dental fluorosis (TF index) Age at assessment: 10 years
Funding	Not stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Low risk	The sampling frame was made up of children registered with the School dental service and children were accessed via schools. All eligible children were invited to take part in the study
Confounding	High risk	Information on other sources of fluoride was collected and more children in the non-fluoridated area took fluoride supplements. SES was not stated

Riordan 2002 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	Low risk	Outcome of interest reported
Other bias	Low risk	No other apparent bias

Ruan 2005

Methods	**FLUOROSIS STUDY** Country of study: China Geographic location: urban - Bao Ji and Jing Bian Year of study: 2002 Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: not stated Exclusion criteria: absent or unavailable; non-permanent residents Other sources of fluoride: no fluoride supply was provided by dental service and no fluoride supplement program was implemented in any of the communities Ethnicity: not stated Social class: the selected schools served rural communities where socioeconomic standards were comparable Residential history: permanent residents Other confounding factors: not stated
Interventions	All natural fluoridation Group 1: 0.4ppm Group 2: 1.0 ppm Group 3: 1.8 ppm Group 4: 3.5 ppm Group 5: 5.6 ppm
Outcomes	Dental fluorosis (TF Index); caries data also evaluated within the study but excluded from review due to study design Age at assessment: 12 and 13 years
Funding	The study was supported by the Norwegian State Educational Loan Fund
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Ruan 2005 (*Continued*)

Sampling	Unclear risk	13 schools were contacted and all children were invited to participate. The sampling frame for schools was not specified
Confounding	High risk	Even though fluoride supplement and fluoride supply by dental service were taken into account, the use of fluoride toothpaste (a common source) was not mentioned. It is not clear why it was not acknowledged or investigated
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The fluoride concentration of the local drinking-water supplies was unknown to the examiner at the time of the clinical examinations, which took place with the students seated on ordinary chairs outside the school building
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	High risk	Partial reporting of outcome - only reported prevalence of fluorosis with TF score ≥ 3 (fluorosis of aesthetic concern)
Other bias	Low risk	No other apparent bias

Rugg-Gunn 1997

Methods	**FLUOROSIS STUDY** Country of study: Saudi Arabia Geographic location: Jeddah (low F); Riyadh (moderate F); and Quassim (high F) Year of study: 1992 Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: lifetime residents of study areas; boys aged 14 years; parental consent Exclusion criteria: photographs that failed to show whole buccal surface; out of focus photographs Other sources of fluoride: not stated Social class: schools grouped according to the socioeconomic status of residential areas in the urban community; family income and parental education measured using questionnaire Ethnicity: not stated Residential history: lifetime residents Other confounding factors: nutritional status

Rugg-Gunn 1997 (*Continued*)

Interventions	All natural fluoridation Group 1: 2.7 ppm Group 2: 0.8 ppm Group 3: < 0.3 ppm	
Outcomes	Dental fluorosis (index unclear) Age at assessment: 14 years	
Funding	Not stated	
Notes		

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Low risk	Quote: "All school were grouped according to SES of the residential area in the urban community only and schools sampled randomly"
Confounding	High risk	Schools were grouped according to the SES of residential areas however it is not clear whether the study areas were balanced in this regard. No detail was reported on the use of fluoride from other sources
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data appears to have been presented for all participants
Selective reporting (reporting bias)	High risk	Data not in suitable format for analysis
Other bias	High risk	No other apparent bias

Russell 1951

Methods	**FLUOROSIS STUDY** Country of study: USA Geographic location: Colorado Springs (F); Boulder (non-F), Colorado Year of study: 1950 Year of change in fluoridation status: NA Study design: cross sectional
Participants	Inclusion criteria: white native residents listed in school census record for 1920, 1930 or 1940 and as resident in current city directory; mothers living in study area at time of birth; age 20-44 years; residence and usage of local water unbroken except for periods not exceeding 60 days during calcification and eruption of permanent teeth Exclusion criteria: none stated Other sources of fluoride: not stated Social class: workers in 2 communities followed similar occupations and had similar average salaries Ethnicity: native born white = 98% of Boulder population, and 96% of Colorado Springs population. This study only reports upon white participants (not clear if this was coincidence or purpose) Residential history: lifetime residents Other confounding factors: Colorado Springs 3 times size of Bolder, similar altitude and climate, neither population ageing nor young, both were highly literate, water systems similar
Interventions	All natural fluoridation Group 1: 2.5 ppm Group 2: < 0.1 ppm
Outcomes	Dental fluorosis (Dean's Index); caries data also evaluated within the study but excluded from review due to study design Age at time of measurement: 20-44 years
Funding	Not stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Low risk	Samples came from official registries in the areas (school, electoral, marriage etc). Authors estimate 5/6ths of eligible people participated
Confounding	Unclear risk	Considering the age of the study, other sources of fluoride are unlikely to affect the results. Although no measure of SES was provided, populations are reported as homogenous

Russell 1951 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding was not undertaken
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data for all participants appeared to be present.
Selective reporting (reporting bias)	High risk	Only data on fluorosis of aesthetic concern reported as opposed to all severities
Other bias	High risk	All examinations were made by the senior author, however, there was no mention of examiner calibration

Rwenyonyi 1998

Methods	**FLUOROSIS STUDY** Country of study: Uganda Geographic location: 4 areas of Uganda located at different altitudes Year of study: not stated Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: lifetime residents of study areas Exclusion criteria: none stated Other sources of fluoride: not stated Social class: not stated Ethnicity: not stated Residential history: lifetime residents Other confounding factors: mothers interviewed about water intake and food habits of child during early childhood; altitude
Interventions	All natural fluoridation Group 1: 2.5 ppm (low altitude) Group 2: 2.5 ppm (high altitude) Group 3: 0.5 ppm (low altitude) Control: 0.5 ppm (high altitude)
Outcomes	Dental fluorosis (index not stated) Age at assessment: 10-14 years
Funding	The Norwegian Universities' Committee for Development Research and Education and the Committee for Research and Postgraduate Training, University of Bergen
Notes	

Risk of bias

Rwenyonyi 1998 (*Continued*)

Bias	Authors' judgement	Support for judgement
Sampling	Unclear risk	Children were selected from schools for study in a quasi-random way
Confounding	High risk	While SES and use of fluoride toothpaste were reported as being similar across groups, there appeared to be a higher intake of tea (and therefore fluoride from water) among the participants in Kasese (0.5 ppm) than Kisoro (2.5 ppm)
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data appear to have been presented for all participants
Selective reporting (reporting bias)	Unclear risk	Outcome of interest was reported mainly in graphic form and was unclear
Other bias	Low risk	Examinations were carried out by a single examiner. Intra-rater reliability was tested (kappa > 0.8)

Rwenyonyi 1999

Methods	**FLUOROSIS STUDY** Country of study: Uganda Geographic location: Kasese (low F); Kisoro (high F) Year of study: 1996-1997 Year of change in fluoridation status: NA Study design: cross sectional
Participants	Inclusion criteria: children aged 10-14 years (born between 1982 and 1987); lifetime residents of study areas; consumed drinking water from same source for first 6 years of life; parental consent Exclusion criteria: absence from the village for more than 1 month per year Other sources of fluoride: fluoride exposure from liquid estimated by daily liquid intake - subjects from high fluoride area had higher intake of water, consumed more boiled water and consumed less tea than subjects from control area, higher consumption of fluoride from Trona in control group Social class: most families were small scale farmers and all appeared to be of similar social class Ethnicity: all children were ethnic Bantu Africans from the Bafumbria and Bakonjo tribes

Rwenyonyi 1999 (*Continued*)

	Residential history: lifelong residents Other confounding factors: vegetarianism (associated with fluorosis); altitude (results presented separately for different altitudes) - no association found between altitude and fluorosis
Interventions	All natural fluoridation Group 1: 2.5 (altitude = 2800 m) Group 2: 2.5 (altitude = 1750 m) Group 3: 0.5 (altitude = 2200 m) Group 4: 0.5 (altitude = 900 m)
Outcomes	Dental fluorosis (TF Index) Age at time of measurement: mean age 12.2 years (SD 1.3)
Funding	Norwegian Universities Committee for Development Research and Education and the Committee for Research and Postgraduate Trianing, University of Bergen
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Unclear risk	Quasi-random stratified sample of all eligible children
Confounding	High risk	SES was broadly similar, however, multivariate analysis revealed that factors that were not accounted for were associated with fluorosis. These included: daily intake of water (amount), altitude, water storage, vegetarianism and infant formula use
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Examiners were blind to fluoride concentrations at the start of the study and tests were carried out on the water after the children's teeth were examined
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data appear to be presented for all participants
Selective reporting (reporting bias)	Low risk	All data appears to have been reported
Other bias	Low risk	No other bias was detected

Saravanan 2008

Methods	**FLUOROSIS STUDY** Country of study: India Geographic location: Tamil Nadu Year of study: not stated Year of change of fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: the coverage of children was confined only to primary schools as each village had a primary school and 99% of the children of primary school age group in the study area were attending schools Exclusion criteria: high school children were not included as only 85% of the children of high school age group (11-16 years) in the study area were attending schools Other sources of fluoride: not stated Ethnicity: not stated Social class: the majority of people in the study setting were of lower socioeconomic class Residential history: lifetime residents Other confounding factors: not stated
Interventions	All natural fluoridation Group 1: < 0.1 ppm Group 2: < 0.1 ppm Group 3: 0.25 ppm Group 4: 0.56 ppm Group 5: 0.66 ppm Group 6: 0.67 ppm
Outcomes	Dental fluorosis (Dean's Index) Age at assessment: 5-10 years
Funding	Not stated
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Low risk	All eligible children were invited to participate
Confounding	High risk	No details were reported on the use of fluoride from other sources
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Around 1.1% of the school children were eventually excluded because of absen-

Saravanan 2008 (*Continued*)

		teeism. It is not clear which fluoride areas they belonged to, however, these participants are unlikely to have been systematically different from those that completed the study
Selective reporting (reporting bias)	Low risk	Outcome of interest reported
Other bias	Unclear risk	High school children were not included as only 85% of the children of high school age group (11-16 years) in the study area were attending schools; examiners were calibrated and intra-and inter-examiner reliability assessed, however, Kappa scores not reported

Scheinin 1964

Methods	**FLUOROSIS STUDY** Country of study: Finland Geographic location: Artjarvi, Askola, Elimaki, Litti, Myrskyla, Parikkala, Taipalsaari, Valkeala, Vehkalahti Year of study: not stated Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: children aged 11 Exclusion criteria: children resident in area for < 6 years; fluoride concentration of drinking water unknown Other sources of fluoride: not stated Social class: not stated Ethnicity: not stated Residential history: residence for < 6 years Other confounding factors: not stated
Interventions	All natural fluoridation Group 1: 0-0.1 ppm Group 2: 0.11-0.39 ppm Group 3: 0.40-0.99 ppm Group 4: 1.0-1.59 ppm Group 5: 1.6-ppm
Outcomes	Dental fluorosis (community fluorosis index); caries data also evaluated within the study but excluded from review due to study design Age at assessment: 11 years
Funding	Not stated

Scheinin 1964 (*Continued*)

Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Sampling	Low risk	All eligible children were invited to participate
Confounding	High risk	Did not account for the use of fluoride from other sources or SES
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The dental examinations were carried out as a blind study, the examiners having no information of the preliminary fluoride determinations"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	High risk	Data not in suitable format for analysis
Other bias	High risk	No mention of examiner calibration

Segreto 1984

Methods	**FLUOROSIS STUDY** Country of study: USA Geographic location: 16 Texas communities Year of study: 1978-1981 Year of change in fluoridation status: Unclear Study design: cross-sectional
Participants	Inclusion criteria: lifetime residents who may have resided at several different addresses in the same community; absence from community for no more than 3 months during any calendar year; grades 2-6, aged 7-12 years and grades 9-12, aged 14-18 years; city water supply as principal source of drinking water throughout lifetime; non-usage of water treatment systems that result in defluoridation of water Exclusion criteria: subjects with staining attributable to medication such as tetracycline Other sources of fluoride: not stated Social class: not stated Ethnicity: subjects were primarily those with Spanish surnames or white Residential history: lifetime residents Other confounding factors: not stated
Interventions	Unclear if natural or artificial fluoridation Group 1: 0.3 ppm Group 2: 0.3 ppm

Segreto 1984 (*Continued*)

	Group 3: 0.4 ppm Group 4: 1.0 ppm Group 5: 1.3 ppm Group 6: 1.3 ppm Group 7: 1.4 ppm Group 8: 2.3 ppm Group 9: 2.3 ppm Group 10: 2.5 ppm Group 11: 2.7 ppm Group 12: 2.7 ppm Group 13: 2.7 ppm Group 14: 2.9 ppm Group 15: 3.1 ppm Group 16: 4.3 ppm
Outcomes	Mottled enamel (Dean's Index) Age at assessment: 7-12 years and 14-18 years
Funding	Not stated
Notes	Data extracted from Segreto 1984 differs from that presented in CRD review

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Low risk	16 study sites that had a central well as main water supply and sufficient school population were selected
Confounding	High risk	Did not account for the use of fluoride from other sources or SES
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	High risk	Data not in suitable format for analysis
Other bias	High risk	No mention of examiner calibration

Sellman 1957

Methods	**FLUOROSIS STUDY** Country of study: Sweden Geographic location: Malmo (low F); Simirshamn, Astorp and Nyvang (High F) Year of study: 1953 Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: children aged 11-14 years Exclusion criteria: children missed due to illness; children under 11½ and over 14½ Other sources of fluoride: all children received yearly systematic treatment by the School Dental Service Social class: socioeconomic distribution of lifetime residents was similar in all study areas, however distribution was different for non-continuous residents compared to continuous residents Ethnicity: not stated Residential history: only results of lifetime residents were presented Other confounding factors: not stated
Interventions	All natural fluoridation Group 1: 1.0 ppm Group 2: 1.0-1.3 ppm Group 3: 1.3 ppm Control: 0.3-0.5 ppm
Outcomes	Outcome: dental fluorosis (Dean's Index) Age at assessment: 12-14 years
Funding	Not stated
Notes	Data extracted from Sellman 1957 differs from that presented in CRD review

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Unclear risk	There was insufficient detail reported to determine how selection took place
Confounding	High risk	All children received yearly systematic treatment by the School Dental Service, however, it is not clear whether the use of other fluoride sources was balanced across groups
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information

Sellman 1957 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Data appear to be presented for all participants
Selective reporting (reporting bias)	Low risk	All expected outcome reported
Other bias	High risk	No mention of examiner calibration and reliability testing

Selwitz 1995

Methods	**FLUOROSIS STUDY** Country of study: USA Geographic location: Kewanee (optimal), Monmouth (2 x optimal), Abingdon, Elmwood (3 x optimal), Bushneell, Ipava, Table Grove (4 x optimal), Illinois Year of study: 1980 Year study ended: 1990 Year of change in fluoridation status: unclear Study design: repeated cross-sectional
Participants	Inclusion criteria: children aged 8-10 years and 14-16 years; written parental consent; lifetime residents of study areas; continuous use of community water supply Exclusion criteria: none stated Other sources of fluoride: not stated Social class: not stated Ethnicity: not stated Residential history: lifetime residents Other confounding factors: not stated
Interventions	Unclear whether all was natural fluoridation, parts of the optimally fluoridated area may have been artificially adjusted Group 1: 4 ppm Group 2: 3 ppm Group 3: 2 ppm Group 4: 1 ppm
Outcomes	Dental fluorosis (% fluorosed surfaces (TSIF); caries data also evaluated within the study but excluded from review due to study design Age at assessment: 8-10 years and 13-15 years
Funding	Not stated
Notes	Data extracted from Selwitz 1995 differs from that presented in CRD review

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Selwitz 1995 (*Continued*)

Sampling	Unclear risk	There was insufficient detail reported to determine how selection took place. Reference was made to a previous study (Leverett 1986) for further information on sampling, however this study also reported insufficient information on sampling
Confounding	High risk	Did not account for the use of fluoride from other sources or SES
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data presented for all participants
Selective reporting (reporting bias)	High risk	Data not in suitable format for analysis
Other bias	Low risk	No other apparent bias

Selwitz 1998

Methods	**FLUOROSIS STUDY** Country of study: USA Geographic location: Kewanee (F); Holdrege and Broken Bow (non-F) Year of study: 1990-1998 Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: lifetime residents of study areas; parental consent Exclusion criteria: none stated Other sources of fluoride: type of toothpaste currently used and used before age 6; use of dietary fluoride supplements; receipt of professionally applied fluoride treatments Social class: not stated Ethnicity: not stated Residential history: lifetime residents Other confounding factors: use of private well-water
Interventions	All natural fluoridation Group 1: 1 ppm Group 2: < 0.3 ppm
Outcomes	Dental fluorosis (TSIF); caries data also evaluated within the study but excluded from review due to study design Age at assessment: 8-10 years and 13-16 years
Funding	Not stated

Selwitz 1998 (*Continued*)

Notes	Data extracted from Selwitz 1998 differs from that presented in CRD review

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Unclear risk	There was insufficient detail reported to determine how selection took place
Confounding	High risk	Did not account for SES, and there was a difference between groups in the use of fluoride supplements
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	High risk	Data not in suitable format for analysis
Other bias	Low risk	No other apparent bias

Shanthi 2014

Methods	**FLUOROSIS STUDY** Country of study: India Geographic location: 3 strata (according to fluoride concentration) Khammam district, Andhra Pradesh Year of study: not stated Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: school children, aged 9-12 years irrespective of sex, race, and socioeconomic status, who were residents of that particular region and using the same source of drinking water; more than 50% of the crown erupted and no fillings on the facial surface of anterior teeth; co-operative parental consent Exclusion criteria: children who obtained their drinking water from more than one source; those with orthodontic brackets; children with severe extrinsic stains on their teeth; children with any communicable or systemic diseases and fractured anterior teeth Other sources of fluoride: not stated Social class: not stated Ethnicity: not stated Residential history: lifetime residents Other confounding factors: the consumption of sugar in the study population was about 61.3% in boys and 38.7% in girls (not specified by group)

Shanthi 2014 (*Continued*)

Interventions	All natural fluoridation Group 1: < 0.7 ppm Group 2: 0.7-1.2 ppm Group 3: 1.3-3.5 ppm
Outcomes	Dental fluorosis (Dean's Index); caries data also evaluated within the study but excluded from review due to study design Age at assessment: 9-12 years
Funding	Stated no funding
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Low risk	Quote: "A stratified random sampling technique was used"
Confounding	Unclear risk	Insufficient information on characteristics of the groups compared
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding not specified
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of children in each strata not specified; unclear whether all those sampled were evaluated
Selective reporting (reporting bias)	High risk	Fluorosis data not presented by strata
Other bias	Low risk	No other apparent bias

Shekar 2012

Methods	**FLUOROSIS STUDY** Country of study: India Geographic location: Nalgonda district Year of study: 2008 Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: continuous residency; availability on the day of examination Exclusion criteria: not stated Other sources of fluoride: information on oral hygiene practices, dietary habits, source of drinking water, and amount of liquid consumed in a day, use of fluoridated tooth

Shekar 2012 (*Continued*)

	paste was collected but not reported Ethnicity: not stated Social class: the majority of people in the study setting were from lower socioeconomic class Residential history: lifetime residents Other confounding factors: not stated
Interventions	All natural fluoridation Group 1: < 0.7 ppm Group 2: 0.7-1.2 ppm Group 3: 1.2-2 ppm Group 4: 2.1-4 ppm Group 5: > 4 ppm
Outcomes	Dental fluorosis (Dean's Index) Age at assessment: 12 and 15 years
Funding	Not stated
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Low risk	Schools were selected for study using simple random sampling. All children within those schools were invited to participate
Confounding	High risk	SES was broadly similar across groups as was the use of fluoride toothpaste, however, no details were reported regarding use of fluoride supplements
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	Low risk	Outcome of interest reported
Other bias	Low risk	No other apparent bias

Skinner 2013

Methods	**FLUOROSIS STUDY** Country of study: Australia Geographic location: New South Wales Year of study: 2010 Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: school students aged 14-15 years under the jurisdiction of the NSW Department of Education and Training, the Catholic Education Commission and Independent Schools Exclusion criteria: not stated Other sources of fluoride: not stated Ethnicity: aboriginal status was coded from parental responses (not reported by fluoridation status) Social class: self-reported family income data were provided by parents or guardians and was used as a measure of SES (not reported by fluoridation status) Residential history: not stated Other confounding factors: not stated
Interventions	Group 1: fluoridated (artificial; ppm not specified) Group 2: non-fluoridated
Outcomes	Dental fluorosis (TF); caries data also evaluated within the study but excluded from review due to study design Age at assessment: 14 and 15 years
Funding	The Centre for Oral Health Strategy NSW
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Low risk	Quote: "random sample"
Confounding	Low risk	Quote: "initial weights were adjusted to ensure the distribution of the sample reflected the regional population distribution of 14-15-year-olds in NSW"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	High risk	Particpation rate low (23%). Did not account for all participants in analysis

Skinner 2013 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Observed enamel fluorosis/defects were recorded for both the central incisors; not all data reported
Other bias	Unclear risk	No other apparent bias

Skotowski 1995

Methods	**FLUOROSIS STUDY** Country of study: USA Geographic location: Iowa Year of study: 1991 Year of change in fluoridation status: NA Study design: case-control study
Participants	Inclusion criteria: children aged 8-17 years; patients attending Iowa College of Dentistry's Paediatric clinic; all permanent incisors and first molars present and erupted; parent who could provide consent and details of fluoride exposure accompanied child Exclusion criteria: children with fixed orthodontic appliances; all permanent incisors and first molars present and erupted Other sources of fluoride: dietary fluoride supplement use; age began brushing with toothpaste; toothpaste usage in 8 years; mouth rinse usage; professional fluoride treatments Social class: not stated Ethnicity: not stated Residential history: not stated Other confounding factors: not stated
Interventions	All natural fluoridation Group 1: 3.1 ppm Group 2: 5.6 ppm
Outcomes	Dental fluorosis (TSIF) Age at assessment: 8-17 years
Funding	Not stated
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	High risk	The study population was a convenience sample of children receiving treatment at the clinic

Skotowski 1995 (*Continued*)

Confounding	High risk	Did not account for SES. When analysed for effect of duration of residence and use of other fluoride sources, the results were found to have been influenced by duration of exposure and toothpaste usage in 8 years, however the results were not adjusted for these factors
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The examiner had no previous knowledge of subjects' dental fluorosis status or fluoride exposures"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	High risk	Fluorosis prevalence was not reported according to fluoridation status or fluoride concentration
Other bias	High risk	The examiner was not calibrated. Quote: "Because of the burden that replicated examination would cause for the children and their parents, formal reliability assessments were not conducted"

Spadaro 1955

Methods	**FLUOROSIS STUDY** Country of study: Italy Geographic location: Barcelona, Pozzo di Gotto, Sicily Year of study: 1954 Year of change in fluoridation status: unclear Study design: cross-sectional
Participants	Inclusion criteria: children attending schools in study areas Exclusion criteria: none stated Other sources of fluoride: not stated Social class: not stated Ethnicity: not stated Residential history: not stated Other confounding factors: not stated
Interventions	Unclear if natural or artificial fluoridation Group 1: 0.4 ppm Group 2: 1.9 ppm

Spadaro 1955 (*Continued*)

Outcomes	Dental fluorosis (index not stated); caries data also evaluated within the study but excluded from review due to study design Age at assessment: 6-11 years
Funding	Not stated
Notes	Data from original CRD review (data unverified)

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Unclear risk	Unable to make a judgement as study was unavailable
Confounding	High risk	Did not account for the use of fluoride from other sources or SES
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unable to make a judgement as study was unavailable
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unable to make a judgement as study was unavailable
Selective reporting (reporting bias)	Unclear risk	Unable to make a judgement as study was unavailable
Other bias	Unclear risk	Unable to make a judgement as study was unavailable

Stephen 2002

Methods	**FLUOROSIS STUDY** Country of study: Scotland Geographic location: Burghead, Kinloss and Findhorn Year of study: not stated Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: not stated Exclusion criteria: not stated Other sources of fluoride: information on the use of fluoridated tooth paste was collected but not reported Ethnicity: not stated Social class: the socioeconomic analyses showed that 17% of F subjects were in the 'high' SES groups I or II, 75% in 'non-manual' group III, and 8% in 'manual' groups IV or V. For non-F children, the corresponding percentages were 23%, 60% and 17%, thus

Stephen 2002 (*Continued*)

	revealing a higher percentage of non-F subjects at either end of the SES scale Residential history: the participants were either lifetime or school-lifetime (i.e. permanently present therein since commencing full-time schooling at approximately 5 years of age) residents Other confounding factors: information about oral hygiene practices, dietary habits, source of drinking water, and amount of liquid consumed in a day
Interventions	All natural fluoridation Group 1: 1-2.4 ppm Group 2: 0.03 ppm
Outcomes	Dental fluorosis (TF Index); caries data also evaluated within the study but excluded from review due to study design Age at assessment: 5-6 years (caries only) and 8-12 years (caries and fluorosis)
Funding	Supported by a Scottish Office Department of Health grant
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Unclear risk	There was insufficient detail reported to determine how selection took place, however it was reported that about one-fifth (21.9%) of the eligible participants were not examined because of non-consent (9.4%) and unavailability for examination (12.6%)
Confounding	Unclear risk	Matched by SES, details on the use of fluoride sources show that fluorosis prevalence was not influenced by the use of other fluoride sources. Similar use of fluoride supplements across groups. The age at which brushing with fluoridated paste began did not appear to affect the prevalence of fluorosis, however information on brushing history was only available for the parents who were able to recall
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants were examined without knowledge of their fluoridation status. Slides were viewed blind and scored randomly under standardised projection conditions by the assessors with a 10% random reviewing for inter and intra-observer agreement calculations

Stephen 2002 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	Low risk	Only lifetime residents between 8 and 12 years were assessed for fluorosis and data for all of them presented
Other bias	Unclear risk	The study involved children between the age of 5-6 years and 8-12 years, but the investigators only conducted fluorosis assessments on 8- to 12-year olds so data have been extracted for only children for whom fluorosis assessment was conducted

Sudhir 2009

Methods	**FLUOROSIS STUDY** Country of study: India Geographic location: Andhra Pradesh Year of study: 2006-2007 Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: school children aged 13-15 years; lifelong residence of the region; use of the same source of drinking water from birth to 10 years of age; having permanent teeth with at least > 50% of the crown erupted and no fillings on facial surface Exclusion criteria: migration from some other place; change of source of drinking water; drinking water from more than 1 source; having orthodontic brackets; having teeth with severe extrinsic stains Other sources of fluoride: information was collected on aids used for oral hygiene maintenance (fluoridated or non-fluoridated); no data on aids used for oral hygiene maintenance reported Ethnicity: not stated Social class: not stated Residential history: lifetime residents Other confounding factors: the questionnaire consisted of information in 2 parts: the first part consisted of information on demographic data, permanent residential address, source of drinking water, duration of use of present source of drinking water, staple food, liquids routinely consumed
Interventions	All natural fluoridation Group 1: < 0.7 ppm Group 2: 0.7-1.2 ppm Group 3: 1.3-4 ppm Group 4: > 4 ppm
Outcomes	Outcome: fluorosis prevalence (TF Index); Age at assessment: 13-15 years

Sudhir 2009 (*Continued*)

Funding	Not stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Low risk	Used a stratified random sampling technique. The entire geographical area of Nalgonda district was divided into 4 strata based on different levels of naturally occurring fluoride in drinking water supply. So in each stratum, or for each level, several villages were involved. Sample size was divided equally among all the 4 strata, and representation from both the sexes was included in the sampling
Confounding	High risk	Data were collected on aids used for oral hygiene maintenance (fluoridated or non-fluoridated) but not reported
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data presented for all participants
Selective reporting (reporting bias)	High risk	Data not in suitable format for analysis
Other bias	Low risk	No other apparent bias

Szpunar 1988

Methods	**FLUOROSIS STUDY** Country of study: USA Geographic location: Hudson, Redford, Richmond (F); Cadillac (non-F), Michigan Year of study: not stated Year of change in fluoridation status: not stated Study design: cross-sectional
Participants	Inclusion criteria: lifetime residents of study areas; children aged 6-12 years Exclusion criteria: none stated Other sources of fluoride: use of fluoride supplements; dental attendance; time interval since last dental visit; age began brushing (parent & child); age at start of F rinsing; feeding method in 1st year of life

Szpunar 1988 (*Continued*)

	Social class: not stated Ethnicity: not stated Residential history: lifetime residents Other confounding factors: not stated
Interventions	Group 1: 1.2 ppm (artificial fluoridation) Group 2: 1.0 ppm (artificial fluoridation) Group 3: 0.8 ppm (artificial fluoridation) Group 4: 0.0 ppm (natural fluoridation)
Outcomes	Dental fluorosis (TSIF); caries data also evaluated in the study but not included in the review due to study design Age at assessment: 6-12 years
Funding	NIH National Research Service Award
Notes	Data extracted from Szpunar 1988 differs from that presented in CRD review

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Unclear risk	Classroom teachers distributed and collected permission slips
Confounding	High risk	Did not appear to account for the use of fluoride from other sources or SES
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data collected for 1103 participants but only lifetime resident data (n = 556) presented
Selective reporting (reporting bias)	Low risk	Relevant fluorosis outcome data
Other bias	Low risk	No other apparent risk of bias

Tabari 2000

Methods	**FLUOROSIS STUDY** Country of study: UK Geographic location: Northumberland and Newcastle upon Tyne Year of study: 1998 Year of change in fluoridation status: 1969 Study design: cross-sectional
Participants	Inclusion criteria: parental consent; lifetime residency Exclusion criteria: not stated Ethnicity: not stated Other sources of fluoride: data on the use of fluoride drops and tablets collected but not presented. Data on toothbrushing habit/frequency presented in detail and appeared to be similar in F and non-F areas Social class: the subjects from Newcastle tended to reside in more underprivileged areas than those in Northumberland. The mean Jarman UPA8 score was 16.3 (SD = 19.1) for subjects in Newcastle and 7.3 (SD = 15.0) for Northumberland (P value < 0.001). However, the authors were reported to have chosen schools to provide children from a spectrum of SES backgrounds Residential history: lifetime residents Other confounding factors: not stated
Interventions	Group 1: 1 ppm (artificial fluoridation) Group 2: 0.1 ppm (natural fluoridation)
Outcomes	Dental fluorosis (TF Index); Age at assessment: 8-9 years
Funding	Not stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Unclear risk	In Newcastle and Northumberland, 14 and 15 schools respectively were chosen. However, there was insufficient information on how the selection was done
Confounding	High risk	There was a significant difference in measure of deprivation between the 2 study areas
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessment was by the use of photographs in order to allow examination of teeth of children without the examiner being aware of which area the child was from

Tabari 2000 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	In the 2 groups, 78% and 79% of the eligible children had complete data. It was not clear whether those whose photographs were unacceptable (examined but not analysed) were systematically different from those who remained in the study
Selective reporting (reporting bias)	Low risk	Outcome of interested reported
Other bias	Low risk	No other apparent bias

Tessier 1987

Methods	**CARIES STUDY** Country of study: Canada (province of Québec) Geographic location: Windsor (F) and Richmond (non-F) Year study started: 1977 Year study ended: 1986 Year of change in fluoridation status: 1978 Study design: CBA	
Participants	Inclusion criteria: All 6- and 7-year-old schoolchildren Exclusion criteria: children living too far from the fluoridated water supply; or drinking fluoridated water 3 years or less Other sources of fluoride: mouthwash and toothpaste; participants underwent similar fluoride rinse programmes Social class: comparable study areas with similar socioeconomic status and lifestyles Ethnicity: not stated Residential history: not stated Other confounding factors: similar access to dental care, oral hygiene and levels of dental plaque	
Interventions	Group 1: 'optimal' level - ppm not stated (artificial fluoridation) Control: 'low' level - ppm not stated (natural fluoridation)	
Outcomes	DMFT; % caries prevalence Age at baseline measure: 6 and 7 years Age at final measure: 6 and 7 years	
Funding	Not stated	
Notes	Translated from French	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Tessier 1987 (*Continued*)

Sampling	Low risk	All children aged 6 and 7 years in both study areas were selected
Confounding	High risk	Participants might have had varied exposures to fluoridated water. No details were reported on the dietary habits of the children
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	High risk	Standard deviation not reported
Other bias	High risk	No mention of examiner calibration and reliability testing

Tsutsui 2000

Methods	**FLUOROSIS STUDY** Country of study: Japan Geographic location: not stated Year of study: 1987 Year of change in fluoridation status: naturally occurring fluoride Study design: cross-sectional
Participants	Inclusion criteria: use of municipal water supply and lifelong residency of study area; difference of $\leq$ 0.2 ppm where home and school were located in different water supply areas Exclusion criteria: failure to meet any of the inclusion criteria; other reasons for exclusion were incomplete questionnaire and periodic application of topical fluoride Other sources of fluoride: children that had received periodic applications of topical fluoride were excluded; no children had used fluoride mouth rinses; use of fluoride-containing toothpaste was not determined as the market share was only 12% and thus not commonly used by children at the time Ethnicity: not stated Social class: not stated Residential history: lifetime residents Other confounding factors: not stated
Interventions	All natural fluoridation Group 1: 0-0.2 ppm Group 2: 0.2-0.4 ppm Group 3: 0.4-0.6 ppm Group 4: 0.6-0.8 ppm

Tsutsui 2000 (*Continued*)

	Group 5: 0.8-1 ppm Group 6: 1-1.4 ppm
Outcomes	Dental fluorosis (Dean's Index); caries data also evaluated within the study but excluded from review due to study design Age at assessment: 10-12 years
Funding	Niigata University
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Low risk	All eligible children were invited to participate
Confounding	High risk	Did not account for SES
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The examiners had no knowledge of the concentration of fluoride in the drinking water where they carried out the examinations
Incomplete outcome data (attrition bias) All outcomes	High risk	Out of the 1967 children that were examined, data for 907 (46.1%) were not presented
Selective reporting (reporting bias)	Low risk	Outcome of interest reported
Other bias	Low risk	No other apparent bias

Venkateswarlu 1952

Methods	**FLUOROSIS STUDY** Country of study: India and Switzerland Geographic location: villages in the Visakhapatnam area (India), and 3 villages in Switzerland Year of study: not stated Year of change in fluoridation study: NA Study design: cross-sectional
Participants	Inclusion criteria: children aged 3-14 years; areas with $\leq$ 2 ppm F in water supplies Exclusion criteria: none stated Other sources of fluoride: not stated Social class: not stated Ethnicity: not stated

Venkateswarlu 1952 (*Continued*)

	Residential history: not stated Other confounding factors: not stated
Interventions	All natural fluoridation Group 1: 0.3 ppm Group 2: 0.5 ppm Group 3: 0.5 ppm Group 4: 0.9 ppm Group 5: 0.9 ppm Group 6: 0.9 ppm Group 7: 0.9 ppm Group 8: 1 ppm Group 9: 1.3 ppm Group 10: 1.4 ppm Group 11: 0.5-0.8 ppm Group 12: 0.4-1.6 ppm
Outcomes	Dental fluorosis (Dean's Index); caries data also evaluated within the study but excluded from review due to study design Age at assessment: 3-14 years
Funding	Not stated
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Unclear risk	Children aged 3-14 years belonging to the study areas were examined; as far as possible, at least 100 children per village. It was not clear how exactly these children were selected
Confounding	High risk	Did not account for the use of fluoride from other sources or SES
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	High risk	12 Indian villages were involved in the study; data from 1 village (Malkapuram) with 102 participants not presented
Selective reporting (reporting bias)	High risk	Data not in suitable format for analysis

Venkateswarlu 1952 (*Continued*)

Other bias	High risk	Calibration of examiners not mentioned

Vignarajah 1993

Methods	**FLUOROSIS STUDY** Country of study: Antigua Geographic location: urban and rural areas in Antigua Year of study: not stated Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: children aged 12-14 years; lifetime residents of study areas Exclusion criteria: restored or fractured tooth surfaces Other sources of fluoride: toothpaste swallowing when younger; consumption of mixed sources of water; fluoride mouth rinses Social class: not stated Ethnicity: not stated Residential history: lifetime residents Other confounding factors: not stated
Interventions	All natural fluoridation Group 1: 0.6-1 ppm Group 2: 0.1-0.3 ppm
Outcomes	Dental fluorosis (TSIF) Age at assessment: 12-14 years
Funding	Not stated
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Low risk	A stratified random technique using random number tables was used to select schools and children. Quote: "All the schools were first listed and then divided into two groups, urban and rural…"
Confounding	High risk	Did not account for SES
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information

Vignarajah 1993 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of participants recruited not stated
Selective reporting (reporting bias)	Low risk	Outcome of interest presented
Other bias	Low risk	No other apparent bias

Vilasrao 2014

Methods	**FLUOROSIS STUDY** Country of study: India Geographic location: 7 districts of the Chhattisgarh State Year of study: 2013-2014 Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: none stated Exclusion criteria: none stated Other sources of fluoride: not stated Ethnicity: not stated Social class: not stated Residential history: not stated Other confounding factors: not stated
Interventions	All natural fluoridation Group 1: 3.8 ppm Group 2: 2.5 ppm Group 3: 2.0 ppm Group 4: 3.0 ppm Group 5: 2.2 ppm Group 6: 2.8 ppm Group 7: 3.3 ppm
Outcomes	Dental fluorosis (assessed using: mottled enamel, chalk white, yellowish brown or brownish black, horizontal streaks over teeth); bowing of legs/spine also evaluated
Funding	Ministry of Health and Family Welfare
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Unclear risk	Quote: "door-to-door survey .... randomly selected"

Vilasrao 2014 (*Continued*)

Confounding	High risk	Did not acount for potential confounding factors
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insuffieicnt information
Selective reporting (reporting bias)	High risk	Number of participants by district not reported
Other bias	Unclear risk	No other apparent bias

Villa 1998

Methods	**FLUOROSIS STUDY** Country of study: Chile Geographic location: Rancagua (non-F), Santiago (low-F), La Serena (medium-F), San Felipe and Iquique (high-F) Year of study: 1996 Year of change in fluoridation status: fluoride was naturally occurring Study design: cross-sectional study
Participants	Inclusion criteria: lifetime residents of study areas; children aged 7,12 and 15 years in selected schools in study areas Exclusion criteria: none stated Other sources of fluoride: not stated Social class: children selected from schools graded according to socioeconomic status to give similar socioeconomic distribution in each study area Ethnicity: not stated Residential history: lifetime residents Other confounding factors: temperature
Interventions	All natural fluoridation Group 1: 0.07 ppm Group 2: 0.21 ppm Group 3: 0.55 ppm Group 4: 0.93 ppm Group 5: 1.10 ppm
Outcomes	Dental fluorosis (Deans Index); caries data also evaluated within the study but excluded from review due to study design Age at assessment: 15 years
Funding	Study was supported by the Chilean Council for Scientific and Technological Research (FONDECYT) through grant no. 1960993

Villa 1998 (*Continued*)

Notes	Data extracted Villa 1998 differs from that presented in CRD review

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Low risk	Selection of schools for each community was made at random from the complete list of private schools and publicly supported elementary schools. All eligible children were invited to participate
Confounding	High risk	Did not account for the use of fluoride from other sources
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	Low risk	Data not in suitable format for analysis
Other bias	High risk	There may have been misclassification bias as fluorosis prevalence was reported without taking 'questionable' fluorosis prevalence into account

Vuhahula 2009

Methods	**FLUOROSIS STUDY** Country of study: Tanzania Geographic location: Arusha, Shinyanga, Manyara, Dodoma, Singida and Tabora Year of study: not stated Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: aged 12-18 years; lifelong residence Exclusion criteria: in order to avoid over-scoring, teeth that were tempered with by grinding or other forms of mutilations were excluded Other sources of fluoride: not stated Ethnicity: not stated Social class: not stated Residential history: mostly lifelong residents Other confounding factors: information on 'magadi' consumption was collected, however, participants seemed to be accessing 'magadi' from different sources making the correlation of fluoride in 'magadi' versus dental fluorosis complicated

Vuhahula 2009 (*Continued*)

Interventions	All natural fluoridation Group 1: 2.2 ppm Group 2: 2.4 ppm Group 3: 2.5 ppm Group 4: 4.2 ppm Group 5: 4.7 ppm Group 6: 5.6 ppm
Outcomes	Dental fluorosis (Dean's Index) Age at assessment: 12-18 years
Funding	Funded by the Japanese International Cooperation Agency (JICA) of Tanzania
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Unclear risk	Regions were randomly chosen and then schools within them. Children were quota sampled from these schools
Confounding	High risk	Did not account for the use of fluoride from other sources or SES
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	High risk	Data not in suitable format for analysis
Other bias	Low risk	No other apparent bias

Wang 1993

Methods	**FLUOROSIS STUDY** Country of study: China Geographic location: Hotan, Kaxgar and Aksu, in south Xinjiang Year of study: 1991 Year of change in fluoridation status: NA Study design: cross-sectional

Wang 1993 (*Continued*)

Participants	Inclusion criteria: children aged from 8-15 years living around the water source Exclusion criteria: not stated Other sources of fluoride: not stated Social class: farmers and herdsmen in south Xinjiang Ethnicity: Minority, mainly Uygur ethnic group Residential history: living in study area for a long time ("since many years ago") Other confounding factors: the combined effects of iodine deficiency and high fluorine; the habit of tea drinking
Interventions	All natural fluoridation Group 1: 1.58 ppm Group 2: 1.85-2.00 ppm Group 3: 0.48 ppm Group 4: 2.55 ppm Group 5: 0.43 ppm Group 6: 0.46 ppm Group 7: 0.43 ppm
Outcomes	Dental fluorosis (index not stated) Age at assessment: 15 years
Funding	Not stated in translation
Notes	Paper translated from Chinese

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Unclear risk	Children aged 8-15 living in the vicinity of the water sources were included. Insufficient sampling information
Confounding	High risk	Did not account for the use of fluoride from other sources, residential history not clearly stated
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data for all participants reported
Selective reporting (reporting bias)	Low risk	Outcome of interest presented

Wang 1993 (*Continued*)

Other bias	Unclear risk	Unable to identify information pertaining to the training/reliability of outcome assessors

Wang 1999

Methods	**FLUOROSIS STUDY** Country of study: China Geographic location: Xindiliang Village (high F), Shiligetu Village (lower F) Year of study: 1999 Year of change in fluoridation status: NA Study design: cross sectional study
Participants	Inclusion criteria: not stated Exclusion criteria: not stated Other sources of fluoride: not stated Social class: not stated Ethnicity: not stated Residential history: not stated Other confounding factors: not stated
Interventions	All natural fluoridation Group 1: 1.3 ppm Group 2: 2-4 ppm
Outcomes	Dental fluorosis and skeletal fluorosis (3 grade classification for both) Age at assessment: all ages
Funding	Japan International Cooperation Agency
Notes	Removal of fluoride from the water in these areas was attempted in the 1980s but failed to be applied continuously

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Unclear risk	Households in the villages of study were arbitrarily chosen so that 25% were included in the study
Confounding	High risk	Did not account for the use of fluoride from other sources
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information

Wang 1999 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	Low risk	Outcome of interest presented
Other bias	High risk	There was no mention of examiner calibration

Wang 2012

Methods	**FLUOROSIS STUDY** Country of study: China Geographic location: not stated Year of study: 2008-2009 Year of change in fluoridation status: NA Study design: cross sectional
Participants	Inclusion criteria: not stated Exclusion criteria: not stated Other sources of fluoride: not stated Social class: not stated Ethnicity: not stated Residential history: in the mild, moderate and severe endemic areas, the authors made reference to native-born residents, but it is not clear what proportion of them constituted the entire population Other confounding factors: not stated
Interventions	All natural fluoridation Group 1: 1.3 ppm Group 2: 2-4 ppm
Outcomes	Dental fluorosis (Dean's Index); skeletal fluorosis Age at assessment: 8-12 years for dental fluorosis and > 16 years for skeletal fluorosis
Funding	Supported by the Chinese government for Endemic Disease Control in 2008-2009
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Low risk	Villages were selected at random, and in the selected villages, all eligible children were invited to participate

Wang 2012 (*Continued*)

Confounding	High risk	Did not account for the use of fluoride from other sources or SES
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	Unclear risk	Outcome of interest reported
Other bias	High risk	No mention of examiner calibration

Warnakulasuriya 1992

Methods	**FLUOROSIS STUDY** Country of study: Sri Lanka Geographic location: 4 geographic areas at same altitude and temperature from 4 districts in Sri Lanka (Galewala, Wariyapola, Kekirawa and Rambukkana) Year of study: 1986 Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: lifetime residents of study areas; children aged 14 years Exclusion criteria: children who lived more than 15 miles from school; children absent on day of examination Other sources of fluoride: fluoride containing toothpaste or other fluoride therapies had not been used by or on these children during time of development of primary dentition; tea consumption high Social class: wide ranges of socioeconomic differences not expected Ethnicity: not stated Residential history: lifetime residents Other confounding factors: not stated
Interventions	All natural fluoridation Group 1: <0.39 ppm Group 2: 0.4-0.59 ppm Group 3: 0.6-0.79 ppm Group 4: 0.8-0.99 ppm Group 5: >1.0 ppm
Outcomes	Fluorosis (Dean's Index); caries data evaluated in study but not included in review due to study design Age at assessment: 14 years
Funding	National Water Supply, Sri Lanka

Warnakulasuriya 1992 (*Continued*)

Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Sampling	Low risk	All eligible children in each school were invited to participate
Confounding	Unclear risk	The study authors considered that fluoride supplements or paste were not widely used among the study population and that SES was broadly similar across groups, however no supporting information was provided
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	Low risk	Outcome of interest presented
Other bias	Low risk	No other apparent bias

Warren 2001

Methods	**FLUOROSIS STUDY** Country of study: USA Geographic location: Iowa Year of study: 1997-2000 Year of change in fluoridation status: unclear Study design: cross-sectional data from within cohort study
Participants	Inclusion criteria: not stated Exclusion criteria: not stated. Other sources of fluoride: fluoride dentifrice use = 159/637 (25%); dietary fluoride supplement use = 131/637 (20.6%). There was no difference in fluorosis prevalence between those who used other sources of fluoride and those who did not Ethnicity: not stated Social class: not stated Residential history: mostly lifelong residents Other confounding factors: not stated
Interventions	Group 1: < 0.7 ppm (natural fluoridation) Group 2: 0.7-1.2 ppm (artificial fluoridation) Group 3: > 1.2 ppm (natural fluoridation)

Warren 2001 (*Continued*)

Outcomes	Fluorosis prevalence (TSIF) Age at assessment: 4.5-5 years
Funding	Supported by NIH grants 2ROl-DE09551, 2P30-10126, and CRC-RROOO5
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Unclear risk	Children included in the present study were part of the Iowa Fluoride Study cohort, which had been followed prospectively since birth. Full details were not reported
Confounding	High risk	Did not account for SES
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Outcome data available for 559 out of the 637 (87.8%) participants due to lack of information on water fluoride concentration
Selective reporting (reporting bias)	Low risk	Outcome of interest reported
Other bias	Low risk	No other apparent bias

Wenzel 1982

Methods	**FLUOROSIS STUDY** Country of study: Denmark Geographic location: Naestved (F); Greve (F); Ry (non-F) Year of study: not stated Year of change in fluoridation status: not stated Study design: cross-sectional
Participants	Inclusion criteria: lifetime residents of study areas; girls aged 12-15 years Exclusion criteria: children with orthodontic appliances; history of additional fluoride use Other sources of fluoride: only children without fluoride use were included; no attempt was made to distinguish between users and non-users of fluoridated dentifrice Social class: not stated Ethnicity: not stated Residential history: lifetime residents

Wenzel 1982 (*Continued*)

	Other confounding factors: not stated
Interventions	Group 1: < 0.2 ppm Group 2: 1.0 ppm Group 3: 2.4 ppm
Outcomes	Fluorosis (TF Index); skeletal maturity Age at assessment: 12-14 years
Funding	Sponsored by Colgate Palmolive, Denmark
Notes	Data extracted Wenzel 1982 differs from that presented in CRD review

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Unclear risk	Insufficient detail reported to determine how selection took place
Confounding	High risk	Did not account for SES
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data for all participants presented
Selective reporting (reporting bias)	Low risk	Outcome of interest presented
Other bias	High risk	No information on examiner calibration

Whelton 2004

Methods	**FLUOROSIS STUDY** Country of study: Republic of Ireland (RoI) Geographic location: not stated Year of study: 2001/2002 Year of change in fluoridation status: 1964 Study design: cross-sectional
Participants	Inclusion criteria: children in Junior Infants, Second Class, Sixth Class, and Junior Certificate Exclusion criteria: not stated. Other sources of fluoride: participants in the fluoridated group may have had additional exposure to fluoride tablets and fluoride mouth rinses Ethnicity: not stated

Whelton 2004 (*Continued*)

	Social class: possesion of a medical card was used in this study as a surrogate for disadvantage; RoI medical card vs no medical card = 24% vs 75% (full F = 25.2% vs 74.4%; non-F = 20.3% vs 79.4%); figures do not add up to 100%, however, authors reported that figures included children for whom medical card details were missing Residential history: fluoridated group subjects' home water supply had to have been fluoridated continuously since birth, and the non-fluoridated group subjects' home water supply had never to have been fluoridated. No further details reported Other confounding factors: not stated
Interventions	Group 1: 0.8-1 ppm (artificial fluoridation) Group 2: 'non-fluoridated'
Outcomes	Fluorosis prevalence (Dean's Index); caries data (dmft/DMFT) evaluated in study but not included in review due to study design Age at assessment: 5, 8, 12 and 15 years
Funding	Funded by the Department of Health and Children and the Health Boards in Ireland
Notes	The authors carried out and reported power calculation for the primary outcome (DMFT) but not for the fluorosis outcome

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Low risk	National survey using a cluster sampling technique with schools as the clustering unit and children in Junior Infants, Second Class, Sixth Class and Junior Certificate were selected
Confounding	High risk	SES accounted for in caries analysis; did not account for the use of fluoride from other sources or the dietary habits of the children
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Fluoride codes ascribed after examinations; unlikely to be systematic bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Outcome data presented as a percentage; unclear if accounted for all participants
Selective reporting (reporting bias)	Unclear risk	Fluorosis outcomes presented as percentages; unclear if accounted for all participants
Other bias	Low risk	No other apparent bias

Whelton 2006

Methods	FLUOROSIS STUDY Country of study: Republic of Ireland (RoI) and Northern Ireland (NI) Geographic location: not stated Year of study: 2001/2002 Year of change in fluoridation status:1964 Study design: cross-sectional
Participants	Inclusion criteria: Junior Infants, Second Class, Sixth Class and Junior Certificate in RoI and Primary 1, Primary 4, Year 1 and Year 4 in NI Exclusion criteria: not stated Other sources of fluoride: participants in the fluoridated group may have had additional exposure to fluoride tablets and fluoride mouth rinses Ethnicity: not stated Social class: possession of a medical card (MC) was used in this study as a surrogate for disadvantage in RoI, whilst receipt of low-income benefits (LIB) was used as a surrogate for disadvantage in NI. RoI full-F: MC vs no MC = 25.2% vs 74.4%; NI non-F LIB vs no LIB = 37.3% vs 61.3%; figures do not add up to 100%, however, authors reported that figures included children for whom MC/LIB details were missing Residential history: fluoridated group subjects' home water supply had to have been fluoridated continuously since birth and the non-fluoridation group subjects' home water supply had never to have been fluoridated. No further details reported Other confounding factors: not stated
Interventions	Group 1 (RoI): 0.8-1 ppm (artificial fluoridation) Group 2 (NI): 'non-fluoridated' - ppm not reported
Outcomes	Fluorosis prevalence (Dean's Index); caries data (dmft/DMFT) evaluated in study but not included in review due to study design Age at assessment: 5, 8, 12 and 15 years
Funding	Funded by the Department of Health and Children and the Health Boards in Ireland
Notes	The authors carried out and reported power calculation for the primary outcome (DMFT), but not for the fluorosis outcome

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Low risk	National survey using a cluster sampling technique with schools as the clustering unit and children in Junior Infants, Second Class, Sixth Class and Junior Certificate in RoI and Primary 1, Primary 4, Year 1 and Year 4 in NI
Confounding	High risk	SES accounted for in caries analysis; did not account for the use of fluoride from other sources or the dietary habits of the children;

Whelton 2006 (*Continued*)

		used different measures for assessing SES
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Fluoride codes ascribed after examinations; unlikely to be systematic bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Outcome data presented as a percentage; unclear if accounted for all participants
Selective reporting (reporting bias)	Unclear risk	Fluorosis outcomes presented as percentages; unclear if accounted for all participants
Other bias	Low risk	No other apparent bias

Wondwossen 2004

Methods	**FLUOROSIS STUDY** Country of study: Ethiopia Geographic location: not stated Year of study: 1997 Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: not stated Exclusion criteria: not stated Other sources of fluoride: not stated Ethnicity: not stated Social class: the villages were of approximately the same size and socioeconomic standards and were selected purposively for the study Residential history: fluoridated group subjects' home water supply had to have been fluoridated continuously since birth and the non-fluoridation group subjects' home water supply had to have never been fluoridated. No further details reported Other confounding factors: not stated
Interventions	All natural fluoridation Group 1: 0.3-2.2 ppm Group 2: 10-14 ppm
Outcomes	Fluorosis prevalence (TF Index); caries data evaluated in study but not included in review due to study design Age at assessment: 12-15 years
Funding	Supported by the Norwegian State Educational Loan Fund, NUFU Project 61/96 and the Committee for Research and Postgraduate Training, Faculty of Dentistry, University of Bergen, Norway and the Faculty of Medicine (Fluoride Project), University of Addis Ababa, Ethiopia

Wondwossen 2004 (*Continued*)

Notes		

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Unclear risk	Participants were chosen from a census, however, insufficient detail was reported on individual selection
Confounding	High risk	Did not account for the use of fluoride from other sources
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Intra-oral examination was conducted at the health centers of the areas by two examiners" Blinding not undertaken
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data for all participants presented
Selective reporting (reporting bias)	Low risk	Outcome of interest reported
Other bias	Low risk	No other apparent bias

Zheng 1986

Methods	**FLUOROSIS STUDY** Country of study: China Geographic location: Guangzhou and Fangcun (F); Fushan and Zhaoqing (non-F) Year of study: not stated Year of change in fluoridation status: not stated Study design: cross-sectional
Participants	Inclusion criteria: students who were 7-, 9-, 12-, 15-, and 17-years old Exclusion criteria: not stated Other sources of fluoride: not stated, but time point of 1975 in Guangdong province of China would be mean that exposure to fluoridated toothpaste could be assumed Social class: not stated Ethnicity: chinese Residential history: lifetime residents Other confounding factors: not stated
Interventions	Group 1: 0.6-1.2 ppm (artificial fluoridation) Group 2: 0.4-1.2 ppm (artificial fluoridation) Group 3: 0.2 ppm (natural fluoridation) Group 4: 0.2 ppm (natural fluoridation)

Zheng 1986 (*Continued*)

Outcomes	Outcome: fluorosis prevalence (Dean's Index) Age at assessment: 12-17 years
Funding	Not stated
Notes	Data extracted from Zheng 1986 differs from that presented in CRD review Translated from Chinese

Risk of bias

Bias	Authors' judgement	Support for judgement
Sampling	Unclear risk	Insufficent information to make a judgement
Confounding	High risk	Did not appear to account for SES
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Fluorosis data for all participants reported
Selective reporting (reporting bias)	High risk	The authors seem to have collected caries data at baseline, but reported only the follow-up data
Other bias	Unclear risk	Unable to identify information pertaining to the training/reliability of outcome assessors

Zimmermann 1954

Methods	**FLUOROSIS STUDY** Country of study: USA Geographic location: Aurora, Illinois (F); Montgomery and Prince Georges counties, Maryland (non-F) Year of study: 1953 Year of change in fluoridation status: NA Study design: cross-sectional
Participants	Inclusion criteria: lifetime residents of study areas; white children aged 12-14 years Exclusion criteria: children who had left study areas for periods of time other than for holidays Other sources of fluoride: not stated Social class: not stated Ethnicity: white children only

Zimmermann 1954 (*Continued*)

	Residential history: continuous residents Other confounding factors: not stated
Interventions	All natural fluoridation Group 1: 0.2 ppm Group 2: 1.2 ppm
Outcomes	Fluorosis (Deans Index); caries data evaluated in study but not included in review due to study design Age at assessment: 12-14 years
Funding	Not stated
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sampling	Low risk	All eligible children were invited to participate
Confounding	Low risk	Did not account for the use of fluoride from other sources or SES
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data for all participants presented
Selective reporting (reporting bias)	Low risk	Outcome of interest presented
Other bias	High risk	There was no mention of examiner calibration

Abbreviations
CBA: controlled before-and-after study
CFI: Community Fluorosis Index
CRD: Centre for Reviews and Dissemination
DDE: developmental defects of tooth enamel
dmft: decayed, missing and filled deciduous teeth
DMFT: decayed, missing and filled permanent teeth
F: fluoride/fluoridated
ITS: interrupted time series study
LIB: low-income benefits
NA: not applicable

NI: Northern Ireland
non-F: non-fluoridated
NUFU: Norwegian Programme for Development, Research and Education
RoI: Republic of Ireland
SD: standard deviation
SE: standard error
SES: socioeconomic status
TF Index: Thylstrup-Fejerskov Index
TSIF: Tooth Surface Index of Fluorosis
UPA8: under privileged area 8

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Acharya 2003	Evaluated caries in a single time point cross-sectional study
Agarwal 2014	Evaluated fluorosis levels in single area
Ajayi 2008	Evaluated caries in a single time point cross-sectional study
Akosu 2008	No direct comparison of different fluoride concentrations
Aldosari 2004	Evaluated caries in a single time point cross-sectional study
Aleksejuniene 2004	Naturally high fluoride area was compared to a low fluoride area, however, there was no change in concentration at the 2 time points reported
Alimskii 2000	Unable to locate study
Antunes 2004	Evaluated caries in a single time point cross-sectional study
Anuradha 2002	Evaluation of periodontal disease in relation to fluoride concentration
Archila 2003	Evaluated caries in a single time point cross-sectional study
ARCPOH 2008	Evaluated caries in a single time point cross-sectional study
Armfield 2004	Evaluated caries in a single time point cross-sectional study
Armfield 2005	Evaluated caries in a single time point cross-sectional study
Armfield 2007	Evaluated caries in a single time point cross-sectional study
Armfield 2010	Evaluated caries in a single time point cross-sectional study
Arora 2010	Evaluated caries in a single time point cross-sectional study

(*Continued*)

Attwood 1988	Inappropriate design for studying cessation of water fluoridation
Bailie 2009	Evaluated caries in a single time point cross-sectional study
Baldani 2002	Evaluated caries in a single time point cross-sectional study
Baldani 2004	Evaluated caries in a single time point cross-sectional study
Bihari 2008	No fluorosis data
Binbin 2005	Evaluated caries in a single time point cross-sectional study
Blagojevic 2004	Evaluated caries in a single time point cross-sectional study
Blayney 1960	Data measured at different time points for fluoridated and non-fluoridated areas
Bo 2003	Evaluation of skeletal/dental fluorosis
Bottenberg 2004	No distinct comparison between areas
Bradnock 1984	Evaluated caries in a single time point cross-sectional study
Buchel 2011	Comparison of water fluoridation and salt fluoridation
Burt 2000	Assesses effect of break in water fluoridation in single area
Buscariolo 2006	Evaluated fluorosis levels in single area
Buzalaf 2004	Assessed effect of break in water fluoridation in single area
Campain 2010	Evaluated cost savings from community water fluoridation in Australia
Carmichael 1980	Evaluated caries in a single time point cross-sectional study
Carmichael 1984	Evaluated caries in a single time point cross-sectional study
Carmichael 1989	Evaluated caries in a single time point cross-sectional study
Carvalho 2007	Assessed fluorosis prior to commencing water fluoridation
Catani 2007	Compared areas with 'one with homogenous fluoride concentration and oscillating concentration'
Chen 2009	No direct comparison of different fluoride concentrations
Chen 2012	No distinct comparison between areas

(*Continued*)

Cheng 2000	Compared different ethnic populations receiving similar water fluoride levels
Ciketic 2010	Cost-effectiveness study
Clark 2006	Assessed fluorosis after cessation of water fluoridation
de Lourdes Azpeitia-Valadez 2009	Compared areas but no mention of differing fluoride concentrations
Dini 2000	Comparison of areas with different duration of water fluoridation
Do 2007	Evaluated risk-benefit balance of several fluoride exposures
Dobaradaran 2008	No concurrent control
Evans 1995	Evaluated caries in a single time point cross-sectional study
Evans 2009	Evaluated the effect of a water fluoridation programme in the single area
Faye 2008	Evaluated fluorosis in single city following change in water supply
Gillcrist 2001	Evaluated caries in a single time point cross-sectional study
Gushi 2005	Evaluated caries in a single time point cross-sectional study
Han 2011	Evaluated caries in a single time point cross-sectional study
Hobbs 1994	Inappropriate design for studying cessation of water fluoridation
Hoffmann 2004	Evaluated dental caries between children attending public and private schools in fluoridated city
Hopcraft 2003	Cross-sectional study evaluating caries experience; no comparison of fluoride concentrations and no fluorosis data
Hussain 2013	Focused on evaluation of groundwater concentrations
Ito 2007	Thesis - unable to access
Jones 1997	Evaluated caries in a single time point cross-sectional study
Jones 2000a	Evaluated caries in a single time point cross-sectional study
Jones 2000b	Evaluated caries in a single time point cross-sectional study
Kalsbeek 1993	Inappropriate design for studying cessation of water fluoridation
Khan 2004	Evaluated dose-response relationship between the prevalence of dental caries; did not compare fluorosis levels by fluoride concentration

(*Continued*)

Kirkeskov 2010	Evaluated caries in a single time point cross-sectional study
Kozlowski 2002	Abstract only
Kukleva 2007	Evaluated fluorosis levels in single area (with high use of bottled water)
Kumar 2001	Evaluated caries in a single time point cross-sectional study
Kunzel 2000	Data measured at different time points for fluoridated and non-fluoridated areas
Kunzel 2000a	No concurrent control group
Lee 2004	Evaluated caries in a single time point cross-sectional study
Liu 2006	Evaluated fluorosis with regard to improvement in water supply
Liu 2009	Evaluated fluorosis with regard to improvement in water supply
Murray 1984	Evaluated caries in a single time point cross-sectional study
Murray 1991	Evaluated caries in a single time point cross-sectional study
Nayak 2009	No comparison made
Ncube 2005	Evaluated fluorosis with regard to improvement in water supply
Nirgude 2010	Evaluated fluorosis levels in single area
Niu 2012	Evaluated fluorosis with regard to improvement in water supply
Pandey 2002	Evaluated fluorosis with regard to improvement in water supply
Pandey 2005	Evaluated fluorosis with regard to improvement in water supply
Pandey 2010	Evaluated fluorosis with regard to improvement in water supply
Peres 2006	Evaluated caries in a single time point cross-sectional study
Provart 1995	Evaluated caries in a single time point cross-sectional study
Rihs 2008	Evaluated caries in a single time point cross-sectional study
Riley 1999	Evaluated caries in a single time point cross-sectional study
Ruan 2004	Evaluated fluorosis with regard to improvement in water supply

(*Continued*)

Rugg-Gun 1977	Evaluated caries in a single time point cross-sectional study
Sagheri 2007	Evaluated caries in a single time point cross-sectional study
Sales-Peres 2002	Evaluated caries in a single time point cross-sectional study
Saliba 2008	Evaluated caries in a single time point cross-sectional study
Sampaio 2000	Evaluated caries in a single time point cross-sectional study
Seppa 1998	Inappropriate design for studying cessation of water fluoridation
Shitumbanuma 2007	Evaluated fluorosis levels associated with drinking water from hot springs
Slade 2013	Evaluated caries in a cross-sectional study; no fluorosis data
Sohu 2007	No clear comparison of fluorosis across different fluoride concentrations
Spencer 2008	Mixed fluoridation status of study areas
Sun 2007	Evaluated fluorosis with regard to improvement in water supply
Tagliaferro 2004	Evaluated caries in a single time point cross-sectional study
Tiano 2009	Evaluated caries in a single time point cross-sectional study
Tickle 2003	Evaluated caries in a single time point cross-sectional study
Vuhahula 2008	Evaluated fluorosis with regard to improvement in water supply
Wang 2005	Evaluated fluorosis with regard to improvement in water supply
Wang 2008	Evaluated fluorosis with regard to improvement in water supply
Wei 2010	Evaluated fluorosis with regard to improvement in water supply
Wong 2006	No concurrent control
Wong 2014	Evaluated fluorosis but no concurrent comparison groups
Wongdem 2001	Focus on measurement of fluoride concentration
Wragg 1999	Inappropriate design for studying cessation of water fluoridation
Wu 2006	Evaluated fluorosis with regard to improvement in water supply

(*Continued*)

Wu 2008	Evaluated fluorosis with regard to improvement in water supply
Zhu 2009	Evaluated fluorosis with regard to improvement in water supply
Zietsman 2003	Thesis - unable to access
Zimmermann 2002	Evaluated caries in a single time point cross-sectional study

Characteristics of studies awaiting assessment *[ordered by study ID]*

Wang 2014

Methods	
Participants	
Interventions	
Outcomes	
Notes	We are in the process of attempting to access this study report

Characteristics of ongoing studies *[ordered by study ID]*

Pretty (ongoing)

Trial name or title	An evaluation of a water fluoridation scheme in Cumbria
Methods	Cohort The study design aims to assess the topical effects of water fluoridation by recruiting groups of children and following them over 6 years
Participants	All children in their first school year in 2013
Interventions	Re-introduction of fluoridated water compared with non-fluoridated area
Outcomes	Caries Age at assessment: 5, 7 and 11 years
Starting date	2013
Contact information	michaela.goodwin@manchester.ac.uk
Notes	

DATA AND ANALYSES

Comparison 1. Initiation of water fluoridation compared with low/non-fluoridated water

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in decayed, missing or filled deciduous teeth (dmft)	9	22134	Mean Difference (IV, Random, 95% CI)	1.81 [1.31, 2.31]
1.1 Studies conducted in 1975 or earlier	7	17039	Mean Difference (IV, Random, 95% CI)	1.82 [1.53, 2.11]
1.2 Studies conducted after 1975	2	5095	Mean Difference (IV, Random, 95% CI)	1.56 [-0.67, 3.80]
2 Change in decayed, missing or filled permanent teeth (DMFT)	10	39382	Mean Difference (IV, Random, 95% CI)	1.16 [0.72, 1.61]
2.1 Studies conducted in 1975 or earlier	7	30499	Mean Difference (IV, Random, 95% CI)	1.41 [0.84, 1.98]
2.2 Studies conducted after 1975	3	8883	Mean Difference (IV, Random, 95% CI)	0.64 [-0.27, 1.55]
3 Change in proportion of caries free children (deciduous teeth)	10	19983	Mean Difference (IV, Random, 95% CI)	-0.15 [-0.19, -0.11]
3.1 Studies conducted in 1975 or earlier	7	11902	Mean Difference (IV, Random, 95% CI)	-0.17 [-0.19, -0.15]
3.2 Studies conducted after 1975	3	8081	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.24, -0.01]
4 Change in proportion of caries free children (permanent teeth)	8	26769	Mean Difference (IV, Random, 95% CI)	-0.14 [-0.23, -0.05]
4.1 Studies conducted in 1975 or earlier	6	17459	Mean Difference (IV, Random, 95% CI)	-0.13 [-0.24, -0.03]
4.2 Studies conducted after 1975	2	9310	Mean Difference (IV, Random, 95% CI)	-0.17 [-0.43, 0.10]

Analysis 1.1. Comparison 1 Initiation of water fluoridation compared with low/non-fluoridated water, Outcome 1 Change in decayed, missing or filled deciduous teeth (dmft).

Review: Water fluoridation for the prevention of dental caries

Comparison: 1 Initiation of water fluoridation compared with low/non-fluoridated water

Outcome: 1 Change in decayed, missing or filled deciduous teeth (dmft)

Study or subgroup	Water fluoridation N	Mean(SD)	Low/non-fluoridated water N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Studies conducted in 1975 or earlier							
Arnold 1956	4931	2.75 (4.99)	1437	1.18 (5.8)		12.6 %	1.57 [1.24, 1.90]
Adriasola 1959	263	2.5 (7.04)	157	0.3 (6.72)		6.8 %	2.20 [0.85, 3.55]
DHSS Wales 1969	1910	2.87 (4.68)	959	0.64 (5.54)		12.3 %	2.23 [1.82, 2.64]
DHSS England 1969	654	3.09 (4.3)	557	1.04 (4.22)		11.9 %	2.05 [1.57, 2.53]
Beal 1971	182	2.46 (5.8)	223	-0.12 (6.27)		7.7 %	2.58 [1.40, 3.76]
Kunzel 1997	3726	1.65 (4.05)	1312	0.13 (5)		12.8 %	1.52 [1.22, 1.82]
Beal 1981	361	2.02 (4.18)	367	0.57 (4.6)		11.0 %	1.45 [0.81, 2.09]
Subtotal (95% CI)	**12027**		**5012**			**75.1 %**	**1.82 [1.53, 2.11]**
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 13.37$, df = 6 (P = 0.04); $I^2 = 55\%$							
Test for overall effect: Z = 12.38 (P < 0.00001)							
2 Studies conducted after 1975							
Guo 1984 (1)	2018	0.23 (5.39)	1696	-2.47 (5.35)		12.6 %	2.70 [2.35, 3.05]
Blinkhorn (unpublished)	813	1.3 (3.56)	568	0.88 (3.74)		12.4 %	0.42 [0.03, 0.81]
Subtotal (95% CI)	**2831**		**2264**			**24.9 %**	**1.56 [-0.67, 3.80]**
Heterogeneity: $Tau^2 = 2.56$; $Chi^2 = 72.72$, df = 1 (P<0.00001); $I^2 = 99\%$							
Test for overall effect: Z = 1.37 (P = 0.17)							
Total (95% CI)	**14858**		**7276**			**100.0 %**	**1.81 [1.31, 2.31]**
Heterogeneity: $Tau^2 = 0.49$; $Chi^2 = 86.18$, df = 8 (P<0.00001); $I^2 = 91\%$							
Test for overall effect: Z = 7.05 (P < 0.00001)							
Test for subgroup differences: $Chi^2 = 0.05$, df = 1 (P = 0.82), $I^2 = 0.0\%$							

(1) Guo 1984 commenced in 1971; possibility of fluoridated toothpaste being introduced during study period

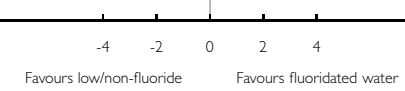
Analysis 1.2. Comparison 1 Initiation of water fluoridation compared with low/non-fluoridated water, Outcome 2 Change in decayed, missing or filled permanent teeth (DMFT).

Review: Water fluoridation for the prevention of dental caries

Comparison: 1 Initiation of water fluoridation compared with low/non-fluoridated water

Outcome: 2 Change in decayed, missing or filled permanent teeth (DMFT)

Study or subgroup	Water fluoridation N	Mean(SD)	Low/non-fluoridated water N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Studies conducted in 1975 or earlier							
Arnold 1956	10647	0.9 (3.2)	2824	0.15 (3.51)		11.2 %	0.75 [0.61, 0.89]
Brown 1965	1097	3.03 (3.31)	1032	0.52 (4.18)		10.7 %	2.51 [2.19, 2.83]
DHSS Wales 1969	1833	0.66 (3.72)	1390	-0.73 (4.95)		10.8 %	1.39 [1.08, 1.70]
DHSS England 1969	939	1.62 (3.92)	725	0.65 (4.39)		10.4 %	0.97 [0.56, 1.38]
Kunzel 1997	6690	1.02 (2.94)	2421	-0.85 (3.26)		11.2 %	1.87 [1.72, 2.02]
Beal 1981	369	0.82 (2.5)	367	0.2 (2.644)		10.5 %	0.62 [0.25, 0.99]
Tessier 1987	76	5.12 (6.16)	89	2.83 (6.18)		3.7 %	2.29 [0.40, 4.18]
Subtotal (95% CI)	**21651**		**8848**			**68.6 %**	**1.41 [0.84, 1.98]**
Heterogeneity: $Tau^2 = 0.51$; $Chi^2 = 184.34$, df = 6 (P<0.00001); I^2 =97%							
Test for overall effect: Z = 4.87 (P < 0.00001)							
2 Studies conducted after 1975							
Hardwick 1982 (1)	144	-3.76 (2.86)	199	-4.85 (3.39)		9.1 %	1.09 [0.43, 1.75]
Guo 1984 (2)	3190	-0.11 (1.69)	4194	-1.14 (2.59)		11.3 %	1.03 [0.93, 1.13]
Blinkhorn (unpublished)	710	0.14 (1.44)	446	0.28 (1.92)		11.1 %	-0.14 [-0.35, 0.07]
Subtotal (95% CI)	**4044**		**4839**			**31.4 %**	**0.64 [-0.27, 1.55]**
Heterogeneity: $Tau^2 = 0.61$; $Chi^2 = 100.70$, df = 2 (P<0.00001); I^2 =98%							
Test for overall effect: Z = 1.37 (P = 0.17)							
Total (95% CI)	**25695**		**13687**			**100.0 %**	**1.16 [0.72, 1.61]**
Heterogeneity: $Tau^2 = 0.46$; $Chi^2 = 351.88$, df = 9 (P<0.00001); I^2 =97%							
Test for overall effect: Z = 5.11 (P < 0.00001)							
Test for subgroup differences: $Chi^2 = 1.96$, df = 1 (P = 0.16), I^2 =49%							



(1) Hardwick 1982 commenced in 1974; possibility of fluoridated toothpaste being introduced during study period

(2) Guo 1984 commenced in 1971; possibility of fluoridated toothpaste being introduced during study period

Analysis 1.3. Comparison 1 Initiation of water fluoridation compared with low/non-fluoridated water, Outcome 3 Change in proportion of caries free children (deciduous teeth).

Review: Water fluoridation for the prevention of dental caries

Comparison: 1 Initiation of water fluoridation compared with low/non-fluoridated water

Outcome: 3 Change in proportion of caries free children (deciduous teeth)

Study or subgroup	Water fluoridation		Low/non-fluoridated water		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
1 Studies conducted in 1975 or earlier							
Ast 1951	246	-0.27 (0.64)	292	-0.05 (0.61)		7.2 %	-0.22 [-0.33, -0.11]
Adriasola 1959	633	-0.16 (1.155)	356	-0.04 (0.425)		7.6 %	-0.12 [-0.22, -0.02]
DHSS Wales 1969	1910	-0.22 (0.669)	959	-0.03 (0.474)		12.0 %	-0.19 [-0.23, -0.15]
DHSS England 1969	654	-0.3 (0.652)	557	-0.14 (0.481)		10.3 %	-0.16 [-0.22, -0.10]
Beal 1971	306	-0.23 (0.63)	223	-0.08 (0.533)		7.7 %	-0.15 [-0.25, -0.05]
Kunzel 1997	3726	-0.2 (0.311)	1312	-0.03 (0.369)		13.1 %	-0.17 [-0.19, -0.15]
Beal 1981	361	-0.17 (0.581)	367	-0.06 (0.517)		9.1 %	-0.11 [-0.19, -0.03]
Subtotal (95% CI)	**7836**		**4066**			**67.1 %**	**-0.17 [-0.19, -0.15]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 5.06$, df = 6 (P = 0.54); $I^2 = 0.0\%$							
Test for overall effect: Z = 18.89 (P < 0.00001)							
2 Studies conducted after 1975							
Guo 1984 (1)	2068	-0.02 (0.464)	1696	0.05 (0.42)		12.8 %	-0.07 [-0.10, -0.04]
Gray 2001	2493	-0.16 (0.509)	443	0.09 (0.644)		10.4 %	-0.25 [-0.31, -0.19]
Blinkhorn (unpublished)	813	-0.24 (0.656)	568	-0.19 (0.689)		9.7 %	-0.05 [-0.12, 0.02]
Subtotal (95% CI)	**5374**		**2707**			**32.9 %**	**-0.12 [-0.24, -0.01]**
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 27.58$, df = 2 (P<0.00001); $I^2 = 93\%$							
Test for overall effect: Z = 2.10 (P = 0.036)							
Total (95% CI)	**13210**		**6773**			**100.0 %**	**-0.15 [-0.19, -0.11]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 56.44$, df = 9 (P<0.00001); $I^2 = 84\%$							
Test for overall effect: Z = 6.95 (P < 0.00001)							
Test for subgroup differences: $Chi^2 = 0.62$, df = 1 (P = 0.43), $I^2 = 0.0\%$							

(1) Guo 1984 commenced in 1971; possibility of fluoridated toothpaste being introduced during study period

Analysis 1.4. Comparison 1 Initiation of water fluoridation compared with low/non-fluoridated water, Outcome 4 Change in proportion of caries free children (permanent teeth).

Review: Water fluoridation for the prevention of dental caries

Comparison: 1 Initiation of water fluoridation compared with low/non-fluoridated water

Outcome: 4 Change in proportion of caries free children (permanent teeth)

Study or subgroup	Water fluoridation N	Mean(SD)	Low/non-fluoridated water N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Studies conducted in 1975 or earlier							
Adriasola 1959	356	0 (0.192)	204	-0.03 (0.219)		12.7 %	0.03 [-0.01, 0.07]
Brown 1965	1097	-0.28 (0.507)	1032	-0.02 (0.328)		12.7 %	-0.26 [-0.30, -0.22]
DHSS Wales 1969	1833	-0.08 (0.655)	1390	0.05 (0.38)		12.7 %	-0.13 [-0.17, -0.09]
DHSS England 1969	939	-0.16 (0.469)	761	-0.07 (0.422)		12.6 %	-0.09 [-0.13, -0.05]
Kunzel 1997	6690	-0.22 (0.417)	2421	0.06 (0.502)		12.9 %	-0.28 [-0.30, -0.26]
Beal 1981	369	-0.11 (0.686)	367	-0.05 (0.489)		11.6 %	-0.06 [-0.15, 0.03]
Subtotal (95% CI)	**11284**		**6175**			**75.3 %**	**-0.13 [-0.24, -0.03]**
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 258.15$, df = 5 (P<0.00001); I^2 =98%							
Test for overall effect: Z = 2.43 (P = 0.015)							
2 Studies conducted after 1975							
Guo 1984 (1)	3657	0.06 (0.617)	4497	0.36 (0.684)		12.8 %	-0.30 [-0.33, -0.27]
Blinkhorn (unpublished)	710	-0.08 (0.639)	446	-0.05 (0.676)		11.8 %	-0.03 [-0.11, 0.05]
Subtotal (95% CI)	**4367**		**4943**			**24.7 %**	**-0.17 [-0.43, 0.10]**
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 40.32$, df = 1 (P<0.00001); I^2 =98%							
Test for overall effect: Z = 1.24 (P = 0.21)							
Total (95% CI)	**15651**		**11118**			**100.0 %**	**-0.14 [-0.23, -0.05]**
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 332.63$, df = 7 (P<0.00001); I^2 =98%							
Test for overall effect: Z = 3.10 (P = 0.0020)							
Test for subgroup differences: $Chi^2 = 0.06$, df = 1 (P = 0.81), I^2 =0.0%							

(1) Guo 1984 commenced in 1971; possibility of fluoridated toothpaste being introduced during study period

ADDITIONAL TABLES

Table 1. dmft data and underlying calculations

Study ID	Age	Fluoridated area						Non/low fluoridated area					
		Baseline (before/at initiation)			Follow-up			Baseline			Follow-up		
		MEAN	SD	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	N
ADRI-A-SOLA 1959	5	8.9	5.03	186	6.4	4.18	340	8.1	4.77	174	7.8	4.67	140
	5	**Mean (SD) change in dmft: 2.5 (7.04)**						**Mean (SD) change in dmft: 0.3 (6.72)**					
ARNO 1956[a]	4	4.19	3.30	323	2.13	2.26	168	5.05	3.66	20	4.46	3.42	63
	5	5.37	3.79	1633	2.27	2.34	853	6.82	4.33	402	5.25	3.74	351
	6	6.43	4.19	1789	2.98	2.73	750	7.17	4.46	462	5.67	3.91	294
	7	6.29	4.14	1806	4.03	3.23	423	6.66	4.28	408	5.77	3.95	223
	8	5.78	3.95	1647	4.12	3.27	470	6.06	4.06	376	5.32	3.77	275
	4-8	**Mean (SD) change in dmft: 2.75 (4.99)**						**Mean (SD) change in dmft: 1.18 (5.8)**					
BEAL 1971	5	4.91	4.86	182	2.45	3.24	182	4.97	4.12	217	5.09	4.84	229
	5	**Mean (SD) change in dmft: 2.46 (5.8)**						**Mean (SD) change in dmft: -0.12 (6.27)**					
BEAL 1981	5	4.29	3.50	196	1.8	2.48	170	4.28	3.58	205	3.49	3.62	180
	8	5	2.89	189	3.42	2.84	167	5.36	3.06	163	4.97	3.00	186
	5/8	**Mean (SD) change in dmft: 2.02 (4.18)**						**Mean (SD) change in dmft: 0.57 (4.6)**					
BLINK 2015	5-7	2.02	3.13	781	0.72	1.63	844	2.09	2.91	523	1.21	2.27	612
	5-7	**Mean (SD) change in dmft: 1.3 (3.56)**						**Mean (SD) change in dmft: 0.88 (3.74)**					
DHSS 1969 (Eng) [a]	3	2.7	2.58	43	0.6	1.11	133	1.4	1.79	44	1.2	1.64	144
	4	3.6	3.03	66	1.3	1.71	131	2.6	2.53	47	1.8	2.06	162
	5	5.4	3.80	148	1.6	1.92	111	5	3.64	110	2.8	2.63	119
	6	5.7	3.92	182	2.5	2.47	130	5.4	3.80	127	4.1	3.26	107

Table 1. dmft data and underlying calculations (*Continued*)

	7	6.4	4.18	192	2.7	2.58	172	6	4.03	121	4.3	3.35	133
	3-7	**Mean (SD) change in dmft: 3.09 (4.3)**						**Mean (SD) change in dmft: 1.04 (4.22)**					
DHSS 1969 (Wales) *a,b*	3	3.9	3.17	310	1.4	1.79	171	4	3.21	146	3.3	2.89	105
	4	5.54	3.86	413	2.6	2.53	267	5.8	3.96	210	4.8	3.56	122
	5	5.5	3.84	556	2.9	2.69	284	5.5	3.84	256	4.8	3.56	138
	6	6.3	4.15	603	3.1	2.79	310	6.2	4.11	331	5.9	4.00	133
	7	6.85	4.35	640	3.65	3.05	266	7.3	4.50	346	6.8	4.33	130
	3-7	**Mean (SD) change in dmft: 2.87 (4.68)**						**Mean (SD) change in dmft: 0.64 (5.54)**					
GUO 1984	3	3	3.4	202	2.6	3.3	79	1.3	3.2	205	3.7	3.9	128
	4	4.6	4	354	4.5	4.7	164	5.6	4.6	246	7.1	4.6	164
	5	6.5	4.4	589	5.5	4.3	345	6.4	4.2	218	8.5	4.6	387
	6	6.7	4.4	695	6.2	4.8	297	5.8	4.2	309	9	4.3	354
	7	5.5	3.7	399	5.6	3.7	240	5.4	3.7	335	7.9	3.6	352
	8	4.2	3	392	4.4	2.9	279	3.5	2.7	343	6	3.1	350
	3-8	**Mean (SD) change in dmft: 0.23 (5.39)**						**Mean (SD) change in dmft: -2.47 (5.35)**					
KUNZEL 1992 *a*	5	2.4	2.415006	688	1.4	1.7857954	1306	3.3	2.88647503	172	2.9	2.68499127	597
	8	4.9	3.6017188	2438	2.8	2.6327431	3020	4.9	3.6017188	777	4.9	3.60171881	1078
	5-8	**Mean (SD) change in dmft: 2.1 (5.01)**						**Mean (SD) change in dmft: 0.13 (5.0)**					

Note: Only data up to the age of 8 years included for the deciduous dentition
a. Imputed standard deviation
b. 2 fluoridated areas combined

Table 2. DMFT data and underlying calculations

Study ID	Age	FLuoridated area						Non/low fluoridated area					

Table 2. DMFT data and underlying calculations (*Continued*)

		Baseline (before/at initiation)			Follow-up			Baseline			Follow-up		
		MEAN	SD	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	N
ARNO 1956[a]	6	0.78	1.29	1789	0.26	0.70	750	0.81	1.31	462	0.8	1.31	294
	7	1.89	2.11	1806	0.84	1.34	423	1.99	2.17	408	1.88	2.11	223
	8	2.95	2.71	1647	1.58	1.91	470	2.81	2.64	376	2.63	2.54	275
	9	3.9	3.17	1639	2.04	2.21	582	3.81	3.13	357	3.52	2.99	277
	10	4.92	3.61	1626	2.93	2.70	141	4.91	3.61	359	4.32	3.36	62
	11	6.41	4.19	1556	3.67	3.06	151	6.32	4.15	293	5.34	3.78	139
	12	8.07	4.76	1685	5.89	3.99	176	8.66	4.95	328	7.71	4.64	48
	13	9.73	5.29	1668	6.6	4.26	497	9.98	5.36	377	9.36	5.18	225
	14	10.95	5.65	1690	8.21	4.81	128	12	5.95	369	11.36	5.77	59
	15	12.48	6.08	1511	8.91	5.03	53	12.86	6.18	292	12.38	6.05	21
	16	13.5	6.35	1107	11.06	5.68	198	14.07	6.50	248	13.16	6.26	155
	6-16	**Mean (SD) change in DMFT: 0.90 (3.20)**						**Mean (SD) change in DMFT: 0.15 (3.51)**					
BEAL 1981	8	1.48	1.51	189	0.65	1.16	167	1.55	1.40	163	1.34	1.50	186
	12	3.53	3.32	192	2.74	2.33	189	4.28	2.47	188	4.11	2.95	197
	8/12	**Mean (SD) change in DMFT: 0.82 (2.50)**						**Mean (SD) change in DMFT: 0.20 (2.64)**					
BLINK 2015[a]		0.59	1.10	777	0.45	0.95	642	0.99	1.47	436	0.72	1.23	455
		Mean (SD) change in DMFT: 0.14 (1.44)						**Mean (SD) change in DMFT: 0.28 (1.92)**					
BROW 1960	9-11	4.07	2.20	595	1.52	1.80	502	4.21	2.63	571	3.68	2.35	521
	12-14	7.68	3.90	593	3.23	2.92	503	7.94	4.41	486	7.46	4.40	485
	9-14	**Mean (SD) change in DMFT: 3.03 (3.31)**						**Mean (SD) change in DMFT: 0.52 (4.18)**					
DHSS 1969	8	2.4	2.42	199	1.08	1.54	95	2.4	2.42	148	1.85	2.09	79

Table 2. DMFT data and underlying calculations (*Continued*)

(Eng) *a*													
	9	3.1	2.79	227	1.5	1.86	135	2.9	2.68	166	2.4	2.42	95
	10	3.6	3.03	134	2	2.18	115	3.8	3.12	160	3.1	2.79	80
	11	4.6	3.48	145	3	2.74	200	4.7	3.52	126	3.9	3.17	122
	12	5.6	3.88	111	3.52	2.99	134	6.1	4.07	51	4.99	3.64	99
	13	7.1	4.43	91	4.9	3.60	132	6.6	4.26	52	6.1	4.07	127
	14	8.4	4.87	70	5.77	3.95	90	7.9	4.71	36	6.74	4.31	108
	8-14	**Mean (SD) change in DMFT: 1.62 (3.92)**						**Mean (SD) change in DMFT: 0.65 (4.39)**					
DHSS 1969 (Wales) *a,b*	8	2.00	2.18	607	1.31	1.72	283	1.95	2.15	351	2.16	2.28	125
	9	2.65	2.55	553	1.98	2.17	260	2.6	2.53	325	2.9	2.68	134
	10	3.35	2.91	502	2.59	2.52	241	3.2	2.84	308	3.6	3.03	133
	11	3.83	3.14	278	2.99	2.73	126	3.3	2.89	270	4.1	3.26	42
	12	4.65	3.50	186	4.38	3.38	108	3.95	3.19	265	6.16	4.09	108
	13	6	4.03	178	5.9	4.00	93	5.2	3.72	274	7.6	4.61	105
	14	6.95	4.38	158	6.73	4.30	93	5.6	3.88	243	7.64	4.62	96
	8-14	**Mean (SD) change in DMFT: 0.66 (3.72)**						**Mean (SD) change in DMFT: -0.73 (4.95)**					
GUO 1984	6	0.2	0.6	695	0.2	0.5	297	0.1	0.4	309	0.5	0.9	354
	7	0.4	0.8	399	0.4	0.9	240	0.3	0.7	335	1.2	1.4	352
	8	0.5	1	392	0.5	1	279	0.4	0.8	343	1.6	1.5	350
	9	0.7	1.1	388	0.8	1.4	275	0.7	1.1	310	2.2	2	352
	10	0.7	1.3	346	1.1	1.5	310	0.8	1.5	323	2.4	2	436
	11	0.8	1.5	330	1.6	1.9	307	0.9	1.4	451	3	2.7	365
	12	1.1	1.7	468	1.7	2.4	208	0.9	1.5	841	3.4	3	493
	13	1.4	2	469	2.1	2.9	232	1.2	1.6	801	3.8	3.3	504
	14	1.2	1.8	322	2.6	2.9	221	1	1.5	795	4.4	3.8	490

Table 2. DMFT data and underlying calculations (*Continued*)

	15	1.7	2.5	164	2.2	2.3	38	1.2	1.7	121	4.2	4	63
	6-15	**Mean (SD) change in DMFT: -0.11 (1.69)**						**Mean (SD) change in DMFT: -1.14 (2.59)**					
HARDWICK 1982	**12**	**Mean (SD) increment in DMFT: -3.76 (2.86)**						**Mean (SD) increment in DMFT: -4.85 (3.39)**					
KUNZEL 1997 *c,d*	6	0.3	0.7		0.2			0.5	0.8		0.4	0.89	
	7	0.7	1.1		0.3			0.9	1.2		1	1.48	
	8	1.3	1.4	2419	0.5	1.00	3016	1.3	1.4	777	1.8	2.06	1076
	9	1.9	1.5		0.9			1.8	1.6		2.4	2.42	
	10	2.4	1.8		1.2			2.4	1.8		3.2	2.84	
	11	3	2		1.6			2.8	1.8		3.9	3.17	
	12	3.7	2.3	1626	2	2.18	2426	3.5	2.1	563	4.8	3.56	925
	13	4.3	2.7		2.6			4.1	2.6		5.5	3.84	
	14	5.3	3.1		3.4			4.7	2.5		6.5	4.22	
	15	5.8	3.5	1995	4	3.22	1897	5.2	3.1	744	7.4	4.54	756
	8/12/15	**Mean (SD) change in DMFT: 1.02 (2.94)**						**Mean (SD) change in DMFT: -0.85 (3.26)**					
LOH 1996		1.6	1.8		2			1.9			3.1		
		4.4			2.1			3.7			4.5		
	Insufficient data to include in further analysis												
TESSII 1987 *a*	6-7	8.28		56	3.16		96	8.23		85	5.4		93
	6-7	**Mean (SD) change in DMFT: 5.12 (6.16)**						**Mean (SD) change in DMFT: 2.83 (6.18)**					

a. Imputed standard deviation
b. 2 fluoridated areas combined
c. Imputed standard deviation for follow-up data only
d. N values only available for ages 8, 12 and 15 years

Table 3. Number of caries-free children: deciduous teeth

Study ID	Age	Fluoridated area				Non/low fluoridated area			
		Baseline (before/at initiation)		Follow-up		Baseline		Follow-up	
		n	N	n	N	n	N	n	N
Adriasola 1959[a]	3	26	151	82	216	9	77	26	135
	4	12	156	55	216	11	76	11	110
	5	4	186	45	340	7	174	14	140
	8	21	493	11	458	17	223	2	226
Ast 1951	5	63	274	108	217	73	259	107	324
Beal 1971[b]	5	62	297	138	314	35	217	55	229
Beal 1981	5	41	196	78	170	43	205	54	180
	8	18	189	31	167	12	163	18	186
Blinkhorn 2015	5-7	397	781	632	844	254	523	412	612
DHSS 1969 (Eng)	3	16	43	96	133	27	44	97	144
	4	23	66	84	131	16	47	89	162
	5	12	148	51	111	15	110	42	119
	6	16	182	47	130	13	127	18	107
	7	13	192	55	172	7	121	24	133
DHSS 1969 (Wales)	3	89	310	100	171	39	146	21	105
	4	78	413	114	267	32	210	27	122
	5	56	556	90	284	18	256	19	138
	6	29	603	78	310	20	331	15	133
	7	17	640	53	266	14	346	5	130
Gray 2001[b]	5	1465	2462	1903	2524	345	466	273	419
Guo 1984	3	67	202	31	79	54	205	39	128

Table 3. Number of caries-free children: deciduous teeth (*Continued*)

	4	74	354	39	164	32	246	14	164
	5	61	589	47	345	18	218	19	387
	6	53	695	56	397	27	309	12	354
	7	41	399	21	240	29	335	11	352
	8	53	392	24	279	50	343	16	350
	8	278	392	204	279	273	343	104	350
Kunzel 1997	5	231	688	682	1306	39	172	192	597
	8	117	2438	746	3020	40	777	61	1078

Note: Only data up to the age of 8 years included for the deciduous dentition
a. Baseline data not available for ages 6 and 7 years
b. Data from all fluoridated areas combined

Table 4. Number of caries-free children: permanent teeth

Study ID	Age	Fluoridated area				Non/low fluoridated area			
		Baseline (before/at initiation)		Follow-up		Baseline		Follow-up	
		n	N	n	N	n	N	n	N
ADRIA-SOLA 1959[a]	8	21	493	11	458	17	223	2	226
	12	7	292	8	419	3	197	9	211
BEAL 1981	8	77	189	115	167	56	163	82	186
	12	51	192	41	189	13	188	14	197
BLINKHO 2015	10 to 12	525	777	486	642	272	436	307	455
BROWN 1960[b]	9 to 11	34	595	220	502	35	571	42	521
	12 to 14	7	593	94	503	3	486	11	485

Table 4. Number of caries-free children: permanent teeth (*Continued*)

DHSS 1969 (Eng)	8	40	199	50	95	33	148	29	79
	9	25	227	57	135	20	166	20	95
	10	13	134	36	115	14	160	10	80
	11	12	145	12	200	3	126	12	122
	12	3	111	20	134	0	51	4	99
	13	3	91	9	132	2	52	8	127
	14	0	70	4	90	2	36	9	180
DHSS 1969 (Wales)	8	143	607	112	283	88	351	26	125
	9	73	553	78	260	49	325	15	134
	10	63	502	44	241	25	308	8	133
	11	30	278	15	126	35	270	0	42
	12	15	186	10	108	27	265	2	108
	13	7	178	0	93	14	274	1	105
	14	8	158	3	93	15	243	1	96
Guo 1984	5	575	589	338	345	214	218	358	387
	6	616	695	266	297	284	309	249	354
	7	305	399	189	240	272	335	162	352
	8	278	392	204	279	273	343	104	350
	9	242	388	167	275	195	310	98	352
	10	215	346	161	310	199	323	84	436
	11	213	330	133	307	245	451	65	365
	12	240	468	90	208	475	841	91	493
	13	227	469	88	232	434	801	77	504
	14	161	322	69	221	455	795	73	490
	15	78	164	11	38	66	121	11	63

Table 4. Number of caries-free children: permanent teeth (*Continued*)

Kunzel 1997	8	1021	2419	2147	3016	334	777	333	1076
	12	120	1626	801	2426	42	563	50	925
	15	118	1995	249	1897	27	744	18	756

a. Baseline data not available for ages 11 and 15 years
b. Data for 16-17-year olds presented but no N

Table 5. Harms: other

Study ID	Outcome	Age	Fluoride level	Assigned F level	Number of subjects	Proportion with outcome
Chen 1993	Skeletal fluorosis	16 to 65	5.5	5.5	28	82.1
			3.1	3.1	114	71.1
			0.4	0.4	50	46
			3.1	3.1	50	86
Wang 2012[a]	Skeletal fluorosis	≥16	2.2	2.2	406,298	10.8
			0.5	0.5	188,400	4.8
Wenzel 1982[b]	Skeletal maturity	12 to 14	2.4	2.4	122	0.59 (0.1)[c]
			< 0.2	0.1	113	0.59 (0.09)[c]
Alarcon-Herrera	Bone fracture	6 to 12	< 1.5	0.75	97	5.2
			1.51-4.99	3.25	112	8.9
			5-8.49	6.75	38	2.6
			8.5-11.99	10.25	27	11.1
			12-16	14	59	8.5
		13 to 60	< 1.5	0.75	192	3.1
			1.51-4.99	3.25	330	7.9
			5-8.49	6.75	146	8.9
			8.5-11.99	10.25	138	7.2
			12-16	14	96	6.3

Table 5. Harms: other (*Continued*)

Jolly 1971[b]	Skeletal fluorosis	Not stated	0.7	0.7	Not stated	3.6
			1.4	1.4	Not stated	2.4
			2.4	2.4	Not stated	17
			2.4	2.4	Not stated	23
			2.5	2.5	Not stated	33
			3	3	Not stated	19.6
			3	3	Not stated	42.2
			3.3	3.3	Not stated	10
			3.3	3.3	Not stated	45
			3.6	3.6	Not stated	33.1
			4.3	4.3	Not stated	19.4
			5	5	Not stated	60
			5.1	5.1	Not stated	44.5
			5.5	5.5	Not stated	31.3
			7	7	Not stated	47.4
			8.5	8.5	Not stated	58.9
			9.4	9.4	Not stated	70.1

a. Participants were diagnosed on the basis of diagnostic criteria for endemic skeletal fluorosis (WS 192-2008)
b. Participants were examined radiologically
c. Reported outcome was mean (standard error) skeletal maturity

Table 6. Disparities in caries across social class

Study ID	Age	Group	Measure	Social class	Baseline				Final			
					F level	N	% caries free	dmft (SD)	F level	N	% caries free	dmft (SD)

Table 6. Disparities in caries across social class (*Continued*)

Beal 1971[a]	5	Balsall Heath	De-scrip-tive	Poor area	Low	115	9	5.16 (0. 44)	1	132	48	1.94 (0. 22)
		North-field		Indus-trial area	Low	182	29	4.91 (0. 36)	1	182	41	2.45 (0. 24)
		Dudley		Indus-trial area	< 0.1	217	16	4.97 (0. 28)	< 0.1	229	24	5.09 (0. 32)
Gray 2000[b]	5	South east Stafford-shire	Jarman score	-23.09	Low	3435	66	1.21 (0. 59)	1	3120	75	0.64 (1. 46)
		Sandwell		18.1	Low	3950	51	1.93 (2. 88)	1	3598	69	0.83 (1. 68)
		Walsall		1.67	Low	3120	54	1.85 (2. 31)	1	363	67	0.94 (1. 77)
		Dudley		-13.68	Low	3657	58	1.6 (2. 54)	1	3474	73	0.78 (1. 75)
		North Birm-ingham		21.57	Low	1965	72	0.88 (1. 97)	1	1904	74	0.71 (1. 65)
		North Stafford-shire		-3.59	Low	464	47	2.24 (3. 04)	Low	1947	59	1.49 (2. 46)
		Here-ford-shire		-13.01	Low	406	57	1.61 (2. 55)	Low	305	50	1.79 (2. 68)
		Shrop-shire		-12.34	Low	366	61	1.29 (2. 22)	Low	311	60	1.33 (2. 33)
		Kidder-minster		-13.13	Low	904	58	1.74 (2. 81)	Low	1053	61	1.4 (2. 52)
Hold-croft 1999[b]	Not stated	North Birm-ingham	Jarman score	-7.85	Not stated	Not stated		2.18	High	Not stated		0.68
		Sandwell		15.03	Not stated	Not stated		2.55	High	Not stated		1.13

Table 6. Disparities in caries across social class (*Continued*)

		North Stafford-shire		-4.07	Not stated	Not stated		2.24	Not stated	Not stated		1.48
		Shrop-shire		-11.73	Not stated	Not stated		1.76	Not stated	Not stated		1.29
		Here-ford-shire		-11.97	Not stated	Not stated		2.56	Not stated	Not stated		1.53

a. Caries data reported as deft (SE)
b. Caries data reported as dmft (SD)

Table 7. WHO region-specific weighted DMFT among 12-year olds

WHO regions	**DMFT**
	2011
Africa	1.19
Americas	2.35
Eastern Mediteranean	1.63
Europe	1.95
South East Asia	1.87
Western Pacific	1.39
GLOBAL	**1.67**

http://www.mah.se/CAPP/Country-Oral-Health-Profiles/According-to-Alphabetical/Global-DMFT-for-12-year-olds-2011/

APPENDICES

Appendix 1. Databases searched in the original systematic review (McDonagh 2000)

- MEDLINE
- EMBASE
- NTIS (National Technical Information Service)
- Biosis
- Current Contents Search (Science Citation Index and Social Science Citation Index)
- Healthstar (Health Service Technology, Administration and Research)
- HSRProj
- TOXLINE
- Chemical Abstracts
- OldMEDLINE
- CAB Health
- FSTA (Food Science and Technology Abstracts)
- JICST- E Plus (Japanese Science and Technology)
- Pascal
- EI Compendex (Engineering Index)
- Enviroline
- PAIS (Public Affairs Information Services)
- SIGLE (System for Information on Grey Literature in Europe)
- Conference Papers Index
- Water Resources Abstracts
- Agricola (Agricultural Online Access)
- Waternet
- AMED (Allied and Complementary Medicine Database)
- Psyclit
- LILACS (Latin American and Caribbean Health Sciences Literature)

Appendix 2. The Cochrane Oral Health Group Trials Register search strategy

#1 ((fluorid* or flurid* or fluorin* or flurin*))
#2 water*
#3 (#1 and #2)

Appendix 3. The Cochrane Central Register of Controlled Trials (CENTRAL) search strategy

#1 MeSH descriptor Fluoridation this term only
#2 MeSH descriptor Fluorides explode all trees
#3 MeSH descriptor Fluorine this term only
#4 (fluorid* in All Text or fluorin* in All Text or flurin* in All Text or flurid* in All Text)
#5 (#1 or #2 or #3 or #4)
#6 MeSH descriptor Dietary supplements this term only
#7 MeSH descriptor Water supply this term only
#8 water* in All Text
#9 (#6 or #7 or #8)
#10 MeSH descriptor Tooth demineralization explode all trees
#11 (caries in All Text or carious in All Text)
#12 (teeth in All Text and (cavit* in All Text or caries in All Text or carious in All Text or decay* in All Text or lesion* in All Text or deminerali* in All Text or reminerali* in All Text))
#13 (tooth in All Text and (cavit* in All Text or caries in All Text or carious in All Text or decay* in All Text or lesion* in All Text or deminerali* in All Text or reminerali* in All Text))

#14 (dental in All Text and (cavit* in All Text or caries in All Text or carious in All Text or decay* in All Text or lesion* in All Text or deminerali* in All Text or reminerali* in All Text))
#15 (enamel in All Text and (cavit* in All Text or caries in All Text or carious in All Text or decay* in All Text or lesion* in All Text or deminerali* in All Text or reminerali* in All Text))
#16 (dentin in All Text and (cavit* in All Text or caries in All Text or carious in All Text or decay* in All Text or lesion* in All Text or deminerali* in All Text or reminerali* in All Text))
#17 (root* in All Text and (cavit* in All Text or caries in All Text or carious in All Text or decay* in All Text or lesion* in All Text or deminerali* in All Text or reminerali* in All Text))
#18 MeSH descriptor Dental plaque this term only
#19 ((teeth in All Text or tooth in All Text or dental in All Text or enamel in All Text or dentin in All Text) and plaque in All Text)
#20 MeSH descriptor Dental health surveys explode all trees
#21 ("DMF Index" in All Text or "Dental Plaque Index" in All Text)
#22 (#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #21) #23 (#5 and #9 and #22)

Appendix 4. MEDLINE (OVID) search strategy

1. Fluoridation/
2. exp Fluorides/
3. Fluorine/
4. (fluorid$ or fluorin$ or flurin$ or flurid$).mp.
5. or/1-4
6. Dietary supplements/
7. Water supply/
8. water$.mp.
9. or/6-8
10. exp TOOTH DEMINERALIZATION/
11. (caries or carious).mp.
12. (teeth adj5 (cavit$ or caries$ or carious or decay$ or lesion$ or deminerali$ or reminerali$)).mp.
13. (tooth adj5 (cavit$ or caries$ or carious or decay$ or lesion$ or deminerali$ or reminerali$)).mp.
14. (dental adj5 (cavit$ or caries$ or carious or decay$ or lesion$ or deminerali$ or reminerali$)).mp.
15. (enamel adj5 (cavit$ or caries$ or carious or decay$ or lesion$ or deminerali$ or reminerali$)).mp.
16. (dentin$ adj5 (cavit$ or caries$ or carious or decay$ or lesion$ or deminerali$ or reminerali$)).mp.
17. (root$ adj5 (cavit$ or caries$ or carious or decay$ or lesion$ or deminerali$ or reminerali$)).mp.
18. Dental plaque/
19. ((teeth or tooth or dental or enamel or dentin) and plaque).mp.
20. exp DENTAL HEALTH SURVEYS/
21. ("DMF Index" or "Dental Plaque Index").mp.
22. or/10-21
23. case reports.pt.
24. Comment/
25. Letter/
26. Editorial/
27. or/23-26
28. exp animals/ not humans.sh.
29. 5 and 9 and 22
30. 29 not (28 or 27)

Appendix 5. EMBASE (OVID) search strategy

1. Fluoridation/
2. exp Fluoride/
3. Fluorine/
4. (fluorid$ or fluorin$ or flurin$ or flurid$).ti,ab.
5. or/1-4
6. Diet supplementation/
7. Water supply/
8. water$.ti,ab.
9. or/6-8
10. exp Dental caries/
11. (caries or carious).ti,ab.
12. (teeth adj5 (cavit$ or caries$ or carious or decay$ or lesion$ or deminerali$ or remineral i$)).ti,ab.
13. (tooth adj5 (cavit$ or caries$ or carious or decay$ or lesion$ or deminerali$ or remineral i$)).ti,ab.
14. (dental adj5 (cavit$ or caries$ or carious or decay$ or lesion$ or deminerali$ or remineral i$)).ti,ab.
15. (enamel adj5 (cavit$ or caries$ or carious or decay$ or lesion$ or deminerali$ or remineral i$)).ti,ab.
16. (dentin$ adj5 (cavit$ or caries$ or carious or decay$ or lesion$ or deminerali$ or remineral i$)).ti,ab.
17. (root$ adj5 (cavit$ or caries$ or carious or decay$ or lesion$ or deminerali$ or remineral i$)).ti,ab
18. Tooth plaque/
19. ((teeth or tooth or dental or enamel or dentin) and plaque).ti,ab.
20. ("DMF Index" or "Dental Plaque Index" or "dental health survey*").ti,ab.
21. or/10-20
22. 9 and 21
23. (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
24. 22 not 23

Appendix 6. Proquest search strategy

ab(fluorid*) AND ab(water*) AND ab(caries OR carious OR dental OR tooth OR teeth OR plaque)

Appendix 7. Web of Science Conference Proceedings search strategy

#1 TS=(fluorid* or fluorin* or flurin* or flurid*)
#2 TS=water*
#3 TS=(caries or carious)
#4 TS=(teeth and (cavit* or caries* or carious or decay* or lesion* or deminerali* or remineral i*))
#5 TS=(tooth and (cavit* or caries* or carious or decay* or lesion* or deminerali* or remineral i*))
#6 TS=(dental and (cavit* or caries* or carious or decay* or lesion* or deminerali* or remineral i*))
#7 TS=(enamel and (cavit* or caries* or carious or decay* or lesion* or deminerali* or remineral i*))
#8 TS=(dentin* and (cavit* or caries* or carious or decay* or lesion* or deminerali* or remineral i*))
#9 TS=(root* and (cavit* or caries* or carious or decay* or lesion* or deminerali* or remineral i*))
#10 TS=((teeth or tooth or dental or enamel or dentin) and plaque)
#11 TS=("DMF Index" or "Dental Plaque Index")
#12 #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
#13 #1 and #2 and #12

Appendix 8. ZETOC Conference Proceedings search strategy

fluoride AND water AND caries
fluoridation AND water AND caries
fluoride AND water AND carious
fluoridation AND water AND carious
fluoride AND water AND dental
fluoridation AND water AND dental
fluoride AND water AND tooth
fluoridation AND water AND tooth
fluoride AND water AND teeth
fluoridation AND water AND teeth

Appendix 9. US National Institutes of Health Trials Registry and WHO International Clinical Trials Registry Platform search strategy

fluoride and water and caries

Appendix 10. Imputation of standard deviations for caries data

Where standard deviations are missing for the DMFT, dmft data we used the equation: log(SD) = 0.17 + 0.56 x log(mean) to estimate the standard deviations for both before and after mean caries values. A sensitivity analysis was undertaken omitting all the data for studies/age groups where the standard deviation was imputed.

The equation we used was obtained from the data we had available to us from the other included studies in the review (102 mean and standard deviation data points). The equation had a similar regression coefficient to those developed by van Rijkom 1996 and Marinho 2003b shown below, although the intercept was smaller. This is probably because both these models had been developed on caries increments whereas the data we have used is cross-sectional caries severity data.

Equation from:

van Rijkom 1996 log(SD) = 0.54 + 0.58 x log(mean), (R^2 = 0.83)

Marinho 2003b log(SD) = 0.64 + 0.55 x log(mean), (R^2 = 0.77)

This review log(SD) = 0.17 + 0.55 x log(mean), (R^2 = 0.90)

Appendix 11. Fluorosis studies

Studies included in the analysis of all level of fluorosis:

Acharya 2005; Adair 1999; Al-Alousi 1975; Alarcon-Herrera 2001; Albrecht 2004; AlDosari 2010; Angelillo 1999; Arif 2013; Azcurra 1995; Beltran-Aguilar 2002; Booth 1991; Brothwell 1999; Chandrashekar 2004; Chen 1989; Chen 1993; Clark 1993; Clarkson 1989; Cochran 2004a; Correia Sampaio 1999; Cutress 1985; Driscoll 1983; Ekanayake 2002; Eklund 1987; Ellwood 1995; Ellwood 1996; Firempong 2013; Forrest 1965; Garcia-Perez 2013; Gaspar 1995; Grimaldo 1995; Grobler 1986; Grobler 2001; Haavikko 1974; Heintze 1998; Heller 1997; Hernandez-Montoya 2003; Hong 1990; Ibrahim 1995; Indermitte 2007; Indermitte 2009; Ismail 1990; Jackson 1975; Jackson 1999; Kanagaratnam 2009; Kotecha 2012; Kumar 2007; Kunzel 1976; Leverett 1986; Levine 1989; Lin 1991; Louw 2002; Machiulskiene 2009; Mackay 2005; Macpherson 2007; Mandinic 2009; Marya 2010; Masztalerz 1990; McGrady 2012; McInnes 1982; Mella 1992; Mella 1994; Milsom 1990; Montero 2007; Nanda 1974; Narbutaite 2007; Narwaria 2013; Nunn 1994a; Ockerse 1941; Pontigo-Loyola 2008; Ray 1982; Riordan 1991; Riordan 2002; Rwenyonyi 1998; Rwenyonyi 1999; Saravanan 2008; Sellman 1957; Shekar 2012; Stephen 2002; Szpunar 1988; Tabari 2000; Tsutsui 2000; Wang 1993; Wang 1999; Wang 2012; Warnakulasuriya 1992; Warren 2001; Wenzel 1982; Wondwossen 2004; Zheng 1986; Zimmermann 1954

Studies included in the analysis of fluorosis of aesthetic concern:

Acharya 2005; Alarcon-Herrera 2001; AlDosari 2010; Angelillo 1999; Arif 2013; Beltran-Aguilar 2002; Chen 1989; Clark 1993; Correia Sampaio 1999; Driscoll 1983; Eklund 1987; Forrest 1965; Gaspar 1995; Grimaldo 1995; Grobler 1986; Grobler 2001; Haavikko 1974; Heller 1997; Hernandez-Montoya 2003; Hong 1990; Ibrahim 1995; Jackson 1999; Kunzel 1976; Leverett 1986; Louw 2002; Macpherson 2007; McGrady 2012; Mella 1992; Mella 1994; Montero 2007; Nanda 1974; Pontigo-Loyola 2008; Ray

1982; Riordan 1991; Riordan 2002; Ruan 2005; Russell 1951; Sellman 1957; Stephen 2002; Tabari 2000; Zheng 1986; Zimmermann 1954

Studies that could not be included in analysis:

Awadia 2000; Bao 2007; Baskaradoss 2008; Birkeland 2005; Butler 1985; Chen 1993; Clarkson 1992; Colquhoun 1984; Cypriano 2003; de Crousaz 1982; Downer 1994; Driscoll 1983; Ermis 2003; Forrest 1956; Franzolin 2008; Harding 2005; Heifetz 1988; Jolly 1971; Kumar 1999; Mandinic 2010; Mazzotti 1939; Rugg-Gunn 1997; Scheinin 1964; Segreto 1984; Selwitz 1995; Selwitz 1998; Shanthi 2014; Skinner 2013; Skotowski 1995; Spadaro 1955; Sudhir 2009; Venkateswarlu 1952; Vilasrao 2014; Villa 1998; Vignarajah 1993; Vuhahula 2009; Whelton 2004; Whelton 2006

WHAT'S NEW

Last assessed as up-to-date: 19 February 2015.

Date	Event	Description
7 September 2015	Amended	Plain Language Summary amended for simplification.

HISTORY

Protocol first published: Issue 12, 2013

Review first published: Issue 6, 2015

Date	Event	Description
19 June 2015	Amended	Minor edit to Plain Language Summary for clarification. Missing referee name added to Acknowledgements.
2 February 2015	Amended	Background updated to justify the need for the review. Change to risk of bias domains, incorporating an item on 'sampling' Change to the handling of missing data; imputation of missing standard deviations for DMFT and dmft data

CONTRIBUTIONS OF AUTHORS

All authors contributed equally to the writing of the protocol in the published format. Authors contributed at different stages of the review process:

- Co-ordinating the review (ZIE, AMG)
- Data collection for the review (RA, ZIE, AMG, LO'M, TW, HW)
- Data management for the review (ZIE, AMG, LO'M, TW, HW)
- Analysis of data (AMG, HW, TW)
- Interpretation of data (JC, ZIE, AMG, LO'M, TW, HW)

- Writing the review (JC, ZIE, AMG, TW, HW)
- Providing general advice on the review (PT, VW)
- Performing previous work that was the foundation of the current review (RA, ZIE, AMG, RM, LO'M, PT, TW, HW, VW)

DECLARATIONS OF INTEREST

Authors on this review have also been involved in the evaluation of the evidence using different methodology for the CDC Task Force Recommendation on Water Fluoridation

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- Types of studies: additional clarification on difference between initiation and cessation studies added; the fact that randomised controlled trials are unfeasible is highlighted.

- Types of outcome measures: added sentence regarding disparities in dental caries across different groups of people. Changed 'fluorosis' to 'dental fluorosis'. Defined what is meant by adverse effects. Highlighted the fact that this review did not aim to provide a comprehensive systematic review of adverse effects other than dental fluorosis.

- Search methods for identification of studies: additional sources added,

- Assessment of risk of bias in included studies: 'sampling' was assessed while 'sequence generation' and 'allocation concealment' were not assessed.

- Measures of treatment effect: dmft and DMFT analyses calculated the difference in mean change scores between fluoridated and control groups. For the proportion caries free we calculated the difference in the proportion caries free between the fluoridated and control groups. For dental fluorosis data we calculated the log odds and presented as probabilities for interpretation.

- Protocol stated that adjusted and unadjusted results were to be presented for non-randomised studies and the unadjusted value used for analysis. Adjusted values were not available,

- Unit of analysis section deleted.

- Addition to Dealing with missing data: where standard deviations were missing for DMFT and dmft data we used the equation:

- log(SD) = 0.17 + 0.56 x log(mean) to estimate the standard deviations for both the before and after mean caries values. This equation was estimated from available data where the standard deviations were given (R^2 = 0.91). We undertook no other imputations. We undertook sensitivity analyses to determine the effect of the imputed standard deviations.

- Data synthesis: the following text has been deleted (to reflect changes in effect estimate): "Risk ratios will be combined for dichotomous data and mean differences combined for continuous data. Meta-analytic fixed-effect and random-effects models (with or without moderators) will be obtained via the linear (mixed-effects) model. In the case of random-effects, the DerSimonian-Laird estimator for the amount of (residual) heterogeneity will be utilised. Appropriate adjustments to the test statistics and confidence intervals due to the uncertainty in the estimate of the (residual) heterogeneity will be undertaken by application of the method by Knapp and Hartung (Knapp 2003).Tables indicating the general effect of fluoridation found in each study will be created for each outcome, and where possible, the point estimate and a measure of statistical significance (using the 95% confidence interval or P value) of the finding will also be included."

- Analysed dmft data only for children 8 years and younger.

- Approach to dental fluorosis data amended (although cut-offs regarding definition of dental fluorosis of aesthetic concern and decision to use data on 5 ppm or lower as primary analysis remain).

- Subgroup analysis and investigation of heterogeneity: we deleted the following text: "The heterogeneity among fluorosis studies will be explored by including variables that may account for the observed heterogeneity in the regression model. Since fluoride concentrations of control (non-fluoridated) groups across studies has been highlighted as a potential source of heterogeneity, a subgroup analysis of studies where the control group has fluoride concentration of 0.2 ppm or less will be undertaken".

INDEX TERMS

Medical Subject Headings (MeSH)

DMF Index; Dental Caries [*prevention & control]; Fluoridation [adverse effects; *methods]; Fluorosis, Dental [epidemiology; etiology]; Observational Studies as Topic; Prospective Studies; Selection Bias

MeSH check words

Adolescent; Child; Child, Preschool; Humans

A systematic review of the efficacy and safety of fluoridation

Australian National Health and Medical Research Council. Canberra: Australian Government; 2007

Scope and purpose The systematic review was commissioned by the Australian National Health and Medical Research Council (NHMRC) to evaluate the scientific literature relating to the health effects of fluoride and fluoridation. The systematic review's research questions relate to the caries-reducing benefits and associated potential health risks of providing fluoride systemically (via addition to water, milk and salt) and the use of topical fluoride agents, such as toothpaste, gel, varnish and mouthrinse. Although the review summarises the recent evidence, it does not constitute health policy or clinical practice recommendations.

Data sources A literature search was undertaken using the Medline and Embase databases (via www.embase.com). In addition, the Cochrane Systematic Review and Clinical Trial databases were searched to help identify additional systematic reviews and original studies. Because of the availability of recent systematic reviews, searches were limited to publications from 1996 onwards . The search was conducted in December 2006 and limited to English-language publications.

Study selection Based on types of intervention (individual or population) and the outcomes assessed (efficacy or safety), the hierarchy of study types considered most relevant for answering each of the clinical questions defined in this review was chosen (Table 1). The levels of evidence used by NHMRC for intervention and aetiological studies are summarised in Table 2.

Data extraction and synthesis Screening of eligible studies was conducted by three reviewers. Data were extracted for all of the included systematic reviews and individual studies using standardised data-extraction forms. This included information about the study design, NHMRC level of evidence, population, intervention, comparator, outcome definitions and results. Information relating to potential biases and study quality were also extracted. Where appropriate, study results were pooled using standard meta-analysis techniques.

Results In total, 5418 nonduplicate citations were identified. After applying the inclusion and exclusion criteria, 408 citations were considered potentially eligible for inclusion in the review. After the review of the full papers of potentially eligible articles, 77 citations were included in the review. The summary of findings was presented in the context of the research questions (Table 3).

Recommendations Fluoridation of drinking water remains the most effective and socially equitable means of achieving community-wide exposure to the caries prevention effects of fluoride. It is recommended (see also www.nhmrc.gov.au/news/media/rel07/_files/fluoride_flyer.pdf) that water be fluoridated in the target range of 0.6–1.1 mg/l, depending on the climate, to balance reduction of dental caries and occurrence of dental fluorosis.n particular with reference to care in hospital for those following stroke.

Address for correspondence: National Health and Medical Research Council, GPO Box 1421, Canberra ACT 2601, Australia. E-mail: nhmrc.publications@nhmrc.gov.au

Commentary

This systematic review of fluoridation is the fourth of the reviews commissioned by the NHMRC in Australia. The first two were carried out in 1985[4] and 1991[5] and focussed on the effectiveness of water fluoridation. The third one[6] included a review of fluoride intake from discretionary fluoride supplements in addition to water fluoridation. The third review was published in 1999, and is presently available on the website of Australian Dental Association (www.ada.org.au/app_cmslib/media/lib/0703/m50958_v1_nhmrc%20fluoride.pdf). The fourth review[7] published in 2007 has once again expanded its scope by including other methods of fluoride delivery, such as milk, salt, toothpaste, gel, varnish and mouthrinse. Fluoride supplements such as drops, chewable tablets and chewing gum tablets have not been explicitly included in the current review, however.

The aim of the most recent review was to synthesise the highest level of evidence to answer each clinical question. It should be noted that the levels of evidence accepted for fluoride intervention at the population level was based on those chosen for the systematic review of water fluoridation by McDonagh et al.[2]

The inclusion and exclusion criteria for the current review were explicit. The search strategy used to identify relevant studies could not be considered to be comprehensive as no controlled vocabulary was used in searching the electronic databases. Moreover, the range of electronic databases searched was rather limited and restricting studies to those published in the English language may also affect the findings. During the literature search, three reviewers assessed the eligibility of abstracts (approximately one third each). It is not clear whether study selection or data extraction was carried out independently or in duplicate.

Included studies were clearly laid out in table format in the appendix. This included information about the study design, population, intervention, comparator, outcomes and results. The quality of studies was assessed using the key questions from the NHMRC.[7] For those study designs such as cross-sectional studies and ecological studies which had no guidance on assessment from the NHMRC, a summary of various factors relating to potential biases was provided. In addition, a global quality rating was given to each individual study. Post-hoc statistical analysis was carried out when necessary.

Two systematic reviews[2,8] and one additional, relevant, original study[9] were identified in the literature search on water fluoridation and dental caries. The York review[2] was chosen to form the evidence base for the effect of water fluoridation on dental caries in the current review, as it provided more detailed and comprehensive results than those shown in the review by Truman et al.[6] It should be noted that 12 of the 21 studies included in the latter were among the 26 studies included in the York review.[2] The lack of overlap between the two reviews is largely because the Truman review[8] assessed both "fluoridation *vs* no fluoridation" and "fluoridation *vs* fluoridation at a lower level" whereas the York review[5] assessed only "fluorida-

Table 1. Hierarchy of evidence accepted for each clinical question

	Study levels for effect:	
	Intervention (prevention of dental caries or dental fluorosis)	Aetiology/ harms (fracture, cancer or other adverse effects)
Population level intervention		
Water fluoridation Milk fluoridation Salt fluoridation	Cohort study (level III-2) Case-control study (level III-2) Comparative cross-sectional study I*† (level IV)	Prospective cohort study (level II) Retrospective cohort study (level III-2) Case–control study (level III-3) Comparative cross-sectional study I* (level IV) Comparative cross-sectional study II† (level IV)
Individual level intervention		
Topical	RCT (level II)	RCT (level II-intervention) Retrospective cohort study (level III-2) Case-control study (level III-3) Comparative cross-sectional study I* (level IV) Comparative cross-sectional study II† (level IV)

RCT, Randomised controlled trial.
*Evaluated at multiple timepoints (for caries assessment), with baseline assessment associated closely with the implementation/ cessation of intervention and the final assessment at a time sufficient for the intervention to have had an effect on the outcome under investigation.
†Evaluated at a single timepoint (for fluorosis, and other harms assessment) with sufficient time for intervention to have had effect on the outcome under investigation.

Table 2. Hierarchy of evidence

Level	Intervention*	Aetiology/ harms†
I‡	Systematic review of level II studies	Systematic review of level II studies
II	RCT	Prospective cohort study
III-1	A pseudo-RCT (alternate allocation of some other method)	All or none¶
III-2	A comparative study with concurrent controls Non-randomised experimental trial§ Cohort study Case–control study Interrupted time series with a control group	A retrospective cohort study
III-3	A comparative study without concurrent controls Historical control study Two or more single arm studies**	A case–control study
IV	Case series with either pre-test/ post-test outcomes	A cross-sectional study

RCT, Randomised controlled trial.
*Definitions of these studies are provided by the NMHRC.[1]
†If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the intervention hierarchy of evidence should be utilised. If it is only possible and/ or ethical to determine a causal relationship using observational evidence (ie, groups cannot be allocated to a potentially harmful exposure), then the aetiology hierarchy of evidence should be utilised.
‡A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence.
¶All or none of the people with risk factor(s) experience the outcome, eg, no smallpox develops in absence of specific virus and clear proof of causal link has come from the disappearance of smallpox after large-scale vaccination.
§This also includes controlled before-and-after (pre-test/ post-test) studies, as well as indirect comparisons (ie, utilise A vs B and B vs C, to determine A vs C).
**Comparing single-arm studies (ie, case-series from two studies).

tion vs no fluoridation". Only one additional original study[9] was identified in the current review and this did not change the conclusion from that of the York one.[2] It should be noted that the benefits from fluoridated public water supply were weakened because beverages and food products processed in fluoridated communities were exported to surrounding non-fluoridated communities.[10] This phenomenon is referred to as the halo effect: Griffin *et al*.[11] attempted to quantify it by analysing data from the 1986–1987 National Survey of

Oral Health in US School Children. Studies measuring the effectiveness of water fluoridation that consider only its direct benefit may have underestimated the total contribution of water fluoridation to caries reduction.

Regarding water fluoridation and dental fluorosis, the literature search identified two systematic reviews[2,12] and 10 additional original studies. It should be noted that in some cases there was a substantial difference in the prevalence of "any fluorosis," both between different countries and within different countries. These differences result from a number of factors including methods (eg, different fluorosis indices), environmental influences (eg, phosphate mines) and lifestyles (eg, higher tea consumption). The authors concluded that although there was a fourfold risk of developing fluorosis of aesthetic concern with optimal water fluoridation compared with suboptimal water fluoridation, the absolute increase in prevalence was small (approx. 4–5%).

The studies cited in the report of the National Research Council[13] have raised the possibility that infants could receive a greater than optimal amount of fluoride through liquid concentrate or powdered baby formula that has been mixed with water containing fluoride during a time when their developing teeth may be susceptible to dental fluorosis. Recently, a systematic review to investigate the association of fluorosis and infant formula has been completed.[14] It concluded that the evidence suggests dental fluorosis might be caused by fluoride content in infant formula or the fluoride levels in the water used to reconstitute infant formula. Confounding factors could not be ruled out, however, and publication bias may also distort the evidence on infant formula and fluorosis.

Although the current review presents a summary of the relevant evidence, the potential effectiveness of any public health intervention must be considered in the context of practicalities associated with implementing the intervention, issues surrounding compliance, and issues related to equity of access.

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Table 3. Summary of findings in context of research questions

Benefit/ risk	Question	Findings
Dental caries		
Water fluoridation	Is intentional water fluoridation more effective than no water fluoridation in prevention of dental caries?	Existing evidence strongly suggests water fluoridation is beneficial at reducing dental caries. After adjustment for potential confounding variables, it was shown[2] that introducing water fluoridation into an area significantly increased proportion of caries-free children, and decreased mean dmft/DMFT scores vs areas that were non-fluoridated over the same time period. These findings[2] also suggest cessation of fluoridation resulted in the difference in caries prevalence narrowing between fluoridated and nonfluoridated populations. Only one additional relevant original study was identified in the current review, which did not change the conclusion.
Milk fluoridation	Is intentional milk fluoridation more effective than no milk fluoridation in prevention of dental caries?	Results of the SR suggest milk fluoridation is beneficial in preventing/ reducing caries but there is less good quality evidence than for water fluoridation. Results of two original studies included represent low levels of evidence but results are consistent with milk fluoridation being associated with caries prevention and cessation of milk fluoridation with worsening dental health.
Salt fluoridation	Is intentional salt fluoridation more effective than no salt fluoridation in prevention of dental caries?	No studies were identified that met criteria for inclusion in review. Results of three before-and-after cross-sectional studies suggest salt fluoridation reduces caries in populations of children of age 6–15 years. Note that these studies were considered of poor methodological quality because of lack of assessment of and adjustment for potential confounding factors.

Topical fluoride supplementation	Is use of topical fluoride supplementation more efficacious than no topical fluoride supplementation in prevention of dental caries?	There is consistent level I evidence from existing SR and a review of additional original studies that topical fluoride agents reduce caries in children vs no topical fluoride supplementation. Compared with placebo/ no treatment, magnitude of the effect achieved with varnish is greater than other topical agents but when compared directly there is no significant difference between agents.
Combination of topical fluoride supplementation	Is a combination of topical fluoride supplementation products more efficacious than a single topical fluoride supplement product in prevention of dental caries?	There is level I evidence that some combinations of topical agents may be more effective at preventing/ reducing caries than single agents.
Dental fluorosis		
Water fluoridation	Does intentional water fluoridation result in dental fluorosis over and above no intentional water fluoridation?	There is consistent level III/IV evidence from existing SR that water fluoridation results in development of dental fluorosis but most of it is mild and not considered to be of aesthetic concern. The NNH with water fluoridation at an optimal level vs no fluoridation to get one additional person with any fluorosis is approx. 6. The corresponding NNH to get one additional person with fluorosis of aesthetic concern is approx. 22. Meta-analysis of additional original studies provides results consistent with those seen in the existing SR.
Milk fluoridation	Does intentional milk fluoridation result in dental fluorosis over and above no intentional milk fluoridation?	One study provided level IV evidence that milk fluoridation is not associated with significant levels of fluorosis. A statistically significant increase in fluorosis was seen in a number of age groups following introduction of milk fluoridation but the majority of this fluorosis was mild and not considered to be of aesthetic concern.
Salt fluoridation	Does intentional salt fluoridation result in dental fluorosis over and above no intentional salt fluoridation?	One level IV study provided evidence of a significantly increased risk of "any fluorosis" associated with salt fluoridation. Two additional supportive studies (not strictly meeting inclusion criteria) agreed with the included study. There were no data relating to risk of fluorosis of aesthetic concern.
Topical fluoride supplementation	Does topical fluoride supplementation result in dental fluorosis over and above no topical fluoride supplementation?	Two level IV studies provide evidence regarding impact of use of topical fluorides on dental fluorosis. One study showed fluoridated toothpaste may be associated with "any fluorosis" but when "fluorosis of aesthetic concern" was examined, no statistically significant difference between higher fluoride dose and control groups was found, and prevalence of fluorosis in higher dose toothpaste group was low (<2%). One poor quality study in which fluorosis was measured after a campaign was implemented to reduce the amount of topical fluoride use in children suggested that a decrease in fluorosis was seen.
Combination of topical fluoride supplementation	Does a combination of topical fluoride supplementation products result in dental fluorosis over and above a single topical fluoride supplementation product?	There is currently no evidence comparing combinations of topical agents with a single topical agent.
Fracture or osteoporosis		
Water fluoridation	Does intentional water fluoridation result in fracture over and above no intentional water fluoridation?	Authors of three existing SR concur that water fluoridation at levels aimed at preventing dental caries has little effect on fracture risk, either protective or deleterious. Results of subsequent original studies support this, but do suggest optimal fluoridation levels of 1 ppm may result in a lower risk of fracture vs excessively high levels (well beyond those experienced in Australia). One study also indicated optimal fluoridation levels may lower overall fracture risk vs no fluoridation (the latter was not the case when hip fractures were considered in isolation).
Milk fluoridation	Does intentional milk fluoridation result in osteoporosis or fracture over and above no intentional milk fluoridation?	There is currently no evidence available to determine impact of milk fluoridation upon fracture risk.
Salt fluoridation	Does intentional salt fluoridation result in osteoporosis or fracture over and above no intentional salt fluoridation?	There is currently no evidence available to determine impact of salt fluoridation upon fracture risk.
Topical fluoride supplementation	Does topical fluoride supplementation result in osteoporosis or fracture over and above no topical fluoride supplementation?	There is currently no evidence available to determine impact of topical fluoride supplementation upon fracture risk.

Combination of topical fluoride supplementation	Does a combination of topical fluoride supplementation products result in osteoporosis or fracture over and above a single topical fluoride supplementation product?	There is currently no evidence available to determine impact of combination topical fluoride supplementation upon fracture risk.
Cancer		
Water fluoridation	Does intentional water fluoridation increase risk of cancer over and above no intentional water fluoridation?	The existing SR[2] concluded there is no clear association between water fluoridation and overall cancer incidence or mortality (for "all cause" cancer, and specifically for bone cancer and osteosarcoma). The authors state that evidence relating fluoridation to cancer incidence or mortality is mixed, with small variations on either side of the effect. The current literature review identified four additional studies investigating relationship between water fluoridation and cancer incidence or mortality, including three level IV ecological studies and one level II-3 matched case–control study.[3] The latter study compares fluoride exposure of histologically-confirmed osteosarcoma cases with that of matched controls (subset of patients from larger case–control study by Harvard School of Dental Medicine yet to report its findings). After adjusting for significant differences at baseline between cases and controls, results[3] suggest an increased risk of osteosarcoma in young males (not females) with water fluoridation but note the letter from co-investigators which points out that they have not been able to replicate these findings in the broader Harvard study which included prospective cases from the same 11 hospitals. The bone samples taken in the broader study also corroborate a lack of association between fluoride content in drinking water and osteosarcoma in new cases. The full study is not yet published and the letter's authors caution readers not to over-interpret results[3] in the interim.
Milk fluoridation	Does intentional milk fluoridation increase risk of cancer over and above no intentional milk fluoridation?	There is currently no evidence available to determine impact of milk fluoridation upon cancer risk.
Salt fluoridation	Does intentional salt fluoridation increase risk of cancer over and above no intentional salt fluoridation?	There is currently no evidence available to determine impact of salt fluoridation upon cancer risk.
Topical fluoride supplementation	Does topical fluoride supplementation increase risk of cancer over and above no topical fluoride supplementation?	There is currently no evidence available to determine impact of topical fluoride supplementation upon cancer risk.
Combination of topical fluoride supplementation	Does a combination of topical fluoride supplementation products increase risk of cancer over and above a single topical fluoride supplementation product?	There is currently no evidence available to determine impact of combination topical fluoride supplementation upon cancer risk.
Other adverse effects		
Water fluoridation	Is intentional water fluoridation associated with other adverse effects over and above no intentional water fluoridation?	Authors of previous SR concluded that studies examining other possible negative effects of water fluoridation provide insufficient evidence to reach a conclusion.
Milk fluoridation	Is intentional milk fluoridation associated with other adverse effect over and above no intentional milk fluoridation?	There is currently no evidence available to determine impact of milk fluoridation upon other harms.
Salt fluoridation	Is intentional salt fluoridation associated with other adverse effects over and above no intentional salt fluoridation?	There is currently no evidence available to determine impact of salt fluoridation upon other harms.
Topical fluoride supplementation	Is topical fluoride supplementation associated with other adverse effects over and above no topical fluoride supplementation?	There is currently no evidence available to determine impact of topical fluorides upon other harms.
Combination of topical fluoride supplementation	Is a combination of topical fluoride supplementation products associated with other adverse effects over and above a single topical fluoride supplementation product	There is currently no evidence available to determine impact of combination topical fluorides upon other harms.

dmft/DMFT, Decayed, missing or filled teeth of the primary or permanent dentition; SR, systematic review; NNH, number needed to harm.

From: Christine Massey [redacted]
Sent: August 8, 2017 10:24 AM
To: Thompson, Allan; Downey, Johanna; Groves, Annette; Innis, Jennifer; Shaughnessy, Barb; Jeffrey, Linda Mayor; Gibson, Grant; Medeiros, Martin; Miles, Gael; Moore, Elaine; Palleschi, Michael; Crombie, Bonnie; Carlson, George; Fonseca, Chris; Iannicca, Nando; Kovac, John; Mahoney, Matt; McFadden, Sue; Parrish, Carolyn; Ras, Karen; Saito, Pat; Starr, Ron; Tovey, Jim; Loh, Lawrence; Polsinelli, Nancy; Szwarc, David; Smith, Janette; Hennings, Jeff; Jim Nardi; ZZG-RegionalClerk; O'Connor, Patrick; Burkiewicz, Justyna; ZZG-WaterQualityInquiries; Sprovieri, John; Hau, Monica; Ward, Megan; Bingham, Kate; Hopkins, Jessica
Subject: Scientist's damning critique of Australian NHMRC 2017 “Sham” fluoridation review

Dear Peel Council / CWFC Members, Dr. Hopkins, Commissioner Polsinelli, Mr. Hennings, Commissioner Smith, CAO Szwarc and Mr. Nardi,

Regarding the so-called "gold standard Australian report" touted by Councillors Tovey and Parrish, please be sure to add the following to the agenda for the next meeting of the CWFC... assuming it won't be permanently disabled through continuous stalling tactics by the committee's pro-fluoridation Chair.

Please also add the letter from Dr. L.G. Horowitz contained in my earlier email sent this morning.

The following comes via the Fluoride Action Network:

Retired scientist Merilyn Haines explains that this is the latest attempt by the NHMRC to mislead the Australian public and decision-makers that water fluoridation is safe, effective and ethical.

According to Haines, "In order for this *government* agency to deliver a "rubber stamp" endorsement of *government* policy, it had to corrupt both science and the democratic process.

Haines hopes that when people see how the NHMRC has behaved there will be so much outcry from citizens and scientists - both inside Australia and around the world - that it will trigger a demand for a Royal Commission investigation.

Haines charges that the 2017 NHMRC review of water fluoridation was unprofessional, unscientific, biased, highly selective, deeply flawed and prevented meaningful scientific and public input and was clearly biased in favor of defending the practice of water fluoridation - a long-standing government policy.

The NHMRC produced a very poor review in 2007 which received extensive criticism from independent scientists. To produce an even more biased and restrictive review in 2017 is even more egregious in lieu of the new science published (or updated) since 2007.

For example, the 2015 Cochrane review (a gold standard when it comes to meta-analysis of health issues) found little in the way of high quality studies to demonstrate the effectiveness of fluoridation.

On safety, there have now been over 300 published animal and human studies indicating that fluoride is neurotoxic. This large body of evidence has been largely ignored by the NHMRC,

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even though it is being currently scrutinized by the National Institute of Health Sciences (NIEHS) and the National Toxicology Program (NTP) in the USA.

In this analysis, 23 specific examples of NHMRC manipulations have been documented. Here is a selection of the 23 examples. The NHMRC,

1. Stacked the fluoride review committee with fluoridation lobbyists and advocates.

2. Broke a promise to include experts opposed to fluoridation.

3. Secretly commissioned a new study on dental effects (previously listed as “out of scope”), when the 2015 Cochrane Collaboration review didn’t deliver a convincing pro-fluoridation position.

4. Falsely claimed that there is no evidence that fluoride interferes with thyroid function.

5. Falsely claimed a low-quality IQ study (Broadbent et al, 2014) was a high-quality study.

6. Downplayed, dismissed or excluded evidence of fluoride’s neurotoxicity.

7. Excluded a significant study linking fluoridation to ADHD (Malin and Till, 2015).

8. Failed to refute the Bassin (2006) osteosarcoma study but still continued to maintain no evidence of a link between fluoridation and cancer.

10. Based its claims of safety largely on its 2007 review, however, its 2007 review was largely a copy of the 2000 York University review, which according to the York Review’s Professor Sheldon did NOT show fluoridation to be safe!

11. Failed to acknowledge that poor kidney function increases uptake of fluoride into the bones and poses risks over a lifetime.

13. Abandoned the normal evaluation method for studies of fluoride’s effectiveness almost certainly in an effort to disguise the fact that most of the studies reviewed were of low, or very low quality.

15. Violated its own selection criteria by including a) an unpublished work; b) a narrative and c) an abstract (all favorable to fluoridation).

17. Claims fluoridation reduces tooth decay by 26-44 % - but without indicating just how small such reductions are in absolute terms – often less than one tooth surface out of over 100 tooth surfaces in a child’s mouth!

18. Dishonestly claims fluoridation is safe by excluding important studies on spurious grounds, ignoring many others, and even cherry-picking weak studies that serve their purpose (e.g. Broadbent on IQ).

20. Perverted the principles of medical ethics by presenting a bogus ethical claim constructed by lobbyists rather than ethicists.

23. The NHMRC’s extraordinary effort to maintain the dubious claims that fluoridation is safe,

effective and ethical, are becoming more and more desperate by the year. NHMRC 2007 was very bad, NHMRC 2017 verges on fraud.

For the full list of the 23 items see Haines media release:

Press Release from Fluoride Action Network Australia: A damning critique and analysis of the NHMRC's 2017 "Sham" review of water fluoridation and appeal for Royal Commission Inquiry: 23 Reasons why Australia needs a Royal Commission into the NH MRC's fraudulent fluoride review. August 3.
http://fluoridealert.org/wp-content/uploads/fan-australia.nhmrc_.fluoridation-critique.exec_.summary.8-3-17.pdf

*For the full report see:

A damning critique and analysis of the NHMRC's 2017 "Sham" review of water fluoridation and appeal for Royal Commission Inquiry: 23 Reasons why Australia needs a Royal Commission into the NHMRC's fraudulent fluoride review. By Merilyn Haines on behalf of Fluoride Action Network Australia. August 3.
http://fluoridealert.org/wp-content/uploads/fan-australia.nhmrc-fluoridation-critique-8-3-17-1.pdf

Below is a Video Presentation by Merilyn Haines
https://www.youtube.com/watch?v=m_8Q-yA4LJA&feature=share

You might also recall that when asked for a comparison of the toxicity of the Region's current and previous industrial fluorosis-causing fluoride acids, Dr. de Villa, despite insisting that both are perfectly safe, couldn't provide an answer. She deferred instead to the Region's so-called "expert" on such matters, Mr. Jeff Hennings.

Mr. Hennings, when probed for details by Councillor Sprovieri, disclosed that he had no knowledge on the long term effects of ingesting low levels of HFSA and that he wasn't prepared to state that there are no ill effects.

And yet you continued to fluoridate our drinking water, with HFSA no less.

Christine Massey, M.Sc.
Fluoride Free Peel

From: Christine Massey [redacted]
Sent: August 21, 2017 10:39 AM
To: Thompson, Allan; Downey, Johanna; Groves, Annette; Innis, Jennifer; Shaughnessy, Barb; Jeffrey, Linda Mayor; Gibson, Grant; Medeiros, Martin; Miles, Gael; Moore, Elaine; Palleschi, Michael; Crombie, Bonnie; Carlson, George; Fonseca, Chris; Iannicca, Nando; Kovac, John; Mahoney, Matt; McFadden, Sue; Parrish, Carolyn; Ras, Karen; Saito, Pat; Starr, Ron; Tovey, Jim; Loh, Lawrence; Polsinelli, Nancy; Szwarc, David; Smith, Janette; Hennings, Jeff; Jim Nardi; ZZG-RegionalClerk; O'Connor, Patrick; Burkiewicz, Justyna; ZZG-WaterQualityInquiries; Sprovieri, John; Hau, Monica; Ward, Megan; Bingham, Kate; Hopkins, Jessica
Subject: Fluoride is the major Cause of Cataract Blindness

Dear Peel Council / CWFC Members, Dr. Hopkins, Commissioner Polsinelli, Mr. Hennings, Commissioner Smith, CAO Szwarc, Regional Clerk Lockyer and Mr. Nardi,

Please see the attached new report, and recall that:

- you have zero randomized controlled studies on water fluoridation using any fluoridation agent whatsoever,
- Council, on the advice of the CWFC that reviewed evidence for 2 years, has already formally admitted uncertainty on the effectiveness of its illegally administered industrial waste fluoride acid drug, HFSA, in drinking water for reducing cavities,
- you have no toxicology studies on HFSA, and no valid experiments to prove that HFSA dissociates 100% in tap water as claimed by Staff,
- you know for a fact that many Peel residents have permanently harmed (hypomineralized) teeth (dental fluorosis) caused by overexposure to fluoride during tooth formation (34% of fluoridated 7 year olds in the Region's commissioned study conducted by Dr. Dick Ito had dental fluorosis, and 4% of Peel children examined had moderate or severe dental fluorosis according to the Region's 2003 oral health report), and that Staff's latest report on dental fluorosis is ludicrously (and in my opinion criminally) unscientific and misleading

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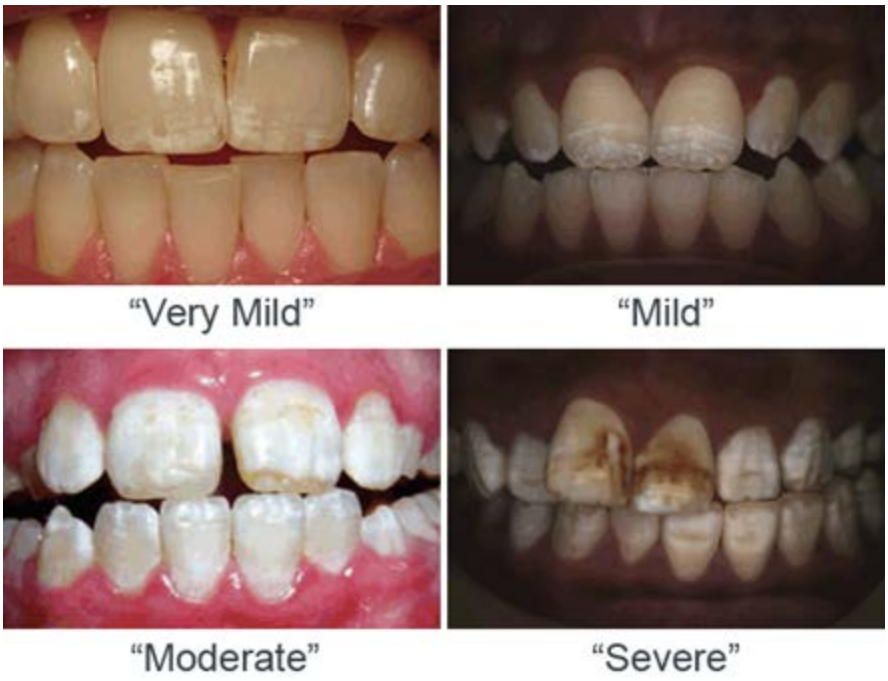

- the Region's so-called "expert" Mr. Jeff Hennings, to whom Medical Officer Dr. de Villa deferred earlier this year, disclosed to Council that he knows nothing about the long term effects of ingesting low levels of HFSA and is not prepared to claim that there are no adverse effects.

Chair Parrish and Regional Clerk Lockyer, please add this email and attachment to the next agenda of the CWFC, assuming that the committee will not be permanently disabled via further anti-democratic maneuvers (in blatant violation of Regional BY- LAW NUMBER 1-2017, "*A by-law to govern the Regional Council Code of Conduct*"), or to the next Council agenda involving fluoride or drinking water or eye health/disease.

For Safe Water,
Christine Massey, M. Sc.

Fluoride is the major Cause of Cataract Blindness

Technical Report · August 2017

DOI: 10.13140/RG.2.2.17390.92483

1 author:

Geoff Pain

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Fluoride is the major Cause of Cataract Blindness

Geoff N Pain

August 2017

Abstract

Cataract blindness affects tens of millions of people, many of whom will never have access to lens replacement surgery. Fluoride from various sources including drinking water, tea, salt and drugs, enhances and stabilizes crystal growth of Hydroxyapatite within the eye. Fluoride is identified as the major risk for cataract and contributes to risk of other eye diseases including macular degeneration.

Keywords: Alkaline Phosphatase, Anticholinesterase agents, Aphakia, Asteroid Hyalosis, Asthma, Bio-accumulation, Blindness, Calcification, Cataract, Conjunctivitis, Diabetes, Fluoride, Fluorocarbon, Glaucoma, Hydroxyapatite, Macular Degeneration, Melatonin, Mortality, Optial Neuritis, Osteosarcoma, Pineal gland, Retina, Smoking, Uveitis

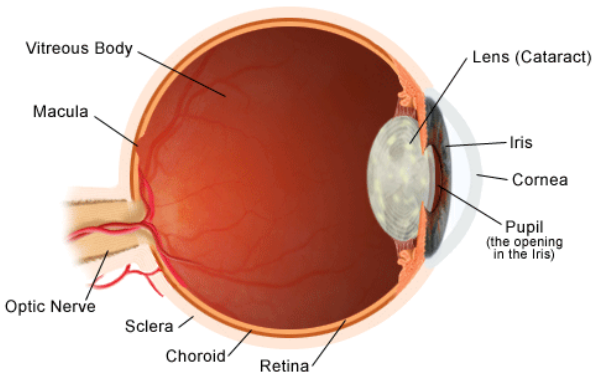
Introduction

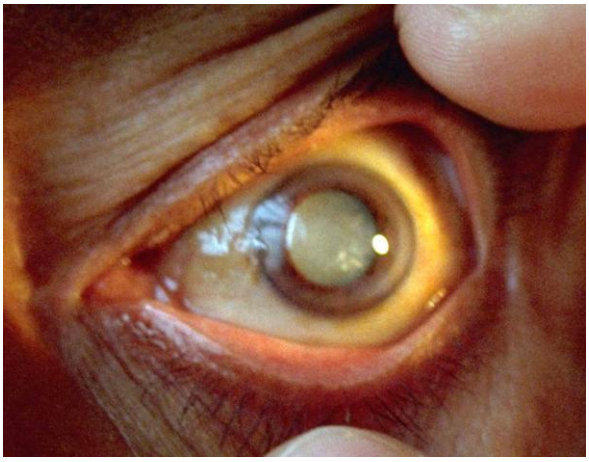
In Australia it is estimated that 40% of visual impairment is due to Cataract, with over 1,460,400 sufferers aged 55 or more (31% of that age group) in 2004. In the same year 429,600 Australians aged 55 or more had undergone cataract surgery, which represents 9.1% of that age group [AIHW 2005]. The risk of falls and bone fractures, automobile accidents, premature death and the rates of depression and anxiety are elevated in those visually impaired by cataract [Smith 2016].

Cataract is the leading cause of visual impairment in Australian Aborigines who suffer earlier onset of cataract in their generally shorter life spans [Landers 2013].

In underdeveloped countries, the incidence of new cases outstrips the surgical capacity, producing a worsening human and economic burden [Khanna 2012]. Surgical rate is a measure of wealth of nations and surgical failure is significant, often resulting in aphakia or eye loss.

There are various types of cataract [Gruebbel 2014], however the focus of this review is the highly mineralized forms, which have been known since 1843 [Jacob 1851] to be due to deposition of needle-like crystals of “phosphate of lime”, now known as Hydroxyapatite. Calcified cataract is normally age-dependent but has been reported in young people [Chiang 2004].





Types of Cataract

There are three main types of Cataracts: nuclear; cortical; and subcapsular.

Nuclear cataracts form deep in the central zone of the lens and are usually associated with aging.

Cortical cataracts occur in the lens cortex, the part of the lens that surrounds the central nucleus and have white, wedge-like opacities that start in the periphery of the lens and work their way to the centre, resembling spokes.

Subcapsular cataract occurs at the back of the lens. People with diabetes or those taking high doses of steroid medications have a greater risk of developing subcapsular cataracts.

Synchrotron hard X-ray imaging of whole lenses has allowed identification of Calcium in both cortical and nuclear cataract crystals [Antunes 2006] while other groups using the technique focused on structural change of protein [Bahrami 2015].

Fluoride doped Hydroxyapatite in Cataract

A study of residents in two towns in Texas with different Fluoride levels in drinking water, Bartlett (8 ppm Fluoride) and Cameron (0.4 ppm Fluoride) found no statistically significant difference due to small sample size and different age distributions [Leone 1954]. The National Research Council remarked about this study "The greater incidence in the high fluoride group (Bartlett) of a certain brittleness and blotching of fingernails, of hypertrophic changes in the spine and the pelvis, and of lenticular opacities of the eyes (Cataracts) requires further investigation." [NRC 2006]. Correlation between the incidence of senile cataract and concentration of fluoride in drinking water was observed in a later studies [Kas'ianenko 1984, Shulka 1991].

Down Syndrome (Mongolism) was established to be linked to consumption of fluoride through statistical studies. It was found that 70% of Down's Syndrome babies were born with cataract [Rapaport 1957; 1957a; 1959].

Early studies of Fluoride content of Cataract found up to 77 ppm Fluoride [Waldbott 1961].

However humans in Balaghat who drank well water at 1.2-2.4 ppm or river water at 2.8 ppm Fluoride, exhibited remarkably high levels of 20,000 to 50,000 ppm Fluoride in their removed cataracts [Shulka 1991].

These levels exceed those that have been reported in the Pineal gland and indicate that high levels of Calcium, Phosphate and Fluoride are available to the lens during cataract formation.

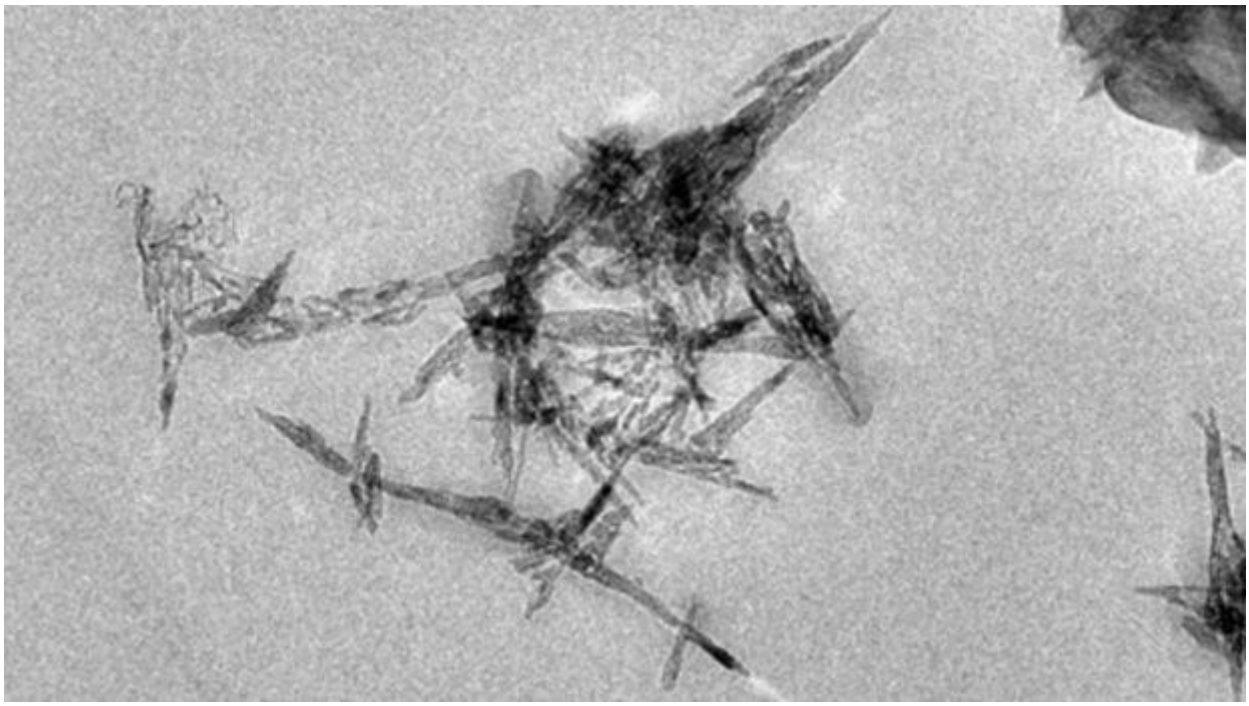
Calcium has been shown to induce opacification and proteolysis in the lens of test animals [Truscott 1990]. Proteases including calpain I, calpain II, and calpastatin are present in the lens [Yoshida 1985].

Effects of industrial Fluoride exposure in humans include opacities of the lens capsule (cataract) and attenuation of the retinal arteries [Karczewicz 1989].

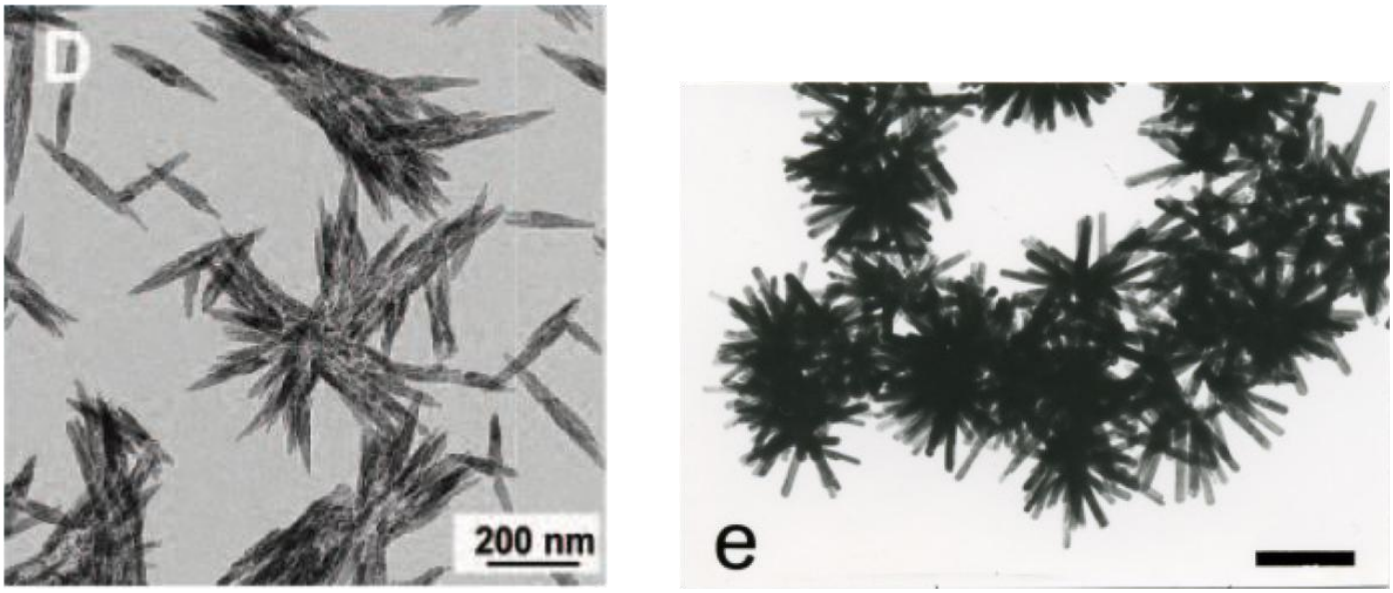
Fluoride doped Hydroxyapatite in cataracts and other tissues is less easily resorbed, leading to bio-accumulation and acceleration of Hydroxyapatite Deposition Disease (HADD). Kidney failure with age, part of which is due to the nephrotoxicty of Fluoride [Pain 2017], produces an exponential retention of Fluoride and risk of cataract growth.

The European Commission adopted a position on Hydroxyapatite in 2016 stating: "The available information indicates that nano-hydroxyapatite in needle-shaped form is of concern in relation to potential toxicity. Therefore, needle-shaped nano-hydroxyapatite should not be used in cosmetic products. It is of note that Material 2 of the submission also includes nanofibres of needle-like structure." [EC 2016].

Recently in Australia a famous manufacturer of infant formula was forced to withdraw product from the market due to discovery of nanocrystals of Fluoride doped Hydroxyapatite in its product [Schoepf 2016, Schoepf 2017,Han 2017]. Energy dispersive x-ray analysis of Hydroxyapatite for Fluoride content can be difficult due to other elements exhibiting peaks in spectra near 7 kEV.



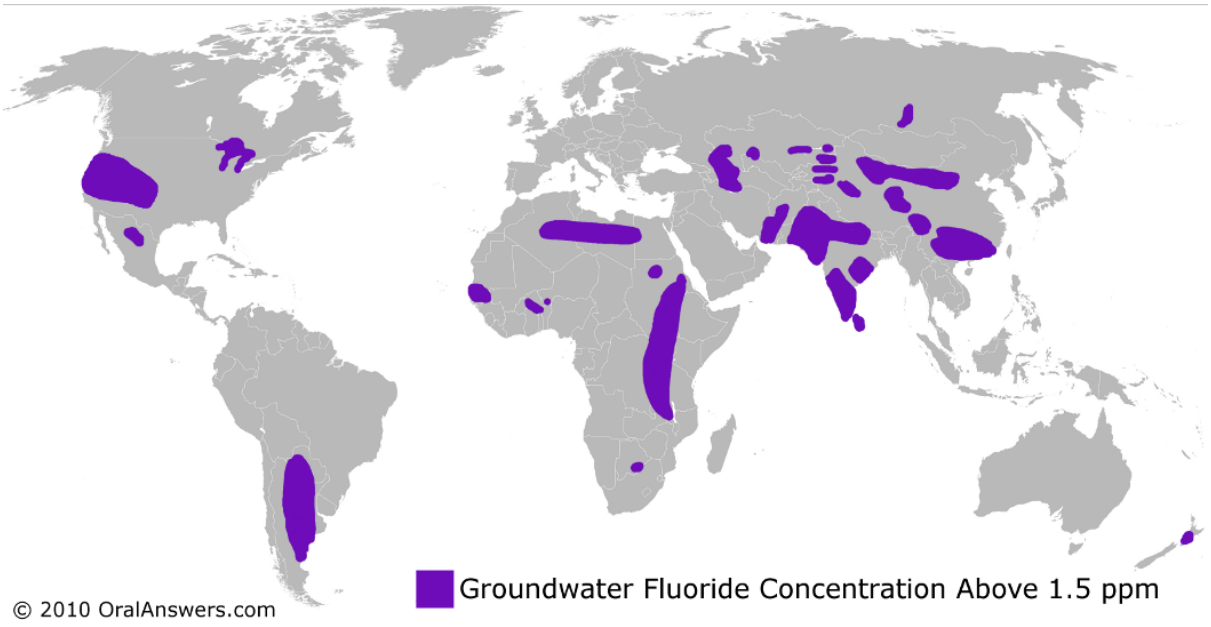
Crystals of Fluoride doped Hydroxyapatite found in infant formula that was withdrawn from the Australian market [Schoepf 2016, Han 2017].

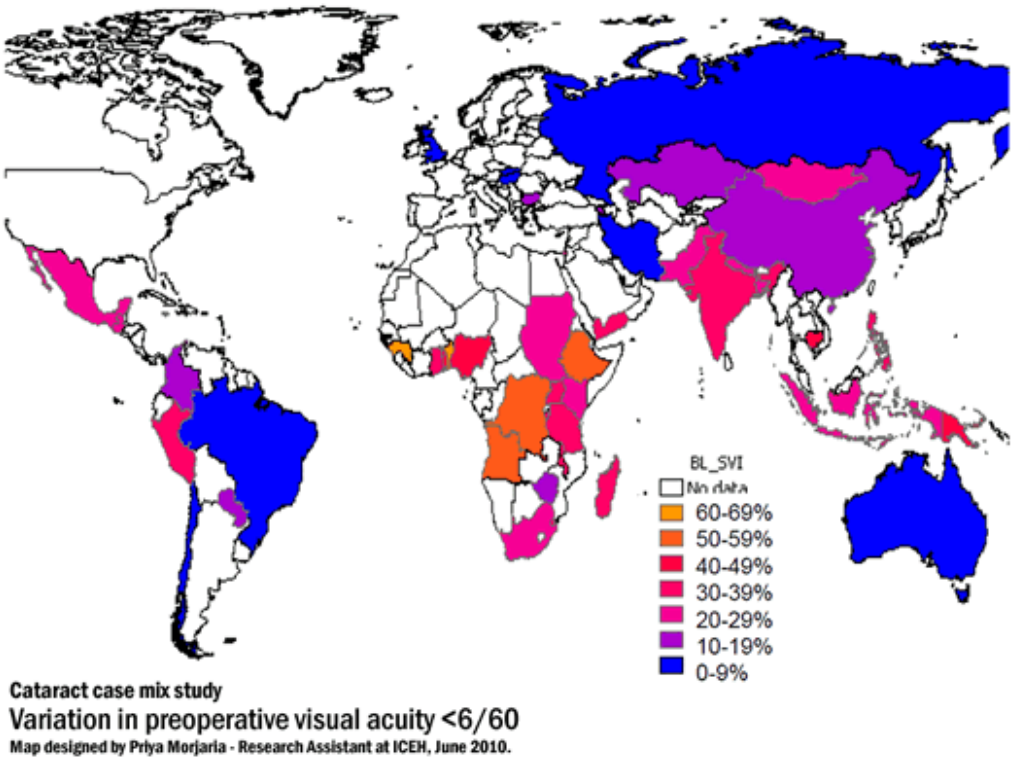


Crystals of Fluoride doped Hydroxyapatite grown by use of Silver Diamine Fluoride (above left) [Mei 2017] or by use of acidulated phosphate fluoride (APF) gel to dissolve human teeth (above right) [Kakei 2012].

Global Incidence of Cataract correlates Fluoride in Drinking Water

Comparison of global Fluoride groundwater contamination with severity of cataract prevalence demonstrates good correlation where data is available.





In addition to the groundwater, many nations are exposed to additional Fluoride hazard from use of rock salt containing up to 250 ppm Fluoride and high tea consumption.

Much higher incidence of cataracts is found in most tea-consuming countries such as India, Pakistan, Bangladesh, Myanmar, People's Republic of China, and other Southeast Asia.

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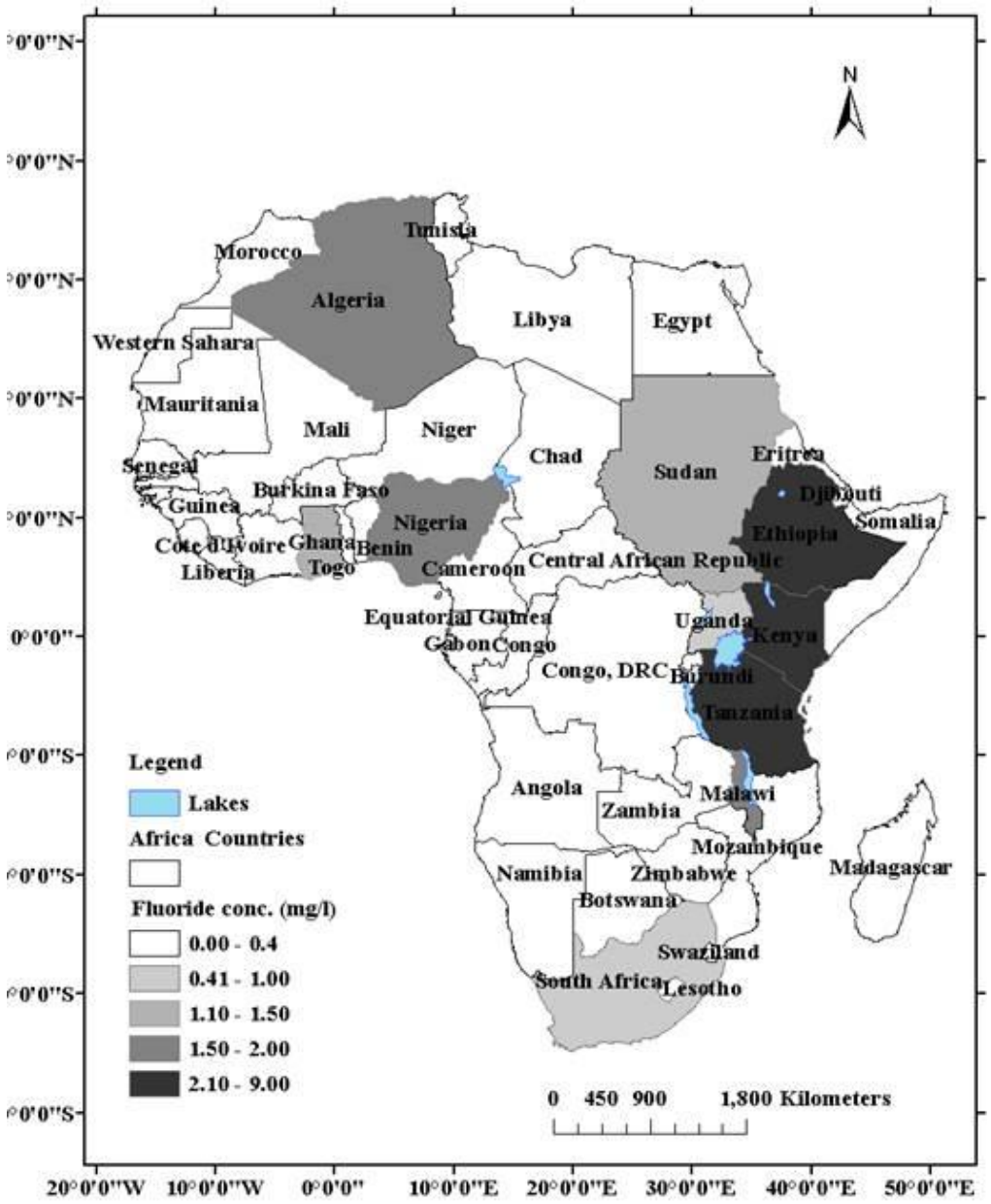


Cataract is the major cause of blindness in Africa [Steinkuller 1983, Rolfe 1997, WHO 2010].

More detailed mapping of Fluoride groundwater contamination shows that the East Africa Rift suffers the effects of a long history of volcanic venting rich in Hydrogen Fluoride. It is not surprising therefore that the Fred Hollows Foundation has chosen to perform its cataract surgery programme in Eritrea, Ethiopia, Kenya, Burundi, Rwanda.

Damage to the Cornea and Retina by Fluoride

It has been known since the 1930s that the Retina is easily damaged by Fluoride [Ashton 1957, Akleyev 2014]. Retinal oedema followed by degenerative changes in 17 out of 94 rabbits occurred within five days of giving sodium fluoride and the effect was enhanced by fasting [Sorsby 1960]. Studies of the action of Sodium Fluoride in destroying the Retina suggested that it involved inhibition of enzymes involved in glucose metabolism and ion pumps [Graymore 1959, Sorsby 1966, Vantsek 1969].

The NHMRC specifically excluded a study finding heavy iridocorneal angle hyperpigmentation and glaucoma associated with fluorosis [Aytuluner 2002]. Likewise NHMRC excluded a study finding that Fluorinated ocular or periocular corticosteroids have caused death as well as glaucoma in children [Romano 2003].

The World Health Organization recognizes Fluoride as a cause of Conjunctival Hyperaernia [WHO 2014].

Experimental generation of Cataract with Fluoride in Man and Animals

In just six weeks a man given Sodium Fluoride developed optical neuritis [Geall 1964].

Immersing mammalian eyes in Sodium Fluoride solution generates cataracts in a matter of hours [Hamar 1965].

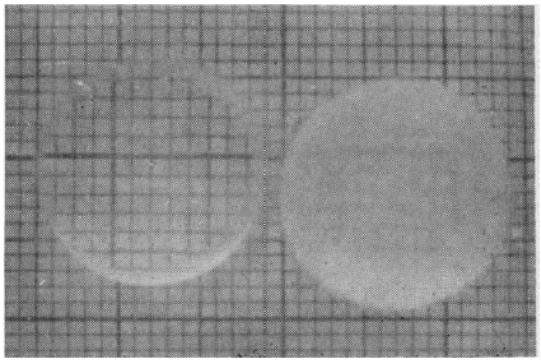


FIGURE.—*Cataract by arrest of the sugar metabolism of the lens.*—The photograph was taken after 24 hrs' perfusion; the lens on the left was in the control solution, that on the right in sodium fluoride (2/1,000). The difference in transparency between the two lenses is well shown. The experimental cataracts produced with the other inhibitors were strictly comparable.

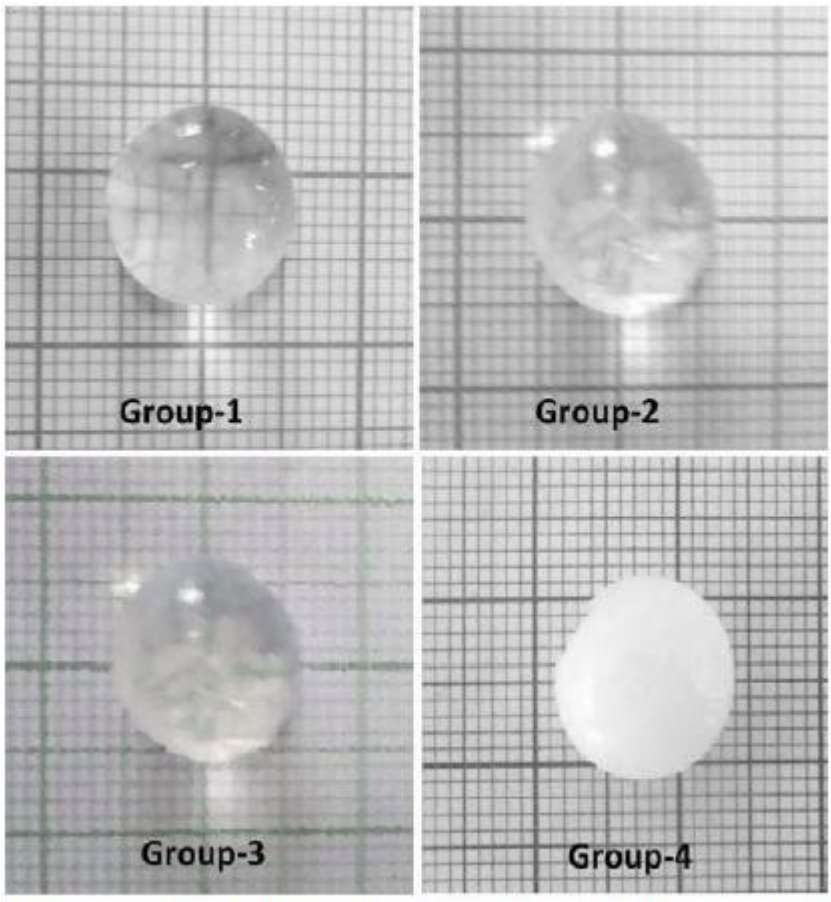


Figure 1: Fluoride induced opecification of goat eye lens (A) control, (B) 50ppm fluoride treated, (C) 100ppm fluoride treated and (C) 200ppm fluoride treated lens.

Above. In 1954 calf eyes were immersed in Sodium Fluoride solution to produce cataracts [Nordmann 1954].

Left. A similar experiment using goat eyes produced the same result [Mishra 2014].

In the experiment with goat eyes, Lipid peroxide level (LPO), and Protein carbonyl content (PC) were significantly ($p<0.001$) increased with the fluoride concentration while glutathione level (GSH) and antioxidant enzymes, superoxide dismutase (SOD) and catalase (CAT) were significantly decreased [Mishra 2014].

Forty percent of rats given commercially available spring water, containing 100 ppm fluoride, for 24 weeks showed opacifications, epithelial proliferation, and growth changes, including reduced body weight, lengths of body, femur and tail, compared to controls [Aytuluner 2003].

Hydroxyapatite crystals grow in as well as on interocular lenses

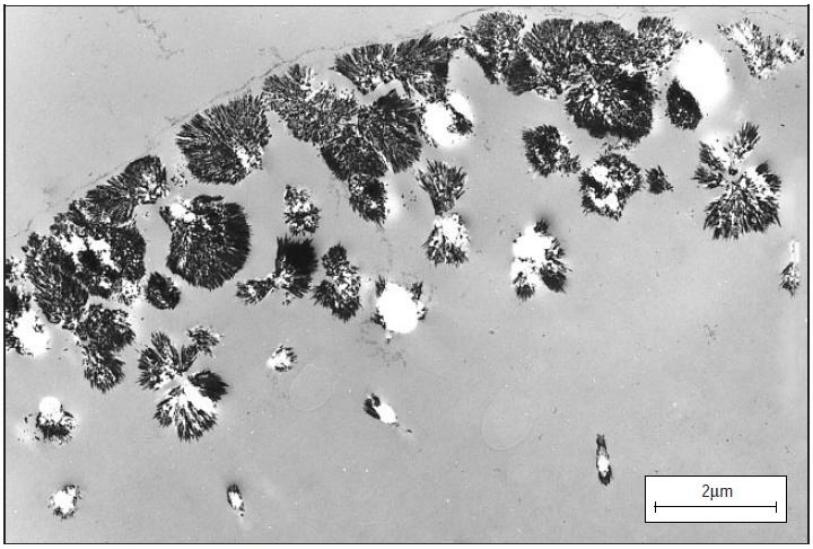


Figure 2. *Undulating surface of the lens from patient 1. Clumps of electron-dense deposits containing needle-shaped crystals were found beneath the surface (transmission electron microscopy, original magnification × 8600).*

A kinetic study showd that Hydroxyapatite crystals in intraocular lenses can be initiated from their interior through the development of sufficiently high local supersaturation, realized through the diffusion of calcium and phosphate ions [Drimtzias 2011]. Carbonate inclusion within hydroxyapatite in both intraocular and human senile cataract was observed by infrared spectroscopy [Lin 2010]. It is significant that fluorine-surface-modified and unmodified lenses for implantation in pediatric aphakia were investigated in research excluded from consideration by the NHMRC in 2007 [Thouvenin 1996]. The NHMRC also excluded a study of the mineralization of intraocular lens [Lai 2005].

Hydroxyapatite and Age-related macular degeneration (AMD)

Macula retinopathy and degenerative changes in the retina in relation to Fluoridation were reported in early studies [Waldbott 1962].

Proof of involvement of Hydroxyapatite in macular degeneration, which involves accumulation of protein and lipid containing deposits external to the retinal pigment epithelium, was found by examination of cadaver eyes using electron microscopy and x-ray diffraction [Thompson 2015]. It was observed that the Hydroxyapatite formed spherules containing amyloid beta (Aβ) peptide or complement factor proteins as well as cholesterol and other lipids.

Hydroxyapatite damage to the Eye and Alzheimer's Disease

The possible link between macular degeneration and Alzheimer's disease arises from the observation that Alzheimer's Aβ-peptide is deposited at sites of complement activation in pathologic deposits associated with aging and age-related macular degeneration [Johnson 2002]. Fluoride doped Hydroxyapatite is also present in Corpora Arenacea or "brain sand" [Wilson 2014].

Glaucoma is found five times more frequently in Alzheimer's disease patients than in aged controls [Bayer 2002].

Calcification of the lens, retina and macular can be assumed, due to reduced light transmission to the retinohypothalamic tract, to interfere with the Pineal gland melatonin regulating retina suprachiasmatic nucleus axis which is implicated in aging and Alzheimer's Disease [Wu 2005].

Accumulation of Fluoride doped Hydroxyapatite is well known in the Pineal gland [Gusek 1983, Alcolado 1986, Jengelski 1989, Schmid 1993, Luke 1997, Kunz 1998, Kunz 1999, Duffy 2003].

Risk factors for Cataract and related disease involving multiple Fluoride sources

Fluoride in drinking water causes cataract and the effect is dose-dependent. Other risks and associations with cataract have been identified and are discussed below. The Appendix lists other reported cataract risks.

Table 2. Risk factors and associations with Fluoride for Cataract and related disease

Risk	Risk Factor	Reference	Linked to Fluoride?	Fluoride Link Reference
Fluoride in drinking water		Kas'ianenko 1984 Tomar 2014	✓	
Tea drinking		Varma 2016	✓	Waugh 2016; 2017
Heavy Beer drinking			✓	Warnakulasuriya 2002 Styburski 2017,Waugh 2017a
Fluoride in Rock Salt		Chatterjee 1992	✓	
Smoker Former	3.75	Prokofyeva 2013	✓	Sutton 1986
Smoker Current	2.34 1.58	Prokofyeva 2013 Leske 1998	✓	Sutton 1986
Obesity Cortical posterior subcapsular	 1.6 2.1	Chang 2011 Younan 2003	✓	Bergman 2013 Vandenberg 2012
Diabetes > 10 years	2.72	Saxena 2004 Prokofyeva 2013	✓	Bergman 2013 Pain 2015c
Fasting Blood Glucose level	1.79	Kanthan 2011	✓	Pain 2015c
Asthma or Chronic Bronchitis	2.04	Prokofyeva 2013	✓	See Fluorocarbon propellants
Cardiovascular Disease	1.96	Delcourt 2000 Prokofyeva 2013	✓	Pain 2016
Angina	2.1	Younan 2003	✓	Pain 2016
History of Coronary Heart Disease	2.25		✓	Pain 2016
Schizophrenia	10.6	Ruigomez 2000	✓	Pain 2017b
Diabetes		Klein 1998	✓	Fluegge 2016
Diabetes mellitus	2.9	Hennis 2004		Pain 2016
Chlorpromazine > 90 days	8.8	Prokofyeva 2013	✓	
High plasma Homocysteine		Sen 2008	✓	Medhi 1990, Weiss 2002
Decreased plasma Folate		Sen 2008	✓	Ratan 2008, Susheela 2010
Decreased plasma Vitamin B12		Sen 2008	✓	Susheela 2010
High glycosylated Haemoglobin Cortical Posterior subcapsular	 3.60 4.93	Klein 1998	✓	Susheela 1981
Decreased plasma cholesterol		Donnelly 1995	✓	Wang 1991
Hypothyroidism (Thyroid Hormone Therapy)		Chang 2011	✓	Peckham 2015
Hypercalcemia		Dawson 1981	✓	Sato 2016
Tetrafluoroethylene		NTP 1997	✓	Fluorocarbon
Flonicamid		Fed Reg 2003	✓	Fluorocarbon
Flufenacet		Fed Reg 1998	✓	Fluorocarbon
Inhaled Corticosteroids > 5 years	3.25	Cumming 1997, Leske 1998, Jick 2001	✓	Valic 1977
Occupational Inhalation		Karczewicz 1989	✓	
Pre-existing posterior subcapsular opacities	6.67	Leske 1998	✓	

Asteroid Hyalosis

Hydroxyapatite forms precipitates in the vitreous humor of the eye, sometimes only unilaterally, in the condition known as Asteroid Hyalosis, previously named Hyalitis [Jervey 1965, March 1975, Winkler 2001, Komatsu 2003, Kador 2008].

Based on Fluoride analyses available for lens calcification, we can anticipate future research will identify Fluoride in the mineral content of these “asteroids”.

Diabetes, metabolic disorders and Cataract

Metabolic cataracts include those associated with Diabetes Mellitus, Galactosaemia, Hypercholesteraemia, Lipidemia, Endocrinological cataract associated with Hypothyroidism and Hypercalcaemia and cataracts associated with certain skin diseases such as Atopic Dermatitis [Dawson 1981, Kador 2008].

Elevated Plasma albumin, bilirubin, calcium, cortisol, glucose, sodium and γ- glutamyl transpeptidase levels in cataract patients were linked to liver disease [Donnelly 1995]. Fluoride is a known hepatotoxin.

Diabetes is associated with severe mitochondrial disorders such as Kearns-Sayre syndrome and Mitochondrial Encephalomyopathy, Lactic Acidosis, and Strokelike episodes (MELAS). Mitochondrial forms of diabetes mellitus occur in conjunction with hearing loss, myopathy, seizure disorder, strokelike episodes, retinitis pigmentosa, external ophthalmoplegia and cataracts. There is evidence of maternal inheritance [van den Ouweland 1992, Khardori 2017]. Increased glycated haemoglobin level was associated with increased risk of nuclear and cortical cataracts in those with diabetes [Klein 1998]. Fluoride is known to cause Diabetes [Pain 2015c].

Diabetes is associated with low birth weight and while there is a genetic component to low birth weight [Wang 2016], Fluoride is known to cause low birth weight in exposed populations [Hart, MacArthur 2013].

Prevalence studies on diabetes complications reported up to the early 1990s gave widely variable figures. These have been reviewed in two studies and include figures ranging from 9 to 16 percent for cataract, 7 to 52 percent for retinopathy, 6 to 47 percent for neuropathy, 6 to 30 percent for nephropathy, and 1 to 5 percent for macroangiopathy [Mbanya 2003; Rolfe 1997].

Women diabetics suffer higher rates of cataract and earlier surgery than men. Risk factors from the Framingham heart study that were significantly associated with cataract formation included: elevated blood sugar, elevated blood pressure, increased serum phospholipids, decreased pulmonary vital capacity, small stature, and less than seven years of schooling [Kahn 1977].

A patient suffering diabetes, ischemic heart disease, hypertension and renal dysfunction and taking insulin developed hydroxyapatite cataracts 4 months after implantation of an intraocular lens. Another patient, diabetic and taking insulin developed hydroxyapatite cataracts 9 months after implantation. Another patient in good overall health developed hydroxyapatite cataracts 15 months after implantation. All patients received dexamethasone sodium phosphate eye drops. [Yu 2001].

Cataract and Smoking

Cataracts associated with smoking have been reported to be dose-dependent [Klein 1993, Solberg 1990, West 1995, Leske 1998, Krishnaiah 2005, Prokofyeva 2013].

Australian data indicated a population attributable risk for smoking and nuclear cataract of 17%, and a risk of 10% for UV-B exposure and cortical cataract [McCarty 2000, Robman 2005].

Fluorinated Organic Compounds including Drugs and Propellants cause Cataract

Treatment of glaucoma with potent, long-acting anticholinesterase agents including isoflurophate, diisopropyl fluorophosphates, for 6 months or longer carries high risk of the development of a specific type of cataract, which begins as anterior subcapsular vacuoles. The incidence of lenticular opacities was as high as 50% with headache, brow pain, blurred vision, phacodinesis, pericorneal injection, congestive iritis, various allergic reactions, and rarely, retinal detachment [Gilman 1985, AMA 1983].

Fluorocarbon anaesthetics are known to be metabolized to yield high concentrations of serum Fluoride ion.

Cataract due to the methoxyflurane anaesthetic metabolite calcium oxalate-monohydrate (Whewellite) has been observed with the pathway for the biotransformation also yielding ionic fluoride [Bullock 1974]. Calcium Oxalate has also been reported in the lenses of patients with Morgagnian cataracts [Zimmerman 1958].

Drugs used in treatment of asthma are known to cause cataracts, including Flunisolide, Fluticasone Anon 2007].Fluorocarbon propellants used to deliver drugs to patients via “puffers”, including asthma sufferers, are known to pose serious health hazards due to their metabolism to free Fluoride ion [Silverglade 1972, Valic 1997, Cumming 1997, Jick 2001]. The observed higher incidence of cataract in users of inhaled drugs is therefore closely associated with the propellant, often overlooked in epidemiology studies of the drugs in question.

Tetrafluoroethylene has been demonstrated to cause cataracts [NTP 1997].

Flonicamid, an insecticide, causes atrophy of striated muscle fibers, cataract and retinal atrophy observed in the high dose female rats [Fed Reg 2003]. Fluazifop-p-butyl causes cataracts in 8 out of 12 dogs [Virgo 1982].

Flufenacet, an herbicide has LOEL of 50 ppm [7.4 mg/kg/day] for males 200 ppm [38.4 mg/kg/day] for females based on cataract incidence and severity [Fed Reg 1998]. Eye effects also included ocular scleral mineralization.

Fluoroquinolones including ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin, norfloxacin, and ofloxacin cause uveitis [Wefers Bettink-Remeijer 2009, Butler 2012, Hinkle 2012, Eadie 2014].

Voriconazole increases serum Fluoride to damaging levels. Among the numerous harms caused by this drug are colour vision change, persistent or severe blurred vision or sensitivity to light.

Visual hallucinations have been found associated with use of fluoxetine and other selective serotonin reuptake inhibitors [Bourgeois 1998, Schuld 2000].

Fluorinated corticosteroids cause death as well as glaucoma in children [Romano 2003].

Cataract association with Cancer

As previously reviewed, Fluoride doped Hydroxyapatite has been shown to cause malignant cancer of the Breast and Thyroid [Pain 2015].

In Taiwan, an increased incidence of breast, liver, and head and neck cancers was observed in patients presenting with Early Onset Cataract [Chiang 2014].

Breast cancer associated with cataracts has also been observed in India [Faridi 2017].

Reactive oxygen species lead to lens opacification through oxidative damage to lens proteins. Increased incidence of cataract is found in subjects with the null genotype of Glutathione S-Transferase M1 subtype (GSTM1) (odds ratio-1.51; $p<0.05$) [Saadat 2012]. The polymorphisms of GSTM1, GSTT1, GSTP1 and GSTO2 have been shown to be associated with increased risk of developing breast cancer [Sohail 2013]. Raised serum sialic acid, caused by Fluoride [Needham 2010], is found associated with both cataract and Osteosarcoma [Sandhu 2011].

Cataract association with increased risk of Death

In non-diabetic women the age adjusted cataract mortality hazard ratios were: nuclear opacity (1.8), cortical opacity (1.9), and posterior subcapsular opacity (2.1). There was no significant difference in mortality risk for men. Among diabetics, the mortality was significantly higher in both men and women with cataract with age and sex adjusted hazard ratio of 2.6 [Reidy 2002].

Other mortality studies have been contradictory. When confined to nuclear cataract, there appears to be a more consistent trend across studies with 11 out of 15 showing significantly increased risk of death. Unfortunately many studies do not distinguish the type of cataract and few refer to calcification [Khanna 2013].

Nuclear opacity (RR, 1.40; 95% CI, 1.12–1.75) and cataract surgery (RR, 1.55; 95% CI, 1.18–2.05) were associated with increased all-cause mortality and with cancer deaths [Clemons 2004].

Higher risks were found for black Barbados residents with cumulative 4-year mortality varied with lens types, increasing from 3.2% for those without cataract to 6.0% for cortical-only, 8.8% for nuclear-only, and 20.9% for mixed opacities. Coexisting diabetes further increased mortality: people with mixed opacities and diabetes had a 2.7-fold increased risk of death [Hennis 2001].

Mechanisms of Fluoride induced Cataract

The toxic effects of fluoride in the eye appear to follow universal mechanisms found in a wide variety of cells [Barbier 2010, Agalakova 2012].

The mechanisms of fluoride toxicity can be summarized [Pain 2017a] under the following headings:

- Mutation and abnormal embryo development with altered expression
- Endocrine disruption
- Altered enzyme levels and enzyme inhibition
- Oxidative stress with generation of reactive oxygen species and radicals
- Apoptosis via mitochondria mediated and Caspase dependent pathways
- Disruption of ion channels affecting pH, cation and anion balance
- Physical damage from calcification

Fluoride Disrupts Phosphate Pathways

Metabolic disturbance, chronic hypocalcemia and hyperphosphatemia, calcitonin reduction, vitamin D insufficiency can be responsible for cataract formation [Stein 1980, Ogiso 1990, Brown 2015].

Elevated phosphate levels have been measured in the aqueous humor of cataract patients compared to glaucoma patients. Variation of various phosphatase levels were also found [Latarya 2012].

Cataract calcification will of course be facilitated by elevated phosphate via enhanced crystal growth of Fluoride doped Hydroxyapatite.

Measurement of Alkaline phosphatase is often used to detect systemic toxic reaction as it is an indicator of abnormal bone turnover and hepatobiliary diseases [Mallik 2016].

Alkaline phosphatase (10.6%), acid phosphatase (24.09%) increased in brains of mice after administration of sodium Fluoride [Reddy 2009].

Fluoride inhibits acid phosphatases (protein phosphoseryl and phosphothreonyl phosphatases or PSPs), which are necessary for the phosphorylation of glucose, adenosine triphosphatase, and enolase, the enzyme responsible for

the formation of phosphopyruvic acid from 2-phosphoglyceric acid [Nordmann 1954]. Sodium Fluoride is sold as a reagent of choice to irreversibly inhibit Acid Phosphatases [Thermo Fisher Scientific 2017].

Mechanistic studies identify Fluoride attack on the metal ion centres in acid phosphatases, notably Iron and Zinc, preventing coordination of water molecules essential for their function [Pinske 1999, Srivastava 2015].

Acid phosphatase and lipid peroxidation have been measured in human cataractous lens epithelium. Lipid peroxidation in mature cataractous lens epithelium was correlated with increased permeability of the plasma membrane [Vasavada 1993].

Fluoride inhibition of acid phosphatase is also related to male infertility [Nag Das 1984] and prostate disease [Reiner 1955].

Congenital Cataracts Facial Dysmorphism Neuropathy Syndrome involves a single-nucleotide substitution producing a nonfunctional protein in formation of Fcp1 which is the main serine phosphatase for the C-terminal domain of eukaryotic RNA polymerase II, which regulates transcription by recruiting different factors to nascent mRNA [Varon 2003].

Alkaline phosphatase, elevated in cataract patients [Donnelly 1995, Fernandes 2011], is also greatly increased in osteosarcoma, a neoplastic proliferation of osteoblasts [Krook 1998].

Alkaline Phosphatase is an enzyme which catalyses the hydrolysis of a number of phosphate esters, transferring the phosphate group to an acceptor molecule. Fluoride has been shown to increase serum alkaline phosphatase that results in increased deposition of Hydroxyapatite [Farley 1983, Khokher 1990, Shanthakumari 2004, Fernandes 2011]. Chronic industrial airborne Fluoride exposure increased worker serum alkaline phosphatase (ALP) and superoxide dismutase (SOD).

Raised levels of alkaline phosphatase induce hypocalcemia, which triggers parathyroid hyperactivity [Krook 1998].

Hypoparathyroidism is an uncommon condition characterized by spontaneously lowered synthesis and/or secretion of parathyroid hormone (PTH), which results in profound hypocalcemia and hyperphosphatemia [Liao 2016]. It is a result of prevention of calcium reabsorption in renal tubulus and bone matrix, as well as insufficiency of the synthesis of 1,25- dihydroxyvitamin D3 [1,25(OH)2D3] from its inactive precursor 25- hydroxyvitamin D.

Fluoride induces cell injury in both osteoblasts and osteocytes, initiating a repair response that results in increased alkaline phosphatase [Krook 1998]. An increase of serum alkaline phosphatase results in enhanced hydroxyapatite deposition measured as increased bone mass following fluoride dosing. Unfortunately, it seems little attention has been paid to the more difficult task of measuring the enhanced deposition of hydroxyapatite in soft tissues.

Alkaline phosphatase is inhibited by Fluoride in the gut of the silkworm [Miao 2005].

Rats treated with Fluoride in drinking water for 90 days show high serum alkaline phosphatase accompanied by hypocalcemia and hyerphosphatemia [Gupta 2016].

Fluoride causes Oxidative Stress leading to Cataracts

Lipid peroxidation is known to cause cataracts from research that was specifically excluded from consideration by the NHMRC in 2007 [Babizhayev 2004]. Further research by the same group found that oxidative stress in mitochondria induces generation of reactive oxygen species (ROS) and redox imbalance of the eye lens leading to human cataract formation with formation of phospholipid hydroperoxides as a common basis for cataract disease [Babizhayev 2011].

Various oxidative stress markers have been studied in human cataract patients [Sawada 2009, Tomar 2014]. A study in Jaipur, India, compared randomly selected patients with cataract from a high Fluoride region, ground water F>2.5

ppm, with age- and sex-matched control patients with cataract from a low-fluoride region, ground water F<1.5 ppm [Tomar 2014]. Oxidative stress markers studied were Lipid peroxide levels (LPO), protein carbonylation (PC), superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH), serum F estimations, and the measurement of trace metallevels (Cu, Zn, Se, and Fe). Significantly higher LPO and PC were found in the high-F region subjects in both serum and lenses. Antioxidant enzyme SOD and GSH were found to be markedly decreased in the blood and lenses of the high-F region subjects [Tomar 2014].

Methylglyoxal is implicated in cataract development by inducing endoplasmic reticulum stress in human lens epithelial cells, and activating an unfolded protein response leading to overproduction of ROS and altering the cellular redox balance toward lens oxidation [Palsamy 2014].

Sialic acid, is a marker for inflammation and oxidative stress and is released from the terminal oligosaccharide chain of some glycoproteins and glycolipids. Cataract is associated with the increase in serum sialic acid level [Mallik 2016]. Fluoride is known to increase sialic acid levels [Susheela 1982].

Gamma glutamyl transpeptidase is another marker for oxidative stress that is elevated in cataract as well as liver and cardiovascular disease [Emdin 2005, Mallik 2016].

Fluoride Disrupts Ion Transport

As discussed above, Fluoride disrupts the anaerobic metabolic pathways which provide the energy for ion transport.

The lens excretes sodium and concentrates potassium in cataracts [Mallik 2016].

Elevated magnesium was found in the serum of cataract patients [Ringvold 1988].

Light damages cation pump activity via superoxide formation, attenuated by ascorbate in the aqueous humour [Varma 1984].

Alteration in ion transport can lead to variation in hydration of the lens, leading to myopia and glaucoma.

Attempted amelioration of Cataract

Antioxidant vitamin supplements have been investigated as a means of slowing, if not preventing, eye disease including cataract and macular degeneration.

Vitamin E showed some promise in one study [Vitale 1993] but proved a risk factor in another [McCarty 2000].

It has been suggested that in Turkey, with the maximum per capita use of tea in the world, supplying up to 376 mg of caffeine per day, that the antioxidant properties of caffeine might lower incidence of cataract [Varma 2016].

Evidence that is consistent with Fluoride inhibition of metallo-enzymes is the observation that Zinc supplements provide a protective effect [Clemons 2004].

Salicylates lower plasma levels of tryptophan and prevent binding to the lens, significantly retarding UV cataract formation in both diabetics and non-diabetics.

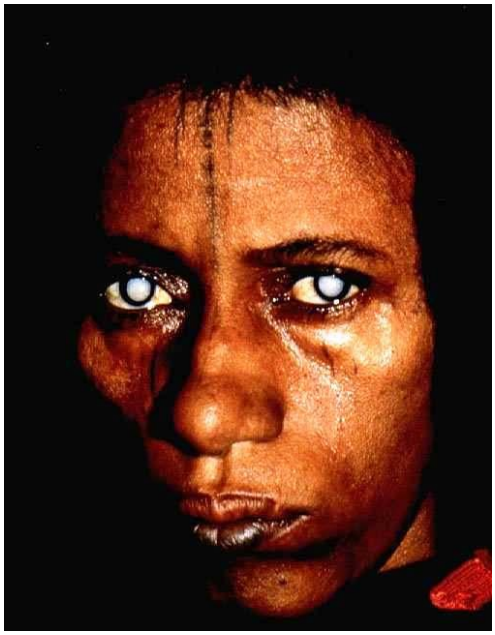
Significantly lower incidences of nuclear cataracts 5 years later occurred in those who took thiazide diuretics (OR=0.79, 95% CI 0.63, 1.00) and aspirin (OR=0.76, 95% CI 0.61, 0.95) at the baseline examination [Klein 2001] with the aspirin result contradicting increased risk found elsewhere [Christen 2001].

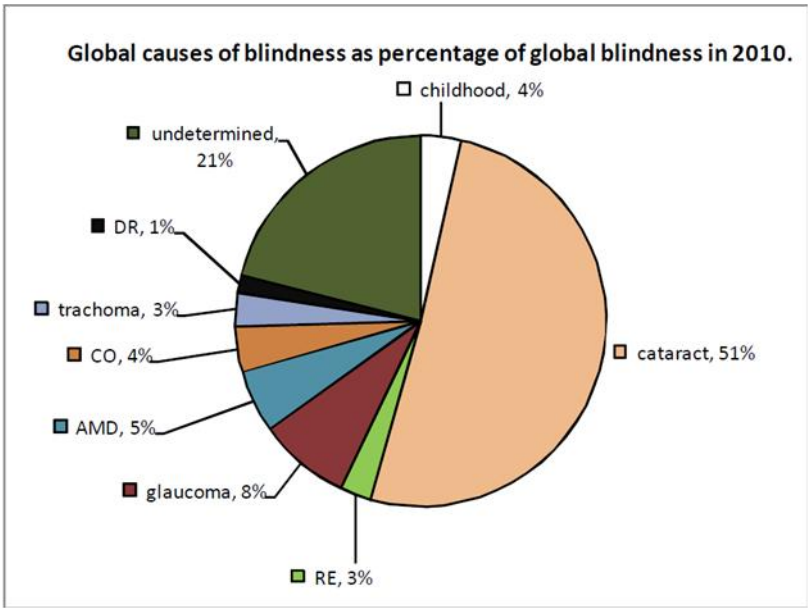
Conclusion

The only safe place for Hydroxyapatite storage is in bone. When deposited in the soft tissues, it resembles asbestos, causing numerous diseases including those leading to blindness and premature death.

Fluoride doping exacerbates this calcification and every effort must be made to reduce Fluoride exposure in the diet. The deliberate addition of Fluoride to milk or salt is reckless.

Elimination of deliberate water Fluoridation programmes and defluoridation of contaminated groundwater will greatly reduce the global burden of preventable eye disease.





Fluoride contribution to incidence of age-related macular degeneration, diabetic retinopathy, glaucoma and a proportion of “undetermined cause” global blindness should be recognized in epidemiology studies and future plans to remedy the suffering.

The World Health Organization should update its warnings about Fluoride as a chemical of concern with added emphasis on loss of vision so that the few remaining countries that have not banned water Fluoridation will have extra incentive to act [WHO 2010;2014].

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Appendix: Risk factors for Cataract other than Fluoride

Risk factors for Cataract include physical injury to the eye, exposure to solar radiation (UV-B), intense heat and dehydration, rare genetic disorders and dietary supplements, not discussed in any detail here.

Below is a brief tabulation of references that discuss identified risk factors for cataract that do not involve Fluoride. However it is worth noting that some multivitamin preparations do contain deliberately added Fluoride, despite the USFDA ban on the practice.

Table 1. Cataract Risk Factors not Associated with Fluoride

Risk	Risk Factor	Reference
Family History of Cataract	1.39	Leske 1998
Multivitamin / Mineral supplements	2.00	Maraini 2008
Selenite		David 1984, Hightower 1987, Mishra 2013
Vitamin C		Rautiainen 2010
Lycopene	1.43	Valero 2002
Retinol	1.52	
Solar, UVB radiation, X-rays	2.26	Hollows 1981 Vrensen
Galactosemia		Dawson 1981
Dexamethasone sodium phosphate eye drops		Yu 2001
Vitrectomy		Shui 2009
Australian Aboriginal	1.37	Randall 2014
Age		
Female	1.1 - 1.5	Chang 2001, Laitinen 2009
Genetic Predisposition	1.51	
UVB radiation	2.26	Hollows 1981 Vrensen
Ambient Temperature		Sasaki 2002
Latitude (light intensity)		Javitt 1994
Bone Marrow Transplantation radiation		Aristei 2002
Measles, Mumps and Rubella Vaccination		Ferrini 2013
Anti-Hypertensive drugs	3.0	Younan 2003
Gout medications, Allopurinol	2.32	Leske 1998
Vitamin E		McCarty 2000
Aspirin	1.2	Cumming 1998, Christen 2001
Amitriptyline	2.03	Klein 2001
Oral hypoglycaemic agents	2.06	Klein 2001
Insulin	3.38	Klein 2001

The cataracts associated with bone marrow transplantation are thought to be caused by the radiation [Aristei 2002].

X-rays were noted to induce cataracts in human subjects during the first two decades of the 20th century.

Solar radiation and especially its Ultraviolet component produces significantly more cataracts in people over 65 years of age living in regions with more hours of sunshine. Comparison of human lenses removed for cataract in Rochester,

New York, Tampa, Florida, and Manila, The Philippines revealed a significant correlation between the prevalence of black cataracts, proximity to the equator, and outdoor occupation.

Black or brown cataracts are different to mineralized cataracts and exhibit damage to protein and organic structure and are formed of brown pigments from tryptophan (significantly elevated in UV cataract patients) and free radical cross-linking of lens proteins in the absence of adequate sulfhydryl groups in glutathione. Tryptophan and its metabolite, kynurenine, bind to lens protein.

Young children with the inborn error of metabolism, galactosaemia, develop cataract as part of this fatal disorder. It has been postulated that the excess galactose is metabolized by aldose reductase to dulcitol, which accumulates in the lens and leads to cataract formation. Similarly, it has been shown that male subjects who lack glucose-6-phosphate dehydrogenase in their red blood cells have an increased rate of presenile cataract formation in adult life [Dawson 1981].

Calcium-activated proteolysis has been studied in the lens nucleus during selenite cataractogenesis [David 1984, Hightower 1987, Mishra 2013].

From: Christine Massey [redacted]
Sent: September 12, 2017 3:42 PM
To: Thompson, Allan; Downey, Johanna; Groves, Annette; Innis, Jennifer; Shaughnessy, Barb; Jeffrey, Linda Mayor; Gibson, Grant; Medeiros, Martin; Miles, Gael; Moore, Elaine; Palleschi, Michael; Crombie, Bonnie; Carlson, George; Fonseca, Chris; Iannicca, Nando; Kovac, John; Mahoney, Matt; McFadden, Sue; Parrish, Carolyn; Ras, Karen; Saito, Pat; Starr, Ron; Tovey, Jim; Loh, Lawrence; Polsinelli, Nancy; Szwarc, David; Smith, Janette; Hennings, Jeff; Jim Nardi; ZZG-RegionalClerk; O'Connor, Patrick; Burkiewicz, Justyna; ZZG-WaterQualityInquiries; Sprovieri, John; Hau, Monica; Ward, Megan; Bingham, Kate; Hopkins, Jessica; ehoskins.mpp@liberal.ola.org; Mark Corlett; Vladimir Gagachev
Subject: pioneer fluoride/caries investigator admitted under oath: studies seriously flawed

Dear Peel Council / CWFC Members, Medical Officer Hopkins, Commissioner Polsinelli, Commissioner Smith, CAO Szwarc, Regional Clerk Lockyer, Mr. Hennings, Mr. Nardi and Health Minister Hoskins,

[Please include this email in the agenda of the next meeting of the Community Water Fluoridation Committee, or the next Regional Council meeting involving fluoridation or oral health.]

H. Trendley Dean, DDS was the chief dental officer at the US Public Health Service and responsible for the "classic" fluoride/caries studies done in the 1940's.

When cross-examined before the Public Utilities Commission of the State of California in Oroville on October 20-21, 1955, under oath Dr. Dean admitted to serious weaknesses in those studies.

None of them were randomized controlled studies, the water sources were not consistent, there was no consideration for nutrition, oral hygiene or dental care, etc., etc.

Former Principal Dental Officer for the Auckland Health District, New Zealand, John Colquhoun, BDS, PhD wrote about Dean's studies, and the Grand Rapids-Muskegon trial, in a 1990 article published in what is now known as the Australian and New Zealand Journal of Public Health:

> *"...*
> *Yet data from earlier caries surveys in hundreds of communities were available to Dean. The question arises: why did Dean present only 21 of them? ...*
>
> *... A critical examination of other early fluoridation trials revealed similar flaws, also detected by others. The basic limitations of the classic fluoridation trials were described over 30 years ago: poor research design including inadequate experimental controls. poor adjustment of sample sizes, lack of 'blind' examinations to safeguard against examiner bias and variability, inadequate baseline measures and negligible statistical analyses." Diesendorf has subjected the Australian fluoridation trials to similar critical analysis. Textbook accounts, both of the caries-fluoride relationship and of the fluoridation trials, do not reveal the flaws which characterize most of the early research."*
> Flawed foundation: a re-examination of the scientific basis for a dental benefit from fluoridation

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RECOMMENDED
DIRECTION REQUIRED _____
RECEIPT RECOMMENDED ✓_____

The Total Daily Intake section of Health Canada's Guidelines for Canadian Drinking Water Quality Technical Document on Fluoride is based on Dean's studies and "guesstimates" (see page 9), and the Guideline contains numerous references to Dean's studies, i.e. page 54:

> *"The critical studies for defining the dose–response relationship between total daily fluoride intake and dental caries/fluorosis were found to be those of Dean et al. (1941, 1942)..."*

Why I Changed My Mind on Fluoridation, by Dr. John Colquhoun:

> *"To explain how I came to change my opinion about water fluoridation, I must go back to when I was an ardent advocate of the procedure. I now realize that I had learned, in my training in dentistry, only one side of the scientific controversy over fluoridation..."*
>
> *Perspect Biol Med. 1997 Autumn;41(1):29-44.*
> *https://www.ncbi.nlm.nih.gov/pubmed/9394474*
> *Full text: http://www.fluoridation.com/colquhoun.htm*

Best wishes,
Christine Massey, M.Sc.
Fluoride Free Peel

From: Fluoride Action Network Australia [mailto:contact@fluoridealertaustralia.org]
Sent: September 13, 2017 4:30 AM
To: Thompson, Allan; Linda.Jeffrey@brampton.ca; Bonnie.Crombie@mississauga.ca; frank.dale@mississauga.ca; Sprovieri, John; McFadden, Sue; Downey, Johanna; Groves, Annette; Innis, Jennifer; Shaughnessy, Barb; Gibson, Grant; Miles, Gael; Moore, Elaine; Palleschi, Michael; Carlson, George; Fonseca, Chris; Iannicca, Nando; Kovac, John; Mahoney, Matt; Parrish, Carolyn; Ras, Karen; Saito, Pat; Starr, Ron; Medeiros, Martin; Tovey, Jim; Lockyer, Kathryn; Hopkins, Jessica; Loh, Lawrence; Smith, Janette; Polsinelli, Nancy; Hennings, Jeff; Szwarc, David; O'Connor, Patrick
Cc: [redacted]
Subject: RE: Fluoride Action Network Australia Submission on Flawed Review of Water Fluoridation from the 2017 National Health and Medical Research Council (NHMRC)

Merilyn Haines B App Sc Med Lab Tech
58 Vied Rd Pallara
Queensland Australia 4110

OPEN LETTER

September 13th, 2017

RE: Flawed Review of Water Fluoridation from the 2017 National Health and Medical Research Council (NHMRC)

Dear Mayors, Regional Councillors, City Solicitors and City Staff:

My name is Merilyn Haines and I live in Brisbane, Australia. I have worked as a medical laboratory scientist for over 30 years (now retired) and I first started researching fluoridation over 20 years ago when a close family member developed severe dermatitis from fluoridated water. I have been actively working to educate members of the public and our government leaders on the many health harms associated with ingested fluoride.

I am writing you today to inform you that **as leaders, you have a judiciary duty of care to protect the health and well-being** of the 1,400,000 residents in which you serve.

On July 6th, 2017 your staff was asked to look into the latest Australian government's review from the National Health and Medical Research Council (NHMRC) and report back to Council.

I have prepared an extensive critique and analysis of the said NHMRC review.

Upon learning this, Liesa Cianchino, Chair of the Concerned Residents of Peel to End Fluoridation reached out to me and requested that I personally send you this important information for your review.

Please find attached my press release of August 3 and a report highlighting my 23-point critique of the NHMRC's defence of this discredited policy.

Fluoride Action Network have kindly uploaded these documents to their website and they can be viewed at the following links -

REFERRAL TO _____
RECOMMENDED
DIRECTION REQUIRED _____
RECEIPT RECOMMENDED ✓_____

▪ **Press Release from Fluoride Action Network Australia**
http://fluoridealert.org/wp-content/uploads/fan-australia.nhmrc_.fluoridation-critique.exec_.summary.8-3-17.pdf

▪ **Full Report on NHMRC review**
http://fluoridealert.org/wp-content/uploads/fan-australia.nhmrc-fluoridation-critique-8-3-17-1.pdf

In this analysis, 23 specific examples of NHMRC manipulations have been documented. Many of these by themselves should disqualify the NHMRC 2017 review from serious consideration, but in combination should question the very existence of the NHMRC as a body that can be relied upon by the public and decision-makers to provide objective analysis of government policy.

A brief summary of these 23 examples are listed below.

Make no mistake, this latest attempt by the NHMRC to mislead the Australian public and decision makers that water fluoridation is safe, effective and ethical will, in no uncertain terms, be challenged by many professionals and well-informed citizens from around the world demanding a **Royal Commission investigation** of both the review itself and the need for establishing a non-governmental agency to objectively review the science underpinning controversial government public health and environmental policies.

Red flags are waving across the miles to alert you to these important facts as presented in my critique and analysis of the NHMRC review.

Today, citizens from around the globe are becoming much better informed and **demanding greater scrutiny and accountability** from all levels of government on **issues affecting human health** and the **environment** and **will hold to account all proponents who continue to deceive the public at large on the safety and efficacy of fluoridation.**

I trust this information will serve you well in your deliberations as the Region of Peel is being challenged on the **safety, efficacy and legality** of artificial water fluoridation.

Respectively Submitted,

Merilyn Haines
Chair Fluoride Action Network Australia Inc
Founding Member Worldwide Alliance to End Fluoridation

A brief summary of the 23 examples of what the NHMRC has done -

1. Stacked the fluoride review committee with fluoridation lobbyists and advocates.
2. Broke a promise that it would include experts opposed to fluoridation.
3. Secretly commissioned a new study on dental effects (previously listed as “out of scope”), when the 2015 Cochrane Collaboration review didn’t deliver a convincing pro-fluoridation position.
4. First misled about its knowledge of a new thyroid study (Peckham et al., 2015) and then dismissed its findings, reaching a biased and false position that there is no evidence that fluoride interferes with thyroid function.

5. Falsely claimed a low-quality IQ study (Broadbent et al, 2014) was a high-quality study.
6. Downplayed, dismissed or excluded most other IQ studies and evidence of fluoride's neurotoxicity.
7. On flimsy grounds excluded a significant study linking fluoridation to ADHD – then failed to even acknowledge its existence.
8. In 2007, the NHMRC used a *promised* study in a Letter-to-the-Editor to negate an unrefuted Osteosarcoma study (Bassin, 2006) to claim there was no link to cancer. Then in its 2017 review the NHMRC failed to acknowledge that the promised study failed to refute the Bassin study but still continued to maintain no evidence of a link between fluoridation and cancer.
9. Selected a publication cut – off date for studies (that would be considered) that would exclude a very significant review by the US NRC (2006) and the Bassin (2006) study that were not given due consideration in its 2007 review.
10. The NHMRC 2017 review based its claims of safety largely on its 2007 review, however, its 2007 review was largely a copy of the 2000 York University review, which according to the York Review's Professor Sheldon did NOT show fluoridation to be safe!
11. Obfuscated on chronic kidney disease even though it is aware that poor kidney function increases uptake of fluoride into the bones poses risks over a lifetime. Such cumulative risks – and the special plight of those with poor kidney function –have never been investigated by NHMRC.
12. On another but related matter, the NHMRC endorsed doubling children's upper safety limits for fluoride ingestion (using data from the 1930s) almost certainly anticipating that the pre-existing limits would be exceeded by bottle-fed infants in which formula is made up with fluoridated tap-water.
13. Used an evidence evaluation system (GRADE) on studies of fluoride's effectiveness almost certainly in an effort to disguise the fact that most of the studies reviewed were of low, or very low quality.
14. NHMRC 2017 rates tooth decay and dental fluorosis as more important end point than other health incomes, including cancer and IQ.
15. Commenced review with strict restrictions for acceptable evidence, then included a) unpublished work; b) a favourable narrative and c) an abstract.
16. Attempted to diminish known dental fluorosis harm by manipulating fluorosis ratings and raising threshold of concern.
17. Misleads the public and decision-makers by claiming fluoridation reduces tooth decay by 26- 44 % - but without indicating just how small such reductions are in absolute terms – often less than one tooth surface out of over 100 tooth surfaces in a child's mouth!
18. Dishonestly claims fluoridation is safe by excluding important studies on spurious grounds, ignoring many others, and even cherry-picking weak studies that serve their purpose (e.g. Broadbent on IQ).
19. Doesn't understand principles of toxicology – concentration is not the same as dose!
20. Perverted the principles of medical ethics by presenting a bogus ethical claim constructed by lobbyists rather than ethicists.
21. Gave an incomplete project of dubious quality a prestigious NHMRC award
22. NHMRC fluoridation public consultations have been shams.
23. The NHMRC's extraordinary effort to maintain the dubious claims that fluoridation is safe, effective and ethical, are becoming more and more desperate by the year. NHMRC 2007 was very bad, NHMRC 2017 verges on fraud.

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23. The NHMRC's extraordinary effort to maintain the dubious claims that fluoridation is safe, effective and ethical, are becoming more and more desperate by the year. NHMRC 2007 was very bad, NHMRC 2017 verges on fraud.

Fluoride Action Network Australia
August 3, 2017

A damning critique and analysis of the NHMRC's 2017 "Sham" review of water fluoridation and appeal for Royal Commission Inquiry:

23 Reasons why Australia needs a Royal Commission into the NHMRC's fraudulent fluoride review

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EXECUTIVE SUMMARY

August 3, 2017, was the deadline for very limited public comment on a draft Public Statement on Water Fluoridation by the Australian government's National Health and Medical Research Council (NHMRC). This Public Statement was drawn largely from these documents:

> 2017: National Health and Medical Research Council (NHMRC). Information Paper - Water Fluoridation: dental and other human health outcomes. July.
>
> 2016: Health Effects of Water Fluoridation: Technical Report. Report to the National Health and Medical Research Council (NHMRC), Canberra. By Jack B, Ayson M, Lewis S, Irving A, Agresta B, Ko H, Stoklosa A. August 24, 2016, (released in September). 322 pages.
>
> 2016: Health Effects of Water Fluoridation: Evidence Evaluation Report. Report to the National Health and Medical Research Council (NHMRC), Canberra. By Jack B, Ayson M, Lewis S, Irving A, Agresta B, Ko H, Stoklosa A. August 24, 2016, (released in September). 284 pages.

On behalf of the Fluoride Action Network Australia, Merilyn Haines is calling for a Royal Commission to investigate the manner in which the Australian government's NHMRC conducted its review of the safety, effectiveness and ethics of Water Fluoridation.

Haines charges that a) the 2017 NHMRC review of water fluoridation was unprofessional, unscientific, biased, highly selective, deeply flawed and prevented meaningful scientific and public input and b) other NHMRC activities - outside this review (see items 12 and 21 below) - clearly demonstrate a bias of the NHMRC (a federal government agency) in favor of both promoting and defending the practice of water fluoridation - a long-standing government policy.

In examining the manner in which the panelists were selected, the way studies were selected and excluded, the very limited opportunities for public participation and independent scientific input, Haines argues that it is hard to come to any other conclusion than that this review was designed simply to defend a long-standing government policy and not to genuinely examine the science (or lack of science) on which it is based. This is not the first time this has happened.

The NHMRC produced a very poor review in 2007 which received extensive criticism from independent scientists. To produce an even more biased and restrictive review in 2016 is even more egregious in lieu of the new science published (or updated) since 2007.

For example, on effectiveness, the 2015 Cochrane review (a gold standard when it comes to meta-analysis of health issues) found little in the way of high quality studies to demonstrate the effectiveness of fluoridation. On safety, there have now been over 300 published animal and human studies indicating that fluoride is neurotoxic. This large body of evidence has been largely ignored in the 2017 NHMRC review, even though it is being currently scrutinized by the National Institute of Health Sciences (NIEHS) and the National Toxicology Program (NTP) in the USA.

In this analysis, 23 specific examples of NHMRC manipulations have been documented. Many of these by themselves should disqualify the NHMRC 2017 review from serious consideration, but in combination should question the very existence of the

NHMRC as a body that can be relied upon by the public and decision-makers to provide objective analysis of government policy.

Here are the 23 examples:

The NHMRC,

1. Stacked the fluoride review committee with fluoridation lobbyists and advocates.

2. Broke a promise that it would include experts opposed to fluoridation.

3. Secretly commissioned a new study on dental effects (previously listed as "out of scope"), when the 2015 Cochrane Collaboration review didn't deliver a convincing pro-fluoridation position.

4. First, misled about its knowledge of a new thyroid study (Peckham et al., 2015) and then dismissed its findings, reaching a biased and false position that there is no evidence that fluoride interferes with thyroid function.

5. Falsely claimed a low-quality IQ study (Broadbent et al, 2014) was a high-quality study.

6. Downplayed, dismissed or excluded most other IQ studies and evidence of fluoride's neurotoxicity.

7. On flimsy grounds excluded a significant study linking fluoridation to ADHD (Malin and Till, 2015) – then failed to even acknowledge its existence.

8. In 2007, the NHMRC used a *promised* study in a Letter-to-the-Editor to negate an unrefuted Osteosarcoma study (Bassin, 2006) to claim there was no link to cancer. Then in its 2017 review the NHMRC failed to acknowledge that the promised study failed to refute the Bassin study but still continued to maintain no evidence of a link between fluoridation and cancer.

9. Selected a publication cut–off date for studies (that would be considered) that would exclude a very significant review by the US NRC (2006) and the Bassin (2006) study that were not given due consideration in its 2007 review.

10. The NHMRC 2017 review based its claims of safety largely on its 2007 review, however, its 2007 review was largely a copy of the 2000 York University review, which according to the York Review's Professor Sheldon did NOT show fluoridation to be safe!

11. Obfuscated on chronic kidney disease even though it is aware that poor kidney function increases uptake of fluoride into the bones and poses risks over a lifetime. Such cumulative risks – and the special plight of those with poor kidney function –have never been investigated by NHMRC.

12. On another but related matter, the NHMRC endorsed doubling children's upper safety limits for fluoride ingestion (using data from the 1930s) almost certainly anticipating that the pre-existing limits would be exceeded by bottle-fed infants in which formula is made up with fluoridated tap-water.

13. Abandoned the normal evaluation method for studies of fluoride's effectiveness almost certainly in an effort to disguise the fact that most of the studies reviewed were of low, or very low quality.

14. NHMRC 2017 rates tooth decay and dental fluorosis as more important end-points than other health incomes, including cancer and lowered IQ.

15. Commenced review with strict restrictions for acceptable evidence, then included a) unpublished work; b) a favourable narrative and c) an abstract.

16. Attempted to diminish known dental fluorosis harm by manipulating fluorosis ratings and raising threshold of concern.

17. Misleads the public and decision-makers by claiming fluoridation reduces tooth decay by 26-44 % - but without indicating just how small such reductions are in absolute terms – often less than one tooth surface out of over 100 tooth surfaces in a child's mouth!

18. Dishonestly claims fluoridation is safe by excluding important studies on spurious grounds, ignoring many others, and even cherry-picking weak studies that serve their purpose (e.g. Broadbent on IQ).

19. Doesn't exhibit an understanding of, or appreciate, the basic principles of toxicology – concentration is not the same as dose!

20. Perverted the principles of medical ethics by presenting a bogus ethical claim constructed by lobbyists rather than ethicists.

21. Gave an incomplete project of dubious quality a prestigious NHMRC award

22. NHMRC fluoridation public consultations have been shams.

23. The NHMRC's extraordinary effort to maintain the dubious claims that fluoridation is safe, effective and ethical, are becoming more and more desperate by the year. NHMRC 2007 was very bad, NHMRC 2017 verges on fraud.

Conclusions

The NHMRC has ignored its Duty of Care and betrayed the Australian public with its poor and perverted fluoride review. The NHMRC's fluoride review should be shredded.

We request that citizens and scientists from inside Australia and around the world will call for a Royal Commission inquiry to investigate the NHMRC's behavior in this matter. Hopefully they will call for a new review to be commissioned by the Federal government but carried out by an independent organization, with the panel comprised of unbiased scientists and professionals.

In terms of reviewing government policies in general, it is requested that the Royal Commission investigate the wisdom of using a government department such as NHMRC to review the science of controversial programs, when those programs have been part of long-standing government policy. Under such circumstances it is urged that the Royal Commission recommend such reviews be organized by a non-governmental agency. This agency would be required to select panels completely independent of governmental influence. Ideally such panels would consist of experts drawn from both sides of the issue in question, and those who have not taken a position on the issue: a good model would be the panel selected by the U.S. National Research Council for its review of fluoride's toxicity in 2006.

The following is a detailed analysis of the 23 items:

23 REASONS WHY AUSTRALIA NEEDS A ROYAL COMMISSION INTO THE NHMRC's FRAUDULENT FLUORIDE REVIEW

1. NHMRC stacked the fluoride review committee with fluoridation lobbyists and advocates.

The NHMRC appointed at least 10 known fluoridation advocates and lobbyists to its Fluoride Reference Group (FRG) that conducted the recent NHMRC review on the health effects of water fluoridation. Four of the committee members (dentists Profs John Spencer and Kaye Roberts-Thomson from Adelaide University, Colgate Professor dentist Mike Morgan from Melbourne University and former NSW Chief Dental Officer Clive Wright) **are well known fluoridation lobbyists** who have all also received significant grant funding from the NHMRC and all have used their own publications to promote fluoridation. **Two of NHMRC's FRG members Profs John Spencer and Clive Wright, have even participated in court cases to help fluoridation be forced on NSW residents.**

An additional six members of the FRG committee are also known to have publicly advocated for water fluoridation – making fluoridation lobbyists and advocates to be a two–thirds majority of the 15 member NHMRC committee. The NHMRC deliberately stacked the FRG committee with members extremely biased towards fluoridation. Additionally, when the names of the FRG members were first publicly listed (well after the FRG had already started meeting) the listing of the FRG's committee member's conflicts of interests were delayed and severely downplayed. The name of one FRG appointee (Prof Corbett) a

fluoridation advocate from as early as 1993, was not even listed on the NHMRC website until after the 2014 public call for evidence had already closed.

2. NHMRC broke a promise that it would include experts opposed to fluoridation.

Right from the very beginning, the NHMRC was misleading about its proposed review committee. Before the NHMRC appointed the FRG members, the NHMRC had privately communicated to members of the public that a new fluoride review committee, when set up, would include representation of people opposed to fluoridation. As an example, an extract of an email from the NHMRC on 15 Jan 2014 **–**

> ***"We aim to include representation from the relevant areas of science, public health, policy area, consumer/community views and as we have discussed, from those opposed to population level fluoridation"***

However, the NHMRC was misleading because they never allowed that promised representation. The 2006 National Research Council that reviewed health effects of fluoride for the US Govt's National Academy of Science had a balanced panel comprised of experts who were in favour of fluoridation and also experts who were opposed to fluoridation – **in contrast, the NHMRC would not allow anyone who was opposed to fluoridation to be on its FRG committee.**

3. NHMRC secretly commissioned a new study on dental effects (previously listed as "out of scope"), when the 2015 Cochrane Collaboration found that there were few, if any, high-quality studies that were supportive of fluoridation)

Because the Cochrane Collaboration was already examining fluoride's dental effects, the new NHMRC review was ONLY to examine health effects other than dental. In August 2014 when the public was invited to submit evidence for the NHMRC to review, dental effects were listed as strictly *"out of scope"* with the NHMRC review only to examine other health effects of fluoridation. The NHMRC was only to "critically appraise" the Cochrane review on tooth decay and fluorosis – the NHMRC were not to do their own review on dental effects.

When the Cochrane Collaboration review **(1)** was published in June 2015 it was not flattering to fluoridation with the review finding little evidence to support fluoridation being effective. Newsweek gave an overview - http://www.newsweek.com/fluoridation-may-not-prevent-cavities-huge-study-shows-348251

For tooth decay, the Cochrane review used a high standard protocol, it only used studies looking at tooth decay in both fluoridated communities and non- fluoridated communities measured at least two different points in time. That protocol would provide controls to take in account temporal decreases in tooth decay that could not be attributed to fluoridation. This is important as large decreases in tooth decay in non- fluoridated communities has been seen world-wide – see http://fluoridealert.org/studies/caries01/ The published Cochrane review findings, did not fit NHMRC's apparent agenda of protecting fluoridation. **In response to this, the NHMRC secretly commissioned their own review of tooth decay where they could include dental publications that were unsuitable for the Cochrane review.** Many publications that the NHMRC then allowed to be included in their secretly commissioned review had been written by Australian fluoridation lobbyists who were members of the NHMRC FRG committee. The NHMRC's 2017 Information Paper cites 24 dental publications co-authored by FRG member John Spencer, 8 publications co-authored by FRG member Kay Roberts- Thomson, 2 publications co- authored by FRG member Mike Morgan and 2 publications co- authored by FRG member Clive (aka Frederick) Wright.

4. NHMRC first misled about its knowledge of a new thyroid study (Peckham et al., 2015) and then dismissed its findings, reaching a biased and false position that there is no evidence that fluoride interferes with thyroid function.

On 24th Feb 2015 (with the new NHMRC fluoride review barely underway) a Fairfax journalist was interacting with the NHMRC and sent the NHMRC information about a new study from the UK by Peckham et al **(2)** which was still media embargoed. This study linked water fluoridation to hypothyroidism. Very early the following day the NHMRC published a statement from the CEO re-affirming the 2007 NHMRC's recommendation and claimed that based on the work conducted in the review so far, the NHMRC was expected to maintain its support for fluoridation as effective and safe.

In later correspondence NHMRC staff claimed that the NHMRC had not known about this new thyroid study until the 25th Feb 2015 and in other correspondence also claimed that the new thyroid study was not the reason for the release of the CEO's Statement. The NHMRC claimed:

> ***"NHMRC first became aware of the Peckham et al 2015 study on 25 Feb 2015, one day after it was first published online. A Member of the Fluoride Reference Group (FRG) informed the Fluoride Project Team (FTP) that there had been some media activity surrounding its release".***

Emails in released Freedom of Information documents proves that the NHMRC knew about the Peckham thyroid study earlier than what they claimed. Apart from being misleading about when the NHMRC knew about this thyroid study, the NHMRC was also misleading about the source that informed them of the study. Even though the NHMRC denied it, it is obvious it was the new thyroid study that had triggered the release of the CEO's Statement and it was obviously written and released by the NHMRC to protect fluoridation**. Knowing of this new study and its implications, the NHMRC still put out a statement asserting that fluoridation was safe. This NHMRC statement was put out some 18 months before the NHMRC published even its draft Information Paper.**

When the NHMRC eventually published its 2017 information paper, instead of acknowledging concerns about possible adverse thyroid health effects it severely downplayed the Peckham thyroid study.

The downplaying by the NHMRC's FRG was largely based on two fact-poor commentaries (not scientific studies) particularly one written by a Queensland Health dentist who is a very active lobbyist for forced fluoridation. **Instead of investigating further, or even acknowledging potential risk of harm to thyroid function the NHMRC claimed fluoridation was safe by misleadingly claiming this new study was "unreliable evidence".**

Additionally, the NHMRC is well aware that the 2006 US National Research Council report "Fluoride in Drinking Water" NRC 2006 (3) acknowledged risk for thyroid harm, specifically stating:

> ***"In humans, effects on thyroid function were associated with fluoride exposures of 0.05-0.13 mg/kg/day when iodine was adequate and 0.01-0.03 mg/kg/day when iodine intake was inadequate."***

Despite knowing this, the NHMRC has denied fluoridation poses a risk to thyroid function.

5. NHMRC falsely claimed a low-quality IQ study was a high-quality study.

The NHMRC falsely claimed that a study (4) conducted by New Zealand dentist/ fluoridation lobbyist Jonathon Broadbent was a high quality study. Broadbent claimed that the study showed no link with fluoridation and IQ deficit.

The NHMRC only had to read the opening paragraphs of Broadbent study to see that he was clearly a protagonist in the fluoridation debate, with a keen interest in how the practice was being pursued in NZ.

> Community water fluoridation (CWF) is a cost- effective,[1,2] safe,[3] and environmentally friendly[4] means of reducing dental caries rates[3] and social inequalities.[5] However, CWF has recently been criticized as a cause of IQ deficits among children,[6] despite a lack of evidence to support that claim. This claim was considered pivotal in the recent rejection of CWF by voters in Portland, Oregon,[7] and by local government politicians in Hamilton, New Zealand. It is likely that such claims may continue to be lobbied against CWF worldwide…
>
> Hamilton city (New Zealand's fifth-largest metropolitan area) has had CWF since 1966 and has recently become a target for CWF opponents. Despite a binding 2006 referendum that showed 70% support for CWF among voting Hamiltonians,[10] Hamilton's City Council chose to relitigate CWF and held a tribunal on fluoridation in early 2013. The councillors voted to cease CWF, leading to an outcry from members of the public and health officials. A new referendum was then held (accompanying a local government election), which again showed 70% support for CWF among voting Hamiltonians.[11] The Hamilton City Council elected to await the outcome of a High Court ruling on a challenge to the legality of CWF in another New Zealand city (New Plymouth) before reinstating CWF…(Broadbent et al., 2014)

With such a clear pro-fluoridation agenda at stake the NHMRC should have been far more cautious about labelling this as a "high-quality" study and using it to dismiss or downplay other IQ studies.

If the NHMRC had read the Broadbent study more carefully they would have found it was actually a low-quality study. For example, in the study there were approximately 1000 children who had lived in the fluoridated community but only about 100 in the non- fluoridated community – and of these about half were likely to have taken fluoride tablets. This severely compromised Broadbent's study as there would be little difference in fluoride intake between the 2 groups. This study did not have the scientific power to find a significant difference in IQ between the fluoridated and non- fluoridated area. These criticisms were

published in the same journal where Broadbent published his article (Osmunson et al, 2016: Letters and Responses, American Journal of Public Health, February 2016, Vol 106, No. 2) and should have been cited by NHMRC.

Nor did Broadbent et al consider a number of important confounders such as lead, iodine, arsenic and Maternal IQ. This is ironic considering that Broadbent had been critical of authors of other IQ studies for not considering these confounders. **The NHMRC was advised in 2016 of these and other severe limitations for this study but still claimed in 2017 that Broadbent's study was a high quality study. This was clearly a glaring double standard**.

6. NHMRC Downplayed, dismissed or excluded most other IQ studies and evidence of fluoride's neurotoxicity.

The NHMRC is well aware of a 2012 Harvard University Meta-analysis and Systematic review **(5)** by Choi et al of 27 human IQ - fluoride studies that indicated IQ was lowered in children exposed to fluoride. Overall, there was a drop of nearly 7 IQ points with higher exposures to fluoride. Many of the water fluoride concentrations in studies in the Harvard review that were associated with lower IQ were only 2, 3 or 4 times that of Australian fluoridated water. Despite this, the NHMRC designed their latest fluoridation review with such severe limitations so that this review and the primary studies included in this review would not be taken into consideration. There is not even a mention of this review in the NHMRC's Information Paper.

In February 2014, the British Medical Journal Lancet Neurology published a paper (6) on developmental neurotoxicants and classified fluoride as a substance that can harm children's developing brains. The NHMRC also ignored this.

There are now 50 published human studies indicating fluoride exposure can reduce IQ and 45 animal studies have found that fluoride exposure impairs learning and /or memory capacity – however the NHMRC does not acknowledge this. All citations for the human and animal studies can be seen at http://fluoridealert.org/studies/brain01/ and at http://fluoridealert.org/studies/brain02_/

Because of increasing scientific evidence about fluoride neurotoxicity, the US National Toxicology Program (NTP) has commenced animal studies to investigate this issue**. The NHMRC had advance and detailed knowledge that this research was to commence** when the NHMRC was consulting with the US Govt's National Toxicology Program and National Institute of Environmental Health Services on how to do a systematic review of animal studies**.**

Despite the NHMRC's knowledge that fluoride neurotoxicity was of enough concern that the NTP had commenced expensive and protracted animal studies and was finding some results of concern, to protect fluoridation the NHMRC has done everything they can to deny that fluoride poses any risk to IQ and cognitive function.

7. NHMRC, on flimsy grounds excluded a significant study linking fluoridation to ADHD – then failed to even acknowledge its existence.

The NHMRC in 2016 became aware of a study by Malin and Till (7) published Feb 2015, that linked American water fluoridation to higher rates of medically diagnosed Attention Deficit Hyperactivity Disorder (ADHD). This study fulfilled the NHMRC criteria to be included in the NHMRC review however because the FRG did not like the implications of this peer reviewed study that had been published in Environmental Health, the public will not find any mention of this study in the NHMRC 2017 Information Paper. This could be considered that this lying by omission by the NHMRC.

8. In 2007, the NHMRC used a *promised* study in a Letter-to-the-Editor to negate an unrefuted Osteosarcoma study (Bassin, 2006) to claim there was no link to cancer. Then in its 2017 review the NHMRC failed to acknowledge that the promised study failed to refute the Bassin study but still continued to maintain that there was no evidence of a link between fluoridation and cancer.

When the NHMRC published their previous fluoride review (in 2007), the NHMRC knew of a significant 2006 study by Bassin et al **(8)** linking age- related water fluoridation exposure to Osteosarcoma in boys and young men. **Instead of giving this study due consideration, the NHMRC wriggled around it and unscientifically deferred to a Letter-to-the-Editor by fluoridation lobbyist Chester Douglas** in the same journal in which Bassin had published**.** Douglas had promised that his study would show that Bassins's thesis didn't hold with the larger data base. Bassin's hypothesis - based on her data - was that the critical issue was the **timing of exposure** of young boys to fluoridated water**. Namely, that young boys exposed to fluoride in their 6th, 7th and 8th years had a 5-7 fold increased risk of succumbing to osteosarcoma** (a rare but frequently fatal cancer in young men) **by the age of 20. First, it was a glaring double standard on the part of NHMRC, which had been so fussy about which studies they would**

accept for their review, to accept as evidence the "promise" of the results of a yet unpublished study. This is not a trivial issue - if Bassin was correct fluoridation might actually be killing a few young men each year.

However, by 2011, when Douglass's promised study appeared (five years after the promised date) it didn't even examine Bassin's hypothesis. Kim et al (2011) study **(9)** used fluoride bone levels at diagnosis or autopsy as the metric of exposure. There is no way that such bone levels could gauge exposure of fluoride at critical years of exposure (6th, 7th and 8th years) found by Bassin. Thus, as of 2017 no scientist in the world - including Kim et al. (2011) have refuted Bassin.

The NHMRC's conclusion "that there was no association between fluoridation and osteosarcoma" is highly misleading. To make matters worse NHMRC offered no analysis of the quality of the Kim et al. paper, which had other serious flaws, e.g. they used other bone cancer patients as controls without ruling out that some of these other bone cancers were not caused by fluoride exposure, which might well be the case. Kim et al also included older patients over 20.

For more information on the weaknesses and flaws of the Kim et al Osteosarcoma study and why it does not and could never refute the Bassin study see -http://fluoridealert.org/articles/kim_fan/ .
Through submissions, the NHMRC are aware of this and aware that the findings of the Bassin Osteosarcoma study have never been refuted. In 2017 this was a splendid opportunity for the NHMRC to put the record straight on this issue, but the NHMRC chose not do so. The NHMRC still deceptively asserts there is no link with cancer and water fluoridation.

9. NHMRC selected a publication cut–off date for studies (that would be considered) that would exclude a very significant review by the US NRC (2006) and the Bassin (2006) study that were not given due consideration in its 2007 review.

The cut-off date the NHMRC selected looks very suspicious and self-serving for those wishing to exonerate fluoridation of any harm. In 2014 the NHMRC selected 1 Oct 2006 as the earliest publication date for studies to be included in the new NHMRC review. This date was almost certainly selected by the NHMRC so that they could exclude both the 2006 NRC review and the Bassin Osteosarcoma study which were both published earlier in 2006, but, which were never given proper consideration in the 2007 NHMRC review. To help dismiss the NRC 2006 from consideration in its 2007 review the NHMRC had claimed that the NRC 2006 report was only about adverse health effects with 2 - 4 mg /L fluoride concentrations and that Australian fluoridation was in the range 0.6 – 1.1 mg/L.

There were a number of studies included in the 2006 NRC which had lower concentrations than 2 mg /L, one example was a 1998 rat study by Varner et al (1998 Brain Res. 784 (1-2) 284- 298) that showed rats drinking water fluoridated at 1mg /L for one year had kidney damage, brain damage and a greater uptake of Aluminium into the brain and Beta amyloid deposits thought characteristic of Alzheimer's. **Although the 2007 NHMRC review mentioned the 2006 NRC report, the NHMRC apparently dismissed it from any consideration because not all the studies were at 0.6 - 1.1 mg /L.** This betrayed little understanding of toxicology. When considering harm it is not the concentration that is the critical comparison but DOSE. Some of the studies that have found harm in fluoride studies have found harm at doses which can be easily exceeded especially for high water consumers and those getting fluoride from other sources such as dental products, tea- drinking and pesticide residues.

10. The NHMRC 2017 review based its claims of safety largely on its 2007 review, however, its 2007 review was largely a copy of the 2000 York University review, which according to the York Review's Professor Sheldon did NOT show fluoridation to be safe!

In 2000 the York University published a review of water fluoridation **(10)** by McDonagh et al that had been commissioned by the UK govt. Prof Trevor Sheldon, as Chair of the review's Advisory Committee later wrote to the House of Lords advising that the review did not find water fluoridation to be safe. See Prof Sheldon's letter at - http://fluoridealert.org/content/sheldon-york-review/ **.**

Some of Prof Sheldon's advice on the York University review's findings was that there was little evidence to show that water fluoridation has reduced social inequalities in dental health and that the review did not find water fluoridation to be safe, with the quality of the research being too poor to establish with confidence whether or not there are potentially important adverse effects in relation to the high levels of fluorosis.

In 2007 the NHMRC published their previous fluoride review. The NHMRC 2007 review's section on water fluoridation was largely a copycat of the 2000 York University review. The York University review was titled ***"A Systematic Review of Water Fluoridation".*** Despite the section on water fluoridation in NHMRC's 2007 review basically being a copycat of the 2000 York review, the NHMRC cleverly, and grandly, titled their review as ***"A Systematic Review of the Efficacy and Safety of Fluoridation."*** The 2007 NHMRC review was then used to claim fluoridation was safe. In the NHMRC's recent review the NHMRC has still not produced good

quality research or evidence, but despite this, claims that fluoridation is safe. It is bad enough that they did this in 2007 – but it is even worse that they repeated their misleading claims in 2017 after the public has pointed out Sheldon's commentary.

11. NHMRC obfuscated on chronic kidney disease even though it is aware that poor kidney function increases uptake of fluoride into the bones poses risks over a lifetime. Such cumulative risks – and the special plight of those with poor kidney function –have never been investigated by NHMRC.

In 2007 the NHMRC put out a public statement (NHMRC Recommendation) as part of a brochure. Freedom of Information on draft versions of the brochure show that a warning for people with kidney impairment was included - until two dentists (FRG member John Spencer was one of the 2 dentists) and two South Australian water quality advisors reviewed the brochure – after this the NHMRC removed the kidney warning and any reference to fluoridated water and kidney impairment.

Although the current and past NHMRC Australian Drinking Water Guidelines - Part 5 Fact Sheets Fluoride, acknowledges risk from fluoridated water for those with kidney impairment, ***"People with kidney impairment have a lower margin of safety for fluoride intake. Limited data indicate that their fluoride retention may be up to three times normal",*** the NHMRC's 2017 fluoridation Information Paper makes no mention of kidney impairment.

The new 2017 NHMRC Public Statement claims fluoridation is SAFE, but the NHMRC has totally ignored any potential harm to those with kidney impairment. The NHMRC has never investigated cumulative effects of fluoride on people with kidney impairment even though a NHMRC File Note in NHMRC documents obtained through FOI confirms to do this was a requirement of the NHMRC's 2007 fluoride review. (FOI documents provided by NHMRC early 2008)

Recent Australian data indicates that 10 % of Australian adults aged 18 years and older have biomedical signs of having Chronic Kidney Disease (CKD); those in the 65-74 years old age group have a CKD prevalence of 21 % and those 75 years and above 42 % prevalence of CKD (AIHW http://www.aihw.gov.au/chronic-kidney-disease/prevalence/)

The NHMRC deliberately muddies the waters claiming in the NHMRC's Evidence Statement (a statement written by the FRG which was two – thirds comprised of fluoridation lobbyists and activists***) "There is no reliable evidence of an association between water fluoridation at current Australian levels and chronic kidney disease."***

The NHMRC's FRG apparently are claiming that fluoridation doesn't cause kidney disease - however the NHMRC have totally ignored the real issue of concern that if you have impaired kidney function and can't excrete as much fluoride from your body, you will accumulate more fluoride in your body – and the NHMRC have never investigated the cumulative effects. This issue, in recent years has been the subject of correspondence with the NHMRC so the NHMRC is well aware of it, but still does not acknowledge any risk.

Aboriginals are a group have much higher rates of CKD than other Australians and Diabetics also have a higher risk for CKD – but the NHMRC has not considered health effects of consuming fluoridated water on people with kidney disease, Aboriginals, Diabetics or other vulnerable population sub- groups. The NHMRC has also not considered effects on people with Diabetes insipidus even though it is known that they are higher risk of developing dental fluorosis.

By totally ignoring the issue that people with kidney impairment have potential risk from fluoridated water the NHMRC can ignore advice like this from a kidney specialist at the University of Munich*:*

> ***"A fairly substantial body of research indicates that patients with chronic renal insufficiency are at an increased risk of chronic fluoride toxicity. These patients may develop skeletal fluorosis even at 1 ppm fluoride in the drinking water."*** **- Dr. Helmut Schiffl, MD (2008)**

By not allowing animal studies to be included in the review the NHMRC could ignore evidence like this:

> ***"….the WHO's recommended concentrations in drinking water become nephrotoxic to CKD rats, thereby aggravating renal disease and making media vascular calcification significant."*** **- A. Martín-Pardillos et al. in Effect of water fluoridation on the development of medial vascular calcification in uremic rats. Toxicology. 2014 Apr 6;318:40-50**

By ignoring risks for kidney impaired and then dishonestly claiming water fluoridation is safe, the NHMRC has totally ignored its duty of care to people with kidney impairment.

12. On another but related matter, the NHMRC endorsed doubling children's upper safety limits for fluoride ingestion (using data from the 1930s) almost certainly anticipating that the pre-existing limits would be exceeded by bottle-fed infants in which formula is made up with fluoridated tap-water.

This item goes beyond the NHMRC 2017 review but it goes to the bias of NHMRC in its continued promotion and defence of water fluoridation. Despite the steadily increasing number of human studies indicating fluoride is a developmental neurotoxin, the NHMRC has recently approved the doubling of the upper safety limits of fluoride ingestion for children up to 8 years of age. The new children's fluoride intake safety limits recently endorsed by the NHMRC are now twice as high as the European and USA Upper Tolerable Intake Limits. Apparently the NHMRC thinks that Australian children are biologically different to other children and can safely ingest and tolerate twice as much fluoride as their international counterparts. These new doubled upper safety limits were constructed by a committee of 8 members, including a Queensland Health dentist who is a lobbyist for forced fluoridation, as well as 5 Adelaide University Dental School staff. **At least 6 out the committee of 8 who have doubled the previous Australian fluoride intake safety limits are extremely biased towards fluoridation.** The Queensland Health dentist who was on this committee has been repeatedly reported by Australian media as saying that people who are opposed to fluoridation are nutters, conspiracy theorists and flat-earthers. Why was someone like this even on the committee? And since when did dentists become experts in nutrition and toxicology?

This group based their recommendations to double children's fluoride ingestion safety limits on their chosen extreme endpoint of severe dental fluorosis and then, for their calculations, heavily used fluorosis data collected in the late 1930s from 273 American children in an area where drinking water naturally contained 1.9 mg of fluoride per litre. Seventy – five percent of the children in that group had some level of dental fluorosis but the committee who doubled Australian safety limits totalled ignored that. The NHMRC cannot possibly care about the safety of children when the NHMRC endorses such shoddy and extremely unprofessional work.

The committee who doubled the upper safety limits for children used the fluoride content of processed foods as measured by Food Standards Australia New Zealand in Brisbane – just prior to Brisbane being fluoridated - thus minimising the measured food fluoride content. This committee also ignored any current contribution to fluoride burden contributed by foods fumigated with the pesticide Sulfuryl Fluoride (AKA Profume). Sulfuryl Fluoride was approved for use in Australia in early 2008 and by now could have widespread use in Australia, as in the USA**. Regardless of this, the NHMRC still endorsed the doubling of upper safety limits for fluoride ingestion by children up to 8 years of age.**

Through 2 published studies, one in Australia published 2009 (11) and another one in New Zealand published 2010 (12) the NHMRC is aware that the fluoride intake of bottle- fed infants, if infant formula is reconstituted with water fluoridated at 1.0 mg/Litre breaches the NHMRC's previous upper safety limits - this is almost certainly why the NHMRC was keen to endorse doubling fluoride upper safety limits for children. The NHMRC is aware that it is the fluoride content of the water added to infant formula that is the issue of concern – but the NHMRC obfuscates saying that the fluoride content of infant formula powder is safe. Again, the NHMRC seems to want to protect fluoridation more than it wants to protect children.

13. NHMRC abandoned the normal GRADE evaluation method for studies of fluoride's effectiveness almost certainly in an effort to disguise the fact that most of the studies reviewed were of low, or very low quality.

Here's a quote that says it all (NHMRC 2016 Technical Report p 54)

> "**The GRADE (Grading of Recommendations Assessment Development and Evaluation) system for assessing evidence was not originally designed to consider evidence for public health interventions**. Consequently, for public health interventions like water fluoridation, where evidence of efficacy comes from observational studies, much of the evidence will ultimately be rated as 'low' or 'very low' quality. Due to concerns that the potential pejorative connotations of these descriptors may result in the evidence being disregarded and/or misinterpreted**, the Fluoride Reference Group decided to omit the descriptors and describe the evidence in terms of the confidence in the reported results."**

Essentially the Fluoride Reference Group rejected the standard terms for evidence quality in the assessment system they were using because they would make the evidence look too poor. Those terms are "low" and "very low" quality, and they predicted that the majority of the effectiveness studies would get these ratings. **A study that would have been rated as *"a low quality study"* could then become graded by the NHMRC as *"Our confidence in the reported associations is limited"*. This helped disguise the fact that most of the studies used by the NHMRC were low quality, or very low quality**.

The NHMRC then adopted some very flexible criteria for accepting or rejecting a study into their review. Basically, the person reviewing a particular study has no clear and sharp guidelines, they can use their flexibility and pretty much just say "I don't think

this study is good enough" and reject it. This is shown in the CEO's Administrative Report where in 2016 -17 the FRG using extremely flimsy reasons to refuse the inclusion of many applicable studies that indicated harm.

For example, the 2015 study by Malin and Till (7) linking US water fluoridation to ADHD was excluded by the FRG because (a) they didn't like the hypothesis in the published paper and (b) because the FRG hadn't included it in the 2016 draft information paper – so they wouldn't include (or even ***mention*** it) in the 2017 information paper. A total farce by the NHMRC!

14. NHMRC 2017 rates tooth decay and dental fluorosis as more important end point than other health incomes, including cancer and IQ.

As shown in the NHMRC review's Technical Report (page 53) before the NHMRC review started, the Fluoride Reference Group classified the importance of health outcomes for its decision making. The Fluoride Reference Group classed dental caries and dental fluorosis as *"Critical for decision making."* The Fluoride Reference Group then classed all other health outcomes, including neuro- cognitive effects, renal effects, cancer, thyroid dysfunction etc, as *"Important, but not critical."* The NHMRC and the FRG have got a serious problem with their priorities when they consider tooth decay is a more important health issue than cancer, or harm to IQ.

15. NHMRC commenced review with strict restrictions for acceptable evidence, then included a) unpublished work; b) a favourable narrative and c) an abstract.

Some of the ways the NHMRC excluded relevant studies

a. **Study must be published in English.** The NHMRC thus eliminated many published Chinese and other non-English studies on fluoride and IQ.

b. **No animal studies would be accepted**, even though such studies are required by government regulatory agencies such as the US's EPA and FDA. Animal studies are an essential component of a "weight of evidence" evaluation of the toxicity of a chemical substance or medical intervention. Standard toxicology assessments of a drug or a chemical always start with animal experiments. These can provide more reliable information than human experiments because they can tightly control all the variables except exposure to the chemical in question. You can control everything. The only downside is extrapolating the results from animals to humans, but that is considered an acceptable limitation for important regulatory decisions.

c. **Exposure could only be from fluoride in drinking water.** The NHMRC even rejected studies which used drinking water F exposure when the study additionally considered exposure from other sources such as swallowed toothpaste. This is ridiculous, since it is clearly total exposure that is of interest for both effectiveness and safety studies.

d. **For safety studies, the NHMRC adopted criteria that if the water F concentration is more than 1.5 mg/L, the study will be downgraded or even rejected because it is claimed to be inapplicable to Australia**. This ignores the obvious point that when studying adverse health effects, it is often necessary to study higher exposures than commonly occur to tease out effects in relatively small samples. Furthermore, this ignores the fact when other exposures are included the total F exposure in Australia may be within the range of total F exposure in these (ignored) studies even through the water F level is above 1.5 mg/L.

To fully protect a human population from harm from a known toxic substance a "weight of evidence analysis" is essential. This was one of the key differences between the US NRC review of 2006 and the NHMRC reviews of 2007. This severe limitation of the NHMRC 2007 review was pointed out by scientists in 2007, and it is therefore surprising that they have reproduced their un-protective analysis in 2017. So far the NHMRC has offered no reason to exclude animal studies. This is strange since we know that the NHMRC was in correspondence with the US NIEHS/NTP agencies on how a systematic review of animal studies on fluoride should be conducted! We suspect that it was because in their review these agencies reported that they found low to medium quality animal studies that indicated that fluoride is neurotoxic.

When the NHMRC review commenced, the allowable scope of what the NHMRC would accept as evidence was severely limited by the NHMRC. Evidence of harm via medical notes, case histories, animal studies, non- English text studies, narratives were not to be accepted by the NHMRC for the review. What the NHMRC would accept for evidence had to be full published studies (not abstracts) and was extremely restricted by time frame and scope. It was the heavily biased FRG committee that was the final gatekeeper and arbiter of what evidence would and would not be accepted for the review.

Half way through the NHMRC's review, probably at the request of the FRG – the rules on what evidence was acceptable for the review were changed; the NHMRC's bar was seriously lowered to allow publications other than scientific studies to be included. As can be shown in the Administrative report for the NHMRC CEO, in late 2016 the FRG included in the NHMRC's review a (favourable to fluoridation) narrative as evidence - (*State of the Science community water fluoridation. Colorado Water Research 2015 Cromwell DA, McTigue NE, Hayes S*). Additionally, the FRG even included an unpublished consulting report by Jaguar Consulting *(Impact Analysis: Expanding Water Fluoridation in Victoria: Unpublished*). Jaguar Consulting are economists with no scientific qualifications.

The NHMRC FRG even included an abstract into the NHMRC review - under "Additional Considerations". This dental Abstract was co- authored by FRG members Mike Morgan, Kay Roberts Thomson and (F) Clive Wright.

The NHMRC CEO's Administrative report shows however that the FRG, as the 2017 Information Paper's final gatekeeper excluded all submitted IQ studies and all dental fluorosis studies that were submitted via the Sept – Aug 2016 public consultation. Including these would probably have been potentially damaging to the NHMRC's claim that fluoridation was safe.

The NHMRC's Administrative report also shows that a study linking USA water fluoridation to increased age adjusted incidence of diabetes in 22 states (13) was excluded by the FRG. There is not even a mention of this diabetes study in the 2017 NHMRC's Information paper, even though this study had been submitted to the NHMRC through the Sept - August 2016 public consultation. Although this is a published study that had resulted from an approved Thesis, the FRG claimed they had trouble understanding it. The main reason that the FRG gave for them excluding it from the final NHMRC Information paper (published 4 July 2017) was because it hadn't been included in the 2016 draft NHMRC information paper (published 14 September 2016), so they wouldn't include in the final Information paper. In 2016, diabetes had not even been included as an outcome in the 2016 draft paper. A word search for "diabetes" in the NHMRC's 2017 Information paper returns zero finds. With the FRG just being able to exclude and censor studies at their whim it made a mockery of both the NHMRC's public consultation process and the NHMRC's research and evaluation process.

16. NHMRC attempted to diminish known dental fluorosis harm by manipulating fluorosis ratings and raising threshold of concern.

Data from the NSW 2007 Child Dental Health Survey shows that 25 % of 11-12 year old children in NSW fluoridated areas had some level of dental fluorosis with 3.3 % of them having moderate fluorosis (TF3) and a further 0.5 % having moderate - severe fluorosis (TF4 and above). The NHMRC is now claiming that with expansion of fluoridation dental fluorosis has decreased - down from 25 % in 2007 down to 16.8 % in 2012 – 2014, now with only 0.8% of children having a fluorosis score of TF3 (with NHMRC also now claiming TF3 is only mild fluorosis not moderate fluorosis). The way NHMRC has claimed fluorosis rates are now lower is by manipulation by the NHMRC. The NHMRC has diluted down the rate of fluorosis by now combining fluoridated with non-fluoridated areas. To claim that fluorosis is decreasing the NHMRC has switched goalposts – the previous rate of fluorosis in NSW fluoridated areas is now being compared to an overall whole of Australia rate which could include areas fluoridated as low as 0.6 mg/l and also totally non-fluoridated areas. **The NHMRC is now comparing apples to oranges.**

The NHMRC has also allowed the downplaying and diminishing dental fluorosis by allowing changing the way fluorosis is graded. Previously in Australia very mild fluorosis was graded as TF 1 (Thylstrup Fejerskov index of 1), mild fluorosis as TF 2, and moderate fluorosis as TF3, moderate- severe fluorosis as TF 4 and above. For this NHMRC review a fluorosis grading of TF 3 (previously acknowledged as moderate fluorosis – eg, as in the 2007 NSW child dental survey) is now downgraded by the NHMRC and claimed by the NHMRC to be only mild fluorosis. The NHMRC also simultaneously upgraded the threshold level for fluorosis of aesthetic concern from TF 3 up to a level of TF 4. Dental Fluorosis rates pose a risk for fluoridation programmes, so by downplaying fluorosis and then claiming fluorosis is not a concern, the NHMRC helps protect fluoridation.

In the 1998 Australian Institutes of Health and Welfare (AIHW*) **"Review of Water Fluoridation: New Evidence in The 1990s: Final Report April 1998 "*** FRG member Prof John Spencer (as Executive of that AIHW review) had reported on page 106:

> ***"Hoskin and Spencer (1993) found that children affected by fluorosis and their parents are able to perceive the presence of fluorosis at a very mild level. They concluded that children with mild fluorosis showed a significant adverse psychological response to their dental appearance"*** (this was from findings on the personal perceptions of dental fluorosis of South Australian children as reported to a Dec 1993 Consensus Conference in Perth West Australia).

The NHMRC FRG is now asserting that children with mild and even moderate dental fluorosis perceive no problems with the appearance of their teeth with fluorosis, despite this being completely contradictory to what FRG member John Spencer had previously found and reported.

The NHMRC claims that fluorosis rates have decreased – claiming that Australian child fluorosis is now 16.8 %. This 16.8 % figure is from the 2012 –14 National Child Oral Health Survey that was co- edited by FRG member John Spencer. The NHMRC provided a large part of the funding for the survey. Tooth decay and dental fluorosis was collected on every child in the survey, yet while tooth decay was compared by every state and territory in the survey report, the editors did not report fluorosis data this way. There is a dearth of Australian fluorosis data and this was a perfect opportunity to compare child fluorosis rates in the states and territories, but instead, the authors chose to withhold. This is considered as censorship**.** The current NHMRC CEO Prof Anne Kelso should never have signed off on this NHMRC funded survey when the editors did not even report child fluorosis data by each state and territory.

Dental fluorosis data was also collected on adults in every state and territory for the 2004- 2006 National Adult Oral Health Survey (NAOHS 2004- 6) which was also funded by an NHMRC grant. FRG member John Spencer was a lead author of the adult survey report. To the best of our knowledge the adult dental fluorosis data that FRG member Prof John Spencer had collected in that survey has been withheld for over 10 years and has never been publically reported.

Dental fluorosis is a sign of fluoride toxicity, a biomarker of over exposure to fluoride among young children. The NHMRC would be aware that even the very mildest level of dental fluorosis is proof that children have been over - exposed to fluoride when their teeth are forming in their gums**.** It is commonly accepted that children's permanent teeth are forming in their gums until they are around 8 years of age – thus they are risk of developing dental fluorosis until they are 8 years old, yet the NHMRC claims that this is only until they are 6 years of age!

Good examples of NHMRC's double standards can be found in Appendix B of the NHMRC CEO's Administrative report which can be found at https://www.nhmrc.gov.au/_files_nhmrc/file/your_health/fluoridation/17378_nhmrc_-_administrative_report_for_ceo-web_revised.pdf)

This Administrative report lists an additional 5 Dental Fluorosis studies that met the advertised scope for the Sept – August 2016 public consultation on the draft Information Paper and the Fluoride References Group's assessment. All of these were excluded by the FRG.

Even though the NHMRC had included three Brazilian tooth decay studies for its review and Information paper, the Fluoride Reference Group excluded three Brazilian dental fluorosis studies claiming for each *"Based in Brazil so lacks relevance /not applicable to dental fluorosis in Australia".* Data on tooth decay in Brazil was included in the 2017 NHMRC review on the claim that it was relevant to Australia, but data on dental fluorosis in Brazil was excluded from the NHMRC review on the claim that it was not relevant to Australia.

The FRG also excluded a Colombian dental fluorosis study, partly because it did not take into confounders such as the straightness of teeth. The FRG then also excluded an American dental fluorosis study claiming *"Lacks relevance / not applicable to perceptions of dental fluorosis in Australia. Not just about fluorosis but the shape of the teeth".* The FRG thus excluded one fluorosis study party because it also took into account the shape of children's teeth, while simultaneously excluding another fluorosis study because it didn't also take into account the shape of children's teeth.

17. NHMRC misleads the public and decision-makers by claiming fluoridation reduces tooth decay by 26- 44 % - but without indicating just how small such reductions are in absolute terms – often less than one tooth surface out of over 100 tooth surfaces in a child's mouth!

As referred to in item 3, after the Cochrane Collaboration review on dental effects was published the NHMRC secretly commissioned their own review of dental effects and the NHMRC's FRG added in several publications that some FRG committee members had themselves authored. Based on NHMRC's secretly commissioned review and by including many publications authored by FRG members the NHMRC is now claiming *"water fluoridation reduces tooth decay 26% - 44% in children, teenagers and adults"* Apparently the NHMRC has not heard that correlation is NOT causation, yet they are making their overreaching claim as if it was proven. There are many factors involved in how much tooth decay an individual has and no Random Controlled Trials have been done. Almost every study the NHMRC used was a low quality, observational ecological study.

How much is 26 % or even 44 % relative percentage terms in real terms (the actual absolute difference) in tooth decay? A large claimed percentage difference can actually be a very small absolute difference. In the prelude to forced fluoridation being introduced in Queensland, fluoridation lobbyists, the Australian Dental Assn (Qld) and Queensland Health in newspaper advertisements were claiming that children in fluoridated Townsville had 65 % less tooth decay than children from non-fluoridated Brisbane. This was based on a large study **(14)** published in 1996 that had been co–authored by FRG member John Spencer. This study had measured tooth decay in tooth surfaces**.** The original study publication **shows that the 65 % less tooth**

decay that was claimed by fluoridation advocates was based on a single data point: an absolute difference of only 0.17 tooth surfaces out of over 100 tooth surfaces present in a child's mouth at age 7 years. This study reported children aged 6 to 12 years old, who were life time residents of fluoridated Townsville had an average difference only 0.23 tooth surfaces less decay in their permanent teeth, compared to children of the same age who were life time residents of non- fluoridated Brisbane. To keep this in perspective - **with a life time of exposure to fluoridated water the average difference in tooth decay for children's permanent teeth aged 6 to 12 yrs was only 0.23 tooth surfaces – and there are over 100 tooth surfaces in a child's mouth**.

Relative percentages can obviously give a misleading picture. The NHMRC's Information Paper has only published claimed differences in tooth decay as relative percentages, but not as absolute differences. When fluoridation lobbyists have in the past claimed 65 % less tooth decay for an average absolute difference of less than one quarter of a tooth surface we do not know how small the absolute differences in tooth decay may be to be able to gain a true perspective and the NHMRC certainly do not show their calculations how they came up with those figures of 26% to 44 %.

State and Territory data from the 2004 – 2006 Australian National Adult Oral Health Survey (NAOHS 2004-2006) shows that adults from then virtually non- fluoridated Queensland, when compared to all the other states and territories which are heavily fluoridated, did not have the most tooth decay in any of the 4 adult age groups examined.

In March 2013 some of the authors of the 2004- 2006 NAOHS (who are also members of the NHMRC FRG) using the data from the adult survey published a paper (15) comparing tooth decay in adults who had lived in fluoridated areas and non- fluoridated areas, for varying lengths of their lives. Looking at the generation born between 1960 and 1990 (those born after water fluoridation) comparing adults with more than 75 % of lifetime exposure to fluoridated water to those with less than 25 % exposure to fluoridated water, it was found that those who had prolonged exposure to fluoridated water had nearly 8 teeth with decay, while those who had very little exposure to fluoridated water had nearly nine teeth with decay. For near lifetime exposure to fluoridated water the difference was only 1.14 teeth (approx 11 % difference in tooth decay) For both a pre 1960s born cohort and post cohort there was an approximately 11 % relative difference comparing prolonged vs negligible lifetime fluoridation exposure. An important confounder – access to dental care (e.g., ability to access dentists in more rural areas compared to city areas) was not even considered, so the real differnce may have been even less.

The 11 % difference in adult tooth decay had been measured using the most common standard of measuring tooth decay DMFT – the number of Decayed, Missing and Filled Teeth. However, by using a less common way of measuring decayed tooth surfaces - Decayed Missing Filled (tooth) Surfaces DMFS (with 4 or 5 tooth surfaces per tooth depending on the type of tooth) **AND, then, by totally ignoring or excluding the number of Missing teeth from the equation** (changing DMFS to only DFS) the authors then claimed the difference in tooth decay from fluoridation in the pre-1960 cohort was 30 % and in the post 1960 cohort was 21 % less decay. **This is how 11 % difference in tooth decay in adults can be doubled or even tripled purely by the manipulation of removing some data and can explain how the NHMRC can misleadingly claim at least 26 % less tooth decay for adults from fluoridation.**

The NHMRC makes much of percentages when claiming large reductions in tooth decay – but makes little mention of what can be very small absolute differences – large relative percentages, in absolute differences are often less than a fraction of one tooth on average.

18. NHMRC dishonestly claims fluoridation is safe by excluding important studies on spurious grounds, ignoring many others, and even cherry-picking weak studies that serve their purpose (e.g. Broadbent on IQ).

The NHMRC structured their review so many studies and evidence could not be included. Even with the studies that were left, overall, for both dental benefits and for adverse health effects, the quality of evidence was low or very low.

For adverse effects, these low ratings applied equally to studies claiming no adverse effects as to studies claiming to find an adverse effect. Thus, this NHMRC review could not rule out adverse effects with any degree of confidence.

Here is a quote from the Executive Summary Conclusions:

> "There is **limited evidence that there is no association** between water fluoridation at Australian levels and the IQ of children and adults. There is also **limited evidence that there is no association** between water fluoridation at Australian levels and the outcomes of delayed tooth eruption, tooth wear, osteosarcoma, Ewing sarcoma, total cancer incidence, hip fracture and Down syndrome. The review also identified evidence suggesting that water fluoridation at Australian levels are associated with a small reduction in all-cause mortality; however, our confidence in this association is limited, and this small reduction may be due to chance. For all other outcomes canvassed in this review**, the evidence was of insufficient quality** to draw any conclusions."

For most adverse outcomes there was "limited evidence that there is no association" with fluoride, and for others the quality of evidence was so low that no conclusions could be drawn.

Far from this NHMRC review being a resounding rebuttal of the evidence that fluoridation causes harm, it actually concludes there is insufficient quality evidence to rule out harm. Not a single adverse outcome has sufficient quality evidence to rule it out. Because the onus is on those promoting fluoridation of public water to prove with sufficient confidence that it is safe, this report is a resounding indictment against fluoridation promoters, because it concludes they do not have sufficient quality evidence to confidently conclude it is either safe or effective.

It is shameful that the NHMRC should continue to waste taxpayers' money on reviews like this and instead should put money into well-designed studies in Australia or better still in reviewing the successful methods being used to fight tooth decay in children (including children from low-income families) in non-fluoridated countries.

19. NHMRC doesn't understand principles of toxicology – concentration is not the same as dose!

The **DOSE** of fluoride received from water each day is not the concentration of fluoride in water - is the concentration of fluoride in the water (measured as mg/Litre) multiplied by how much water (how many litres) you drink each day. Someone drinking 2 litres of water fluoridated at 1.0 mg /L ingests as much fluoride as someone drinking 1 litre of water fluoridated at 2 mg/L.

The **TOTAL DOSE** received each day is a combination of how fluoride you get from water, from tea, from food, from dental products, from air pollution and pesticide residues.

When the NHMRC commenced its review it restricted the health studies it would accept to only studies that were at Australian fluoride concentrations – NHMRC's Australian Drinking Water Guidelines allows up to 1.5 mg/L fluoride in drinking water. The NHMRC, by rejecting studies done on fluoride exposures at higher levels than those used for fluoridation ignored the effect of dose in people who drink more water (eg, athletes, outdoor workers, people on certain medications, people with Diabetes insipidus or Diabetes mellitus), people who retain more fluoride (eg, people with kidney disease) and infants fed formula made with fluoridated water and fluoride from other sources (see above). A discussion of fluoride accumulation from chronic ingestion is lacking.

Dr. Kathleen Thiessen, Risk Assessment Scientist on the 2006 National Research Council panel (NRC 2006) has stated –

> ***"The range of individual fluoride exposures at 1 mg/L will overlap the range of individual exposures at 2 mg/L or even 4 mg/L. Thus, even without consideration of differences in individual susceptibility to various effects, the margin of safety between 1 and 4 mg/L is very low"***

The NHMRC either ignores, or does not seem to understand both the issue of dose, and also the issue of individual susceptibility.

20. NHMRC perverted the principles of medical ethics by presenting a bogus ethical claim constructed by lobbyists rather than ethicists.

Water fluoridation is the addition of fluoride chemicals to public drinking water to try and treat people. Water fluoridation by its very nature is mass medication and many countries don't undertake this practice because of consideration that it is unethical, see - http://fluoridealert.org/content/europe-statements/. Additionally, the Queensland government in its official 2003 Position Statement (copied at end**)** had acknowledged that without the express consent of the community fluoridation is unethical mass medication. Fluoridation is both mass medication and medical treatment through public water supplies without individual's consent. In early 2013 Cairns Council ended fluoridation acknowledging the 2012 position of the Local Govt Assn of Qld that without the express consent of the community fluoridation is unethical mass medication. The NHMRC would be aware since 2012, there have been 29 Queensland Councils that have formally rejected fluoridation. Some of the Queensland Councils that have ended fluoridation have done so after commissioning surveys finding approximately 50 % up to 70 % of those surveyed did not support fluoridation. A Referendum in Mount Isa found 89 % of voters did not want fluoridation. Knowing that there is individual and community opposition to fluoridation, the NHMRC still claims fluoridation is ethical. Apparently the NHMRC believes it is ethical to force a medication or a treatment on non-consenting individuals**.**

Nutrients are substances which feed, nourish and sustain growth. **Fluoride is not a nutrient.** In 2005 – 2006 the NHMRC endorsed and published Nutrient Reference Values for Australia and New Zealand. In 2006 the NHMRC had maintained fluoride was classed as essential to human health and included it in the new nutrients values.

The NHMRC FRG in 2017 now intimates that fluoridation is just the same as adding the nutrient Iodine to salt, or the nutrient Folic acid to bread. This is deliberate obfuscation as Iodine and Folic acid are proven nutrients and sufficient intake is essential for life, whereas fluoride is not a nutrient (despite the NHMRC calling it this). The NHMRC would not be able to provide information on a single biological pathway within the human body that requires fluoride, because there are none, yet still claims fluoride is a nutrient.

Despite the NHMRC endorsing fluoridation since 1953, the NHMRC had never examined the ethics of fluoridation. The NHMRC now claims that fluoridation is ethical. The NHMRC claims that fluoridation is ethical based on the NHMRC's claim that fluoridation is safe. The way the NHMRC claims fluoridation is safe is by denying any fluoride risk to thyroid function, denying a significant association with Osteosarcoma bone cancer, excluding, ignoring or downplaying links to ADHD and IQ deficit, and totally ignoring risk of cumulative effects for people with kidney impairment.

As part of their reasons for claiming that fluoridation is ethical the FRG in the ethics section of the information paper claimed that is ***"It is not possible to buy fluoride supplements."***

Apparently the NHMRC's FRG has never heard about eBay where it is easy to buy fluoride tablets (supplements)

Freedom of Information documents (NHMRC FOI 2016-17/019) indicate fluoridation lobbyists in the NHMRC's FRG committee played a large part in writing the Ethics section of the 2017 NHMRC's fluoridation Information Paper. It appears that apart from requesting some small cosmetic changes, The NHMRC's Australian Ethics Committee mostly just signed off on what the FRG had constructed.

21. NHMRC gave an incomplete project of dubious quality a prestigious NHMRC award

As one example of previous NHMRC bias - in August 2008 the NHMRC awarded Profs Clive Wright and Mike Morgan a prestigious NHMRC award – ***"One of the Ten Best Research Projects 2008"*** for their research project on water fluoridation and cost effectiveness. By 2011 the NHMRC had the status of Profs Wright/ Morgan project marked as complete – yet apparently only one published article (16) has ever been resulted from this project and that was published 2 years after Profs Wright/ Morgan were given the NHMRC award. Their article was published only in the Australian Dental Journal in 2010, not in an international dental journal of higher ranking. Profs Clive Wright and Mike Morgan's project lead researcher had died in May 2008 and it was unlikely that any other publications would ever eventuate. In 2014 the NHMRC appointed both Clive Wright and Mike Morgan to the NHMRC Fluoride Reference Group to do the NHMRC's upcoming review on fluoridation.

The Wright/ Morgan project was by supported by a NHMRC grant. Examining the projects Progress Reports to the NHMRC (obtained through Freedom of Information - NHMRC FOI 2011-00643) did not inspire any confidence in the quality of the project data that had been collected – yet the NHMRC still gave its prestigious award to Profs Wright and Morgan on an unfinished project of dubious quality. Also note – any fluoridation cost - effectiveness analyses are always one –sided, they never include the cost of treatment of dental fluorosis or ever consider any other potential adverse health effects.

22. NHMRC fluoridation public consultations have been shams.

The NHMRC had advised in 2016 public consultation would be available when the Information paper was released. However, the NHMRC's public consultations on fluoridation are total shams and farces. The ONLY public consultation submissions that the NHMRC will now accept is on the two sentence NHMRC Public Statement and then the NHMRC will only accept answers to the NHMRC's five very self- serving questions. Submissions and criticism of the actual Information paper, published 4 July 2017 <u>will NOT be accepted.</u> With the public consultation the public are not allowed to submit abstracts or narrative reviews – despite the FRG including an abstract and narrative they had selected**.**

In the NHMRC's 2014 public call for evidence, the NHMRC had limited all public submissions to 500 words. This ludicrous action by the NHMRC created some outrage. In 2016 the NHMRC would also not accept any submissions or criticism of the 2016 Technical Report, or the 2016 Evidence Evaluation report.

In other words, the NHMRC has given the public the opportunity to "vent off steam" but throughout the process has denied independent scientists a genuine opportunity to address the many flaws and weaknesses in this review in a substantial way. The whole thing has been a scam.

NHMRC's farcical public consultations are an insult to the many Australian citizens and scientists who have many years studying this subject in depth. This disdainful approach to seeking genuine and meaningful input is highly suggestive that the NHMRC knows that it is defending a very poor review on a very poor practice.

On the 13th September 2016, the NHMRC had a Webinar for journalists about NHMRC's draft Information Paper that was to be released the following day. The speakers were NHMRC CEO Anne Kelso and FRG member Prof Clive Wright. The NHMRC had prepared a PowerPoint presentation for the media with key messages that Australian fluoridation was safe and was not linked to any harm. Public consultation, restricted to only the NHMRC's draft Information paper, opened on the 14th Sept 2016, yet the NHMRC had already broadcast via Australian media that fluoridation was safe. The 2016 public consultation then was a total sham – there really was no point in letting the public submit contrary evidence when it was going to make no difference to the NHMRC's published claim that fluoridation was safe. In the end when the Information Paper was released on the 4th July 2017, the NHMRC would not even allow the public to submit submissions on it.

23. The NHMRC's extraordinary effort to maintain the dubious claims that fluoridation is safe, effective and ethical, are becoming more and more desperate by the year. NHMRC 2007 was very bad, NHMRC 2017 verges on fraud

The NHMRC administers nearly a BILLION dollars in taxpayer funds every near, yet with its fluoridation review have employed corrupt biased practices that ignore public health risks - and attempted to conceal such a unprofessional review by grossly limiting genuine input from the public - especially those who have studied the issue closely.

NHMRC's actions in its latest fluoridation review, if they had been done in a criminal trial, would be declared as a mistrial because (1) The Judge deliberately appointed a biased jury (2) The Judge declared the verdict of innocence before and also just after the trial had started (NHMRC reaffirmed its 2007 Recommendation statement in June 2013 and on 25 Feb 2015 (3) the Jury excluded or denied critical damaging evidence and then changed the trial to include evidence that had been declared as out of scope.

The NHMRC Recommendation (Public Statement) in 2007 was this –

> ***NHMRC Recommendation: Fluoridation of drinking water remains the most effective and socially equitable means of achieving community wide exposure to the caries prevention effects of fluoride. It is recommended that water be fluoridated in the target range of 0.6 to 1.1 mg/l depending on climate to balance reduction of dental caries and occurrence of dental fluorosis.*** *(Emphasis added)*

NHMRC's new Public Statement (released 4 July 2017) is now this –

> ***NHMRC Statement: NHMRC strongly recommends community water fluoridation as a safe, effective and ethical way to help reduce tooth decay across the population. NHMRC supports Australian states and territories fluoridating their drinking water supplies within the range of 0.6 to 1.1 milligrams per litre (mg/L)*** *(emphasis added)*

In a giant leap, the NHMRC after its biased review, is now claiming that water fluoridation is safe, yet they have ignored health issues (eg, kidney impairment) and denied others (cancer, loss of IQ etc).The NHMRC has never considered differential susceptibility and vulnerability that occurs within the population. The NHMRC, to shore up their public statement even censored any reference to climate, to balance and to fluoridation causing dental fluorosis. The NHMRC even claims fluoridation is ethical, however this claim was constructed by fluoridation lobbyists within the NHMRC and NHMRC FRG.

How can anyone trust the NHMRC after such biased self-serving irresponsible behaviour - and in the name of a public agency?

CONCLUSIONS:

The NHMRC has ignored its Duty of Care and betrayed the Australian public with its poor and perverted fluoride review. The NHMRC's fluoride review should be shredded.

We request that citizens and scientists from inside Australia and around the world will call for a Royal Commission inquiry to investigate the NHMRC's behavior in this matter. Hopefully they will call for a new review to be commissioned by the Federal government but carried out by an independent organization, with the panel comprised of unbiased scientists and professionals.

In terms of reviewing government policies in general, it is requested that the Royal Commission investigate the wisdom of using a government department such as NHMRC to review the science of controversial programs, when those programs have been part of long-standing government policy. Under such circumstances it is urged that the Royal Commission recommend such reviews be organized by a non-governmental agency. This agency would be required to select panels completely independent of governmental influence. Ideally such panels would consist of experts drawn from both sides of the issue in question, and those who have not taken a position on the issue: a good model would be the panel selected by the U.S. National Research Council for its review of fluoride's toxicity in 2006.

Authorised by M Haines on behalf of Fluoride Action Network Australia Inc.
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See table at end for examples on some of the known conflicts of interests on 10 members of the NHMRC Fluoride Reference Group (FRG)

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See following pages for examples on some of the known conflicts of interests on 10 members of the NHMRC Fluoride Reference Group (FRG)

A copy of the Queensland Government's 2003 Position Statement that acknowledges without the express of the community fluoridation is unethical mass medication is shown on the last page.

NHMRC Fluoride Reference Group Committee Member (FRG) 2014- 2017	KNOWN CONFLICTS OF INTEREST (known lobbyist for fluoridation / fluoridation supporter)
1 ***Dr Meenakshi Arora***	Supporter of fluoridation – as cited in interview by Bundaberg News Mail Dec 2009 " *Dr Meenakshi Arora, University of Melbourne research fellow for chemical and biomolecular engineering and a supporter of fluoridation, told a press conference on the subject: "It definitely and significantly reduces the risk of dental caries. But we need to be careful not to overdose people, especially kids in the age range of two to seven years.*" http://fluoridealert.org/news/bundaberg-region-fluoride-in-two-years/
2 ***Assoc Prof Stephen Corbett***	**Corbett's paper "Fluoride : Benefits Far Outweigh Risks" published in 1993 NSW Health Public Health Bulletin** can be downloaded here – http://www.health.nsw.gov.au/phb/Documents/1993-08.pdf or just the 2 actual pages here - http://www.publish.csiro.au/?act=view_file&file_id=NB93040.pdf **Claimed that dental fluorosis in NSW in 1993 was only 3 % (he didn't specify that that would only be the rate of Moderate fluorosis) NOTE – Ass Prof Corbett was only listed as a FRG member AFTER the NHMRC 2014 Call for Evidence had closed**
3 ***Ass Prof Sharon Goldfeld***	Associate Professor Sharon Goldfeld, Chair of the P&CHD Paediatric Oral Health Working Group. (RACP Paediatric & Child Health Division (P&CHD) – "The RACP and the RACDS, through their Child Oral Health Statement, have called for oral health awareness in the training of all health professionals who work with children. Collaborative public health approaches have also been identified, including healthcare professional **training and public water fluoridation for all communities with populations greater than 1,000 people. The RACP and RACDS intend to partner around many of these issues** to effect more positive outcomes on the oral health of children and young people. Source - Bite Magazine 20th Sept 2012 - Member of Public Health Association of Australia (PHAA) joined in 2000. PHAA has for many years actively lobbied for fluoridation – particularly for Qld.
4 ***Prof Alison Jones***	As part of NSW Health team presented the Yes case for fluoridation at Byron Bay public information evening - 16th October 2013**. Was also part of NSW Health team earlier in 2013 giving briefing sessions promoting fluoridation to Lismore and Ballina Councils** http://www.abc.net.au/news/2013-10-17/byron-fluoro-meeting/5028058 "But a medical specialist has described the mythology and fears around fluoridation of drinking water as 'nonsense'. Wollongong University's Dean of Medicine and Toxicology, **Professor Alison Jones told the crowd that there was no evidence to support such claims."**
5 ***Dr Frederic Leusch***	"Too little fluoride, less than 0.1 mg/L in drinking water, leads to poor dental health and high incidence of dental decay" plus other quotes in May 27 2014 Sun Coast News http://www.suncoasttimes.com.au/features/something-in-the-water/

NHMRC Fluoride Reference Group Committee Member (FRG) 2014- 2017	KNOWN CONFLICTS OF INTEREST (known lobbyist for fluoridation / fluoridation supporter)
6 ***Prof Mike Morgan***	NHMRC Podcast 19 Feb 2009 - And the downsides? **"Extremely minimal," Professor Mike Morgan, Colgate Chair of Population Oral Health a**t the Melbourne Dental School tells interviewer Stuart Cameron. http://www.nhmrc.gov.au/media/podcasts/2009/we-know-fluoride-saves-teeth-it-cost-effective Part of Clive Wright's team which won NHMRC 10 of the Best Research Projects of 2008 NHMRC article titled " Linking water fluoridation with good dental health " http://www.oralhealthcrc.org.au/content/professor-mike-morgan-0 "Professor Morgan's principal teaching responsibility is in population oral health, focusing on oral disease causation in relation to common risk factors and disease prevention at a population level **- with an emphasis on community water fluoridation" "**He has been a consultant to the Victorian Government in areas such as the Auditor General's review into public dental services and the recent Victorian Government's expansion of community water fluoridation in Victoria."
7 ***Dr Katherine O 'Donoghue***	**President, Indigenous Dentists' Association - an association which wants all Indigenous communities of more than 500 people fluoridated** *"Indigenous Dentists' Association of Australia - Indigenous Oral Health Goals"* – extract **Goal 1. Community water fluoridation Target** **All indigenous communities with a population of more than 1000 will have a fluoridated water supply by 2015.** **All indigenous communities with a population of more than 500 will have a fluoridated water supply by 2020** **Qld Health dental employee - Service Line Director of Oral Health, Oral Health Services, Queensland Health (Qld Health actively promotes fluoridation)**
8 ***Prof Kaye Roberts-Thomson***	Interim Dean and Head of School of Dentistry and Director, Dental Practice Education Research Unit, Australian Research Centre for Population Oral Health, The University of Adelaide **– has continuously promoted fluoridation for years.** Recipient of grant money from AIHW and NHMRC **- has used emanating publications to promote fluoridation** (child dental health surveys, national adult oral health survey)
9 ***Emeritus Prof A. John Spencer***	**Participated in two NSW Land and Environment court cases - (1) to help Rous Water, Lismore and Ballina Councils be able to fluoridate their jurisdictions (2011) (2) to assist continued fluoridation by Eurobodalla Council (2013)** Former director of Australian Research Centre for Population Oral Health, The University of Adelaide – has continuously promoted fluoridation for years. Recipient of grant money from AIHW and NHMRC – has used emanating publications to promote fluoridation (child dental health surveys, national adult oral health survey). His 1996 study comparing fluoridated Townsville to non-fluoridated Brisbane children was used by Bligh govt in 2007 to mandate Qld fluoridation. More recently recipient of approx $900, 000 from Qld Health to analyse data report on baseline of fluoridation in Qld

NHMRC Fluoride Reference Group Committee Member (FRG) 2014- 2017	KNOWN CONFLICTS OF INTEREST (known lobbyist for fluoridation / fluoridation supporter)
10 *Prof (Frederick) Clive Wright*	**As NSW Chief Dental Officer he had participated in 2011 NSW Land and Environment court cases to help Rous Water, Lismore and Ballina Councils be able to fluoridate their jurisdictions.** Recipient of NHMRC grants which he has used to promote fluoridation. Chief Investigator of team, which won NHMRC 10 of the Best Research Projects of 2008 - NHMRC article titled " Linking water fluoridation with good dental health" – this win despite the research not being completed due to the death of the lead researcher and only one article that was published in the Australian Dental Journal

Queensland Government
Position Statement on Water Fluoridation

Whilst recognising that the balance of the scientific argument favours the use of fluoride in the pursuit of oral health, it is a principle of ethical public health that mass, involuntary medication must never proceed without the express consent of the community. The balance of argument rests on evidence which suggests that the prevalence of dental caries in both adults and children is reduced in communities where the water supply contains certain levels of fluoride.

In Queensland, referendum guarantees the consent of the community under the Fluoridation of Public Water Supplies Act (1963) (the Act). Queensland Government recognises that there is not a unanimity of opinion on the health and environmental impacts of fluoridation, but in view of the prevailing balance of argument, encourages public debate aimed at enhancing oral health.

Water fluoridation was introduced in all Australian States in the 1960's, and about 80 per cent of the population of most states now receive fluoridated water supplies. The Nicklin Government introduced the Act in Queensland in 1963. It places the responsibility for proposing this public health measure to communities, and carrying out their decisions, on individual local governments. At present, only about 5% of the Queensland population have consented to the fluoridation of their water.

Queensland Government supports the introduction of water fluoridation wherever it receives the consent of the community affected. It acknowledges the endorsement of fluoridation by many science and health organisations, including the National Health and Medical Research Council, Federation Dentaire Internationale (FDI), the International Association for Dental Research (IADR), and the World Health Organisation (WHO).

The achievement of improvements in oral health in the population is one of the Key Performance Objectives set out in the Queensland Health Corporate Plan 1996-2001. The fluoridation of water supplies may be one avenue for the achievement of the oral health objectives set out in this document, and the Public Health Services Plan for Achievements 1996-1999

Queensland Government

Queensland Health 2003

Press Release
Fluoride Action Network Australia
August 3, 2017

A damning critique and analysis of the NHMRC's 2017 "Sham" review of water fluoridation and appeal for Royal Commission Inquiry:

23 Reasons why Australia needs a Royal Commission into the NHMRC's fraudulent fluoride review

EXECUTIVE SUMMARY

August 3, 2017, was the deadline for very limited public comment on a draft Public Statement on Water Fluoridation by the Australian government's National Health and Medical Research Council (NHMRC). This Public Statement was drawn largely from these documents:

> 2017: National Health and Medical Research Council (NHMRC). Information Paper - Water Fluoridation: dental and other human health outcomes. July.
>
> 2016: Health Effects of Water Fluoridation: Technical Report. Report to the National Health and Medical Research Council (NHMRC), Canberra. By Jack B, Ayson M, Lewis S, Irving A, Agresta B, Ko H, Stoklosa A. August 24, 2016, (released in September). 322 pages.
>
> 2016: Health Effects of Water Fluoridation: Evidence Evaluation Report. Report to the National Health and Medical Research Council (NHMRC), Canberra. By Jack B, Ayson M, Lewis S, Irving A, Agresta B, Ko H, Stoklosa A. August 24, 2016, (released in September). 284 pages.

On behalf of the Fluoride Action Network Australia, Merilyn Haines is calling for a Royal Commission to investigate the manner in which the Australian government's NHMRC conducted its review of the safety, effectiveness and ethics of Water Fluoridation.

Haines charges that a) the 2017 NHMRC review of water fluoridation was unprofessional, unscientific, biased, highly selective, deeply flawed and prevented meaningful scientific and public input and b) other NHMRC activities - outside this review (see items 12 and 21 below) - clearly demonstrate a bias of the NHMRC (a federal government agency) in favor of both promoting and defending the practice of water fluoridation - a long-standing government policy.

In examining the manner in which the panelists were selected, the way studies were selected and excluded, the very limited opportunities for public participation and independent scientific input, Haines argues that it is hard to come to any other conclusion than that this review was designed simply to defend a long-standing government policy and not to genuinely examine the science (or lack of science) on which it is based. This is not the first time this has happened.

The NHMRC produced a very poor review in 2007 which received extensive criticism from independent scientists. To produce an even more biased and restrictive review in 2016 is even more egregious in lieu of the new science published (or updated) since 2007.

For example, on effectiveness, the 2015 Cochrane review (a gold standard when it comes to meta-analysis of health issues) found little in the way of high quality studies to demonstrate the effectiveness of fluoridation. On safety, there have now been over 300 published animal and human studies indicating that fluoride is neurotoxic. This large body of evidence has been largely ignored in the 2017 NHMRC review, even though it is being currently scrutinized by the National Institute of Health Sciences (NIEHS) and the National Toxicology Program (NTP) in the USA.

In this analysis, 23 specific examples of NHMRC manipulations have been documented. Many of these by themselves should disqualify the NHMRC 2017 review from serious consideration, but in combination should question the very existence of the NHMRC as a body that can be relied upon by the public and decision-makers to provide objective analysis of government policy.

Here are the 23 examples:

The NHMRC,

1. Stacked the fluoride review committee with fluoridation lobbyists and advocates.

2. Broke a promise that it would include experts opposed to fluoridation.

3. Secretly commissioned a new study on dental effects (previously listed as "out of scope"), when the 2015 Cochrane Collaboration review didn't deliver a convincing pro-fluoridation position.

4. First, misled about its knowledge of a new thyroid study (Peckham et al., 2015) and then dismissed its findings, reaching a biased and false position that there is no evidence that fluoride interferes with thyroid function.

5. Falsely claimed a low-quality IQ study (Broadbent et al, 2014) was a high-quality study.

6. Downplayed, dismissed or excluded most other IQ studies and evidence of fluoride's neurotoxicity.

7. On flimsy grounds excluded a significant study linking fluoridation to ADHD (Malin and Till, 2015) – then failed to even acknowledge its existence.

8. In 2007, the NHMRC used a *promised* study in a Letter-to-the-Editor to negate an unrefuted Osteosarcoma study (Bassin, 2006) to claim there was no link to cancer. Then in its 2017 review the NHMRC failed to acknowledge that the promised study failed to refute the Bassin study but still continued to maintain no evidence of a link between fluoridation and cancer.

9. Selected a publication cut–off date for studies (that would be considered) that would exclude a very significant review by the US NRC (2006) and the Bassin (2006) study that were not given due consideration in its 2007 review.

10. The NHMRC 2017 review based its claims of safety largely on its 2007 review, however, its 2007 review was largely a copy of the 2000 York University review, which according to the York Review's Professor Sheldon did NOT show fluoridation to be safe!

11. Obfuscated on chronic kidney disease even though it is aware that poor kidney function increases uptake of fluoride into the bones and poses risks over a lifetime. Such cumulative risks – and the special plight of those with poor kidney function –have never been investigated by NHMRC.

12. On another but related matter, the NHMRC endorsed doubling children's upper safety limits for fluoride ingestion (using data from the 1930s) almost certainly anticipating that the pre-existing limits would be exceeded by bottle-fed infants in which formula is made up with fluoridated tap-water.

13. Abandoned the normal evaluation method for studies of fluoride's effectiveness almost certainly in an effort to disguise the fact that most of the studies reviewed were of low, or very low quality.

14. NHMRC 2017 rates tooth decay and dental fluorosis as more important end-points than other health incomes, including cancer and lowered IQ.

15. Commenced review with strict restrictions for acceptable evidence, then included a) unpublished work; b) a favourable narrative and c) an abstract.

16. Attempted to diminish known dental fluorosis harm by manipulating fluorosis ratings and raising threshold of concern.

17. Misleads the public and decision-makers by claiming fluoridation reduces tooth decay by 26-44 % - but without indicating just how small such reductions are in absolute terms – often less than one tooth surface out of over 100 tooth surfaces in a child's mouth!

18. Dishonestly claims fluoridation is safe by excluding important studies on spurious grounds, ignoring many others, and even cherry-picking weak studies that serve their purpose (e.g. Broadbent on IQ).

19. Doesn't exhibit an understanding of, or appreciate, the basic principles of toxicology – concentration is not the same as dose!

20. Perverted the principles of medical ethics by presenting a bogus ethical claim constructed by lobbyists rather than ethicists.

21. Gave an incomplete project of dubious quality a prestigious NHMRC award

22. NHMRC fluoridation public consultations have been shams.

23. The NHMRC's extraordinary effort to maintain the dubious claims that fluoridation is safe, effective and ethical, are becoming more and more desperate by the year. NHMRC 2007 was very bad, NHMRC 2017 verges on fraud.

Conclusions

The NHMRC has ignored its Duty of Care and betrayed the Australian public with its poor and perverted fluoride review. The NHMRC's fluoride review should be shredded.

We request that citizens and scientists from inside Australia and around the world will call for a Royal Commission inquiry to investigate the NHMRC's behavior in this matter. Hopefully they will call for a new review to be commissioned by the Federal government but carried out by an independent organization, with the panel comprised of unbiased scientists and professionals.

In terms of reviewing government policies in general, it is requested that the Royal Commission investigate the wisdom of using a government department such as NHMRC to review the science of controversial programs, when those programs have been part of long-standing government policy. Under such circumstances it is urged that the Royal Commission recommend such reviews be organized by a non-governmental agency. This agency would be required to select panels completely independent of governmental influence. Ideally such panels would consist of experts drawn from both sides of the issue in question, and those who have not taken a position on the issue: a good model would be the panel selected by the U.S. National Research Council for its review of fluoride's toxicity in 2006.

From: Christine Massey [redacted]
Sent: September 22, 2017 11:25 AM
To: Thompson, Allan; Downey, Johanna; Groves, Annette; Innis, Jennifer; Shaughnessy, Barb; Jeffrey, Linda Mayor; Gibson, Grant; Medeiros, Martin; Miles, Gael; Moore, Elaine; Palleschi, Michael; Crombie, Bonnie; Carlson, George; Fonseca, Chris; Iannicca, Nando; Kovac, John; Mahoney, Matt; McFadden, Sue; Parrish, Carolyn; Ras, Karen; Saito, Pat; Starr, Ron; Tovey, Jim; Loh, Lawrence; Polsinelli, Nancy; Szwarc, David; Smith, Janette; Hennings, Jeff; Jim Nardi; ZZG-RegionalClerk; O'Connor, Patrick; Burkiewicz, Justyna; ZZG-WaterQualityInquiries; Sprovieri, John; Hau, Monica; Ward, Megan; Bingham, Kate; Hopkins, Jessica
Cc: Mark Corlett; Vladimir Gagachev
Subject: new study: Fluoride Exposure in Utero Linked to Lower IQ in Kids

Dear Peel Council / CWFC Members, Medical Officer Hopkins, Commissioner Polsinelli, Commissioner Smith, CAO Szwarc, Regional Clerk Lockyer, Mr. Hennings and Mr. Nardi,

[Please add this email to the next Council agenda.]

A new, highly relevant study entitled "*Prenatal Fluoride Exposure and Cognitive Outcomes in Children at 4 and 6–12 Years of Age in Mexico*" was published 3 days ago (see attached).

"BACKGROUND: Some evidence suggests that fluoride may be neurotoxic to children ...

... CONCLUSIONS: In this study, higher prenatal fluoride exposure, in the general range of exposures reported for other general population samples of pregnant women and nonpregnant adults, was associated with lower scores on tests of cognitive function in the offspring at age 4 and 6–12 y."

[The public may read/download the study here: http://www.fluoridefreepeel.ca/wp-content/uploads/2017/09/2017-Prenatal-Fluoride-Exposure-cognitive-impacts-on-4-and-6-12-year-olds.pdf]

[When reading the following, please keep in mind that dentists defending water fluoridation are the same group that fill cavities with "silver/amalgam", which is in fact 50% mercury, one of the most toxic substances known to humanity - a practice banned in the EU for children, pregnant and breastfeeding women as of July 1, 2018.]

The following summary is from the Fluoride Action Network:
http://fluoridealert.org/articles/fluoride-exposure-in-utero-linked-to-lower-iq-in-kids-new-study-says/

"Fluoride Exposure in Utero Linked to Lower IQ in Kids, New Study Says

In a new study published on September 19, 2017, in the journal *Environmental Health Perspectives*, researchers have found a link between fluoride in the urine of pregnant women and lower measures of intelligence in children.

The Study:

Bashash M, Thomas D, Hu H, et al. 2017. Prenatal Fluoride Exposure and Cognitive Outcomes in Children at 4 and 6–12 Years of Age in Mexico.

REFERRAL TO _____
RECOMMENDED
DIRECTION REQUIRED _____
RECEIPT RECOMMENDED ✓ _____

Excerpt from study: In this study, higher levels of maternal urinary fluoride during pregnancy (a proxy for prenatal fluoride exposure) that are in the range of levels of exposure in other general population samples of pregnant women as well as nonpregnant adults were associated with lower scores on tests of cognitive function in the offspring at 4 and 6–12 y old.

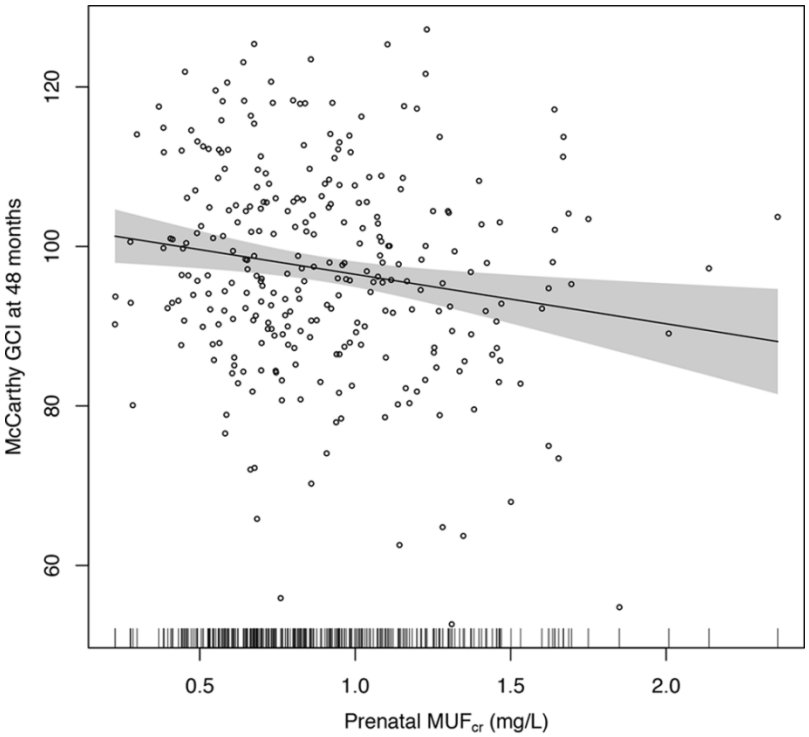
Comment from FAN:

The new study found a very large effect. An increase in urine fluoride of 1 mg/L was associated with a drop in IQ of 5 to 6 points. To put this into perspective with the fluoride levels ingested by the Mexican mothers and the levels ingested in fluoridated parts of the USA, the average fluoride intake in the Mexican mothers was about the same as that in women in the USA. It was not substantially higher. The range of fluoride levels in Mexico also corresponded closely to the range found in most of the USA. The higher levels were similar to what is found in areas in the USA with fluoridated water, and the lower levels were similar to what is found in most unfluoridated parts of the USA.

Most of the Mexican women had urine fluoride between 0.5 and 1.5 mg/L. Studies have found that adults in the USA have between about 0.6 and 1.5 mg/L, almost exactly the same range. From the low end of that range to the high end is a difference of 1 mg/L which is what caused the 5 to 6 IQ point difference in the children of the study mothers.

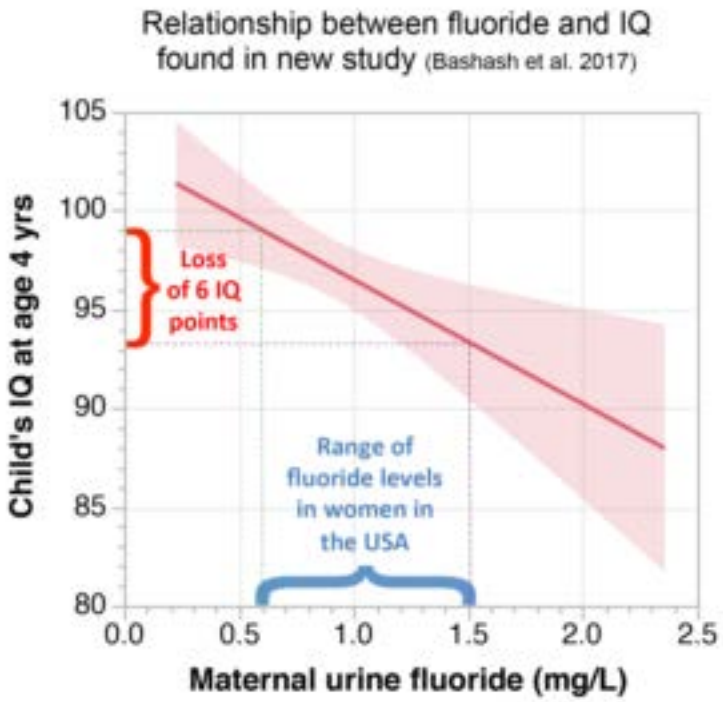
This new study had fluoride exposures almost the same as what is found in fluoridating countries like the USA.

The paper shows the relationship between urine fluoride and IQ in the graph (Figure 2) reproduced here:



The data in this graph has been adjusted for numerous potential confounding factors like sex, birth weight, gestational age, and whether the mother smoked. Other potential confounders had already been ruled out, including lead, mercury, alcohol consumption during pregnancy, mother's education, mother's IQ, and quality of home environment.

FAN has redrawn this graph in simplified form to better illustrate the relationship found between mothers' urine fluoride and childrens' IQ.



This simplified version of the graph highlights the range of urine fluoride levels common in women in the USA with the blue text and bracket. When comparing mothers at the low end to those at the high end of this range, the subsequent loss of IQ in their children was 6 points. The light red shaded zone around the relationship line is the 95% Confidence Interval and demonstrates that the relationship is statistically significant across the entire range of fluoride exposures.

Quotes:

Newsweek, Children's IQ Could Be Lowered By Mothers Drinking Tap Water While Pregnant, by Dana Dovey, September 19:

… "This is a very well-conducted study, and it raises serious concerns about fluoride supplementation in water," says Dr. Leonardo Trasande, a pediatrician who studies potential links between environmental exposures and health problems at New York University Langone Health. (He was not involved in the new study.)

Trasande emphasizes that the levels of fluoride seen among the mothers in this study are slightly higher than what would be expected in U.S., based on current fluoride supplementation levels. However, he also explains that fluoride is known to disrupt thyroid function, which in turn is crucial for brain development.

"These new insights raise concerns that the prenatal period may be highly vulnerable and may require additional reconsideration," Trasande says.

CTV (Canadian TV), Higher levels of fluoride in urine linked to lower IQ scores in children, by Angela Mulholland, September 19:

… Dr. Howard Hu, the study's lead investigator, and a professor of environmental health, epidemiology and global health at [the University of Toronto's] Dalla Lana School of Public Health, says the fact that the fluoride levels in the mothers was most predictive of the drop in test scores may be due to the fact that the brains of babies develop so rapidly while they are in utero.

"This is consistent with a growing appreciation in environmental health that the growing fetal nervous system is more sensitive to exposures than a developed nervous system," he told CTVNews.ca by phone from Sydney.

Both the Montreal Gazette & the National Post ran the same article**:** *Researchers urge caution over study linking fluoride exposure in pregnancy to lower IQs in children,* by Sharon Kirkey, September 21:

… [The article quotes the lead investigator of the study, Dr Howard Hu:] "This is a very rigorous epidemiology study. You just can't deny it. It's directly related to whether fluoride is a risk for the neurodevelopment of children. So, to say it has no relevance to the folks in the U.S. seems disingenuous."

… "Why would anybody rate the equivalency or supremacy of reducing tooth decay by about one cavity a lifetime when what's at stake is the mental development of your children? It's utterly preposterous," said Connett, executive director of the Fluoride Action Network.

Press Releases:

University of Toronto: *Higher levels of fluoride in urine associated with lower intelligence in children*. The study's lead investigator, Dr Howard Hu, is Professor of Environmental Health, Epidemiology and Global Health at the University's Dalla Lana School of Public Health. September 19.

… "Our study shows that the growing fetal nervous system may be adversely affected by higher levels of fluoride exposure," said Dr. Howard Hu, the study's principal investigator … "It also suggests that the pre-natal nervous system may be more sensitive to fluoride compared to that of school-aged children."

American Dental Association Response to Study Regarding Fluoride Intake in Mexico. September 19.

The American Dental Association (ADA) examined a study in Environmental Health Perspectives based on fluoride intake in Mexico, and concludes the findings are not applicable to the U.S. The ADA continues to endorse fluoridation of public water as the most effective public health measure to prevent tooth decay…

Fluoride Free New Zealand issued this press release New US Government Study on Fluoride Damage to Brain on September 21.

[In response to the study] Fluoride Free New Zealand is calling on the 23 councils (out of the total of 67) that still fluoridate, to urgently implement a moratorium on fluoridation to protect the brains of children being born today in their community… This is particularly relevant to New Zealand where half of the population is currently subjected to fluoridation…

Articles:

CTV (Canadian TV), Higher levels of fluoride in urine linked to lower IQ scores in children, by Angela Mulholland, September 19.

Collective Evolution, Fluoride exposure in utero linked to lower IQ in kids, study says, by Kalee Brown, September 20.

Daily Mail (UK), Pregnant women exposed to flouride are more likely to have kids with low IQ, study shows, by Mia De Graaf, September 20.

Medical Xpress, Higher levels of fluoride in pregnant woman linked to lower intelligence in their children, by Nicole Bodnar, September 20.

Montreal Gazette: Researchers urge caution over study linking fluoride exposure in pregnancy to lower IQs in children, by Sharon Kirkey, September 20.

Newsweek, Children's IQ Could Be Lowered By Mothers Drinking Tap Water While Pregnant, by Dana Dovey, September 19.

Readers' Digest, If you drink this type of water during pregnancy, your child's IQ could suffer, by Sam Benson Smith, September 20."

Best wishes,
Christine Massey, M. Sc.

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Prenatal Fluoride Exposure and Cognitive Outcomes in Children at 4 and 6–12 Years of Age in Mexico

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Background: Some evidence suggests that fluoride may be neurotoxic to children. Few of the epidemiologic studies have been longitudinal, had individual measures of fluoride exposure, addressed the impact of prenatal exposures or involved more than 100 participants.

Objective: Our aim was to estimate the association of prenatal exposure to fluoride with offspring neurocognitive development.

Methods: We studied participants from the Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) project. An ion-selective electrode technique was used to measure fluoride in archived urine samples taken from mothers during pregnancy and from their children when 6–12 y old, adjusted for urinary creatinine and specific gravity, respectively. Child intelligence was measured by the General Cognitive Index (GCI) of the McCarthy Scales of Children's Abilities at age 4 and full scale intelligence quotient (IQ) from the Wechsler Abbreviated Scale of Intelligence (WASI) at age 6–12.

Results: We had complete data on 299 mother–child pairs, of whom 287 and 211 had data for the GCI and IQ analyses, respectively. Mean (SD) values for urinary fluoride in all of the mothers ($n = 299$) and children with available urine samples ($n = 211$) were 0.90 (0.35) mg/L and 0.82 (0.38) mg/L, respectively. In multivariate models we found that an increase in maternal urine fluoride of 0.5 mg/L (approximately the IQR) predicted 3.15 (95% CI: −5.42, −0.87) and 2.50 (95% CI −4.12, −0.59) lower offspring GCI and IQ scores, respectively.

Conclusions: In this study, higher prenatal fluoride exposure, in the general range of exposures reported for other general population samples of pregnant women and nonpregnant adults, was associated with lower scores on tests of cognitive function in the offspring at age 4 and 6–12 y. https://doi.org/10.1289/EHP655

Introduction

Community water, salt, milk, and dental products have been fluoridated in varying degrees for more than 60 y to prevent dental caries, while fluoride supplementation has been recommended to prevent bone fractures (Jones et al. 2005). In addition, people may be exposed to fluoride through the consumption of naturally contaminated drinking water, dietary sources, dental products, and other sources (Doull et al. 2006). Whereas fluoride is added to drinking water [in the United States at levels of 0.7–1.2 mg/L (Doull et al. 2006)] to promote health, populations with exceptionally high exposures, often from naturally contaminated drinking water, are at risk of adverse health effects, including fluorosis.

In the United States, the U.S. Environmental Protection Agency (EPA) is responsible for establishing maximum permissible concentrations of contaminants, including fluoride, in public drinking-water systems. These standards are guidelines for restricting the amount of fluoride contamination in drinking water, not standards for intentional drinking-water fluoridation. In 2006 the U.S. EPA asked the U.S. National Research Council (NRC) to reevaluate the existing U.S. EPA standards for fluoride contamination, including the maximum contaminant level goal (MCLG, a concentration at which no adverse health effects are expected) of 4 mg/L, to determine if the standards were adequate to protect public health (Doull et al. 2006). The committee concluded that the MCLG of 4 mg/L should be lowered because it puts children at risk of developing severe enamel fluorosis, and may be too high to prevent bone fractures caused by fluorosis (Doull et al. 2006). The Committee also noted some experimental and epidemiologic evidence suggesting that fluoride may be neurotoxic (Doull et al. 2006).

The National Toxicology Program (NTP) recently reviewed animal studies on the effects of fluoride on neurobehavioral outcomes and concluded that there was a moderate level of evidence for adverse effects of exposures during adulthood, a low level of evidence for effects of developmental exposures on learning and memory, and a need for additional research, particularly on the developmental effects of exposures consistent with those resulting from water fluoridation in the United States (Doull et al. 2006; NTP 2016). Human studies have shown a direct relationship between the serum fluoride concentrations of maternal venous blood and cord blood, indicating that the placenta is not a barrier to the passage of fluoride to the fetus (Shen and Taves, 1974). Fluoride was shown to accumulate in rat brain tissues after chronic exposures to high levels, and investigators have speculated that accumulation in the hippocampus might explain effects on learning and memory (Mullenix et al. 1995). An experimental study on mice has shown that fluoride exposure may have adverse effects on neurodevelopment, manifesting as both cognitive and behavioral abnormalities later in life (Liu et al. 2014).

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Most epidemiologic studies demonstrating associations between fluoride exposure and lower neuropsychological indicators have been conducted in populations living in regions with endemic fluorosis that are exposed to high levels of fluoride in contaminated drinking water. The epidemiologic evidence is limited, however, with most studies using an ecologic design to estimate childhood exposures based on neighborhood measurements of fluoride (e.g., drinking water levels) rather than personal exposure measures. Moreover, almost all existing studies of childhood outcomes are cross-sectional in nature, rendering them weak contributors towards causal inference.

The main objective of this study was to assess the potential impact of prenatal exposures to fluoride on cognitive function and test hypotheses related to impacts on overall cognitive function. We hypothesized that fluoride concentrations in maternal urine samples collected during pregnancy, a proxy measure of prenatal fluoride exposure, would be inversely associated with cognitive performance in the offspring children. Overall, to our knowledge, this is one of the first and largest longitudinal epidemiologic studies to exist that either address the association of early life exposure to fluoride to childhood intelligence or study the association of fluoride and cognition using individual biomarker of fluoride exposure.

Methods

This is a longitudinal birth cohort study of measurements of fluoride in the urine of pregnant mothers and their offspring (as indicators of individual prenatal and postnatal exposures to fluoride, respectively) and their association with measures of offspring cognitive performance at 4 and 6–12 y old. The institutional review boards of the National Institute of Public Health of Mexico, University of Toronto, University of Michigan, Indiana University, and Harvard T.H. Chan School of Public Health and participating clinics approved the study procedures. Participants were informed of study procedures prior to signing an informed consent required for participation in the study.

Participants

Mother–child pairs in this study were participants from the successively enrolled longitudinal birth cohort studies in Mexico City that comprise the Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) project. Of the four ELEMENT cohorts [that have been described elsewhere (Afeiche et al. 2011)], Cohort 1 and Cohort 2B recruited participants at birth and did not have archived maternal-pregnancy urine samples required for this analysis; they were thus excluded. Mothers for Cohort 2A ($n = 327$) and 3 ($n = 670$) were all recruited from the same three hospitals in Mexico City that serve low-to-moderate income populations. Cohort 2A was an observational study of prenatal lead exposure and neurodevelopmental outcomes in children (Hu et al. 2006). Women who were planning to become pregnant or were pregnant were recruited during May 1997–July 1999 and were considered eligible if they consented to participate; were ≤ 14 wk of gestation at the time of recruitment; planned to stay in the Mexico City study area for at least 5 y; did not report a history of psychiatric disorders, high-risk pregnancies, gestational diabetes; did not report current use of daily alcohol, illegal drugs, and continuous prescription drugs; and were not diagnosed with preeclampsia, renal disease, circulatory diseases, hypertension, and seizures during the index pregnancy.

Cohort 3 mothers were pregnant women (≤ 14 wk of gestation) recruited from 2001 to 2003 for a randomized trial of the effect of calcium supplementation during pregnancy on maternal blood lead levels (Ettinger et al. 2009). Eligibility criteria were the same as for Cohort 2A, and 670 agreed to participate.

Exposure Assessment

By virtue of living in Mexico, individuals participating in the study have been exposed to fluoridated salt (at 250 ppm) (Secretaría-de-Salud 1995, 1996) and to varying degrees of naturally occurring fluoride in drinking water. Previous reports, based on samples taken from different urban and rural areas, indicate that natural water fluoride levels in Mexico City may range from 0.15 to 1.38 mg/L (Juárez-López et al. 2007; Martínez-Mier et al. 2005). Mean fluoride content for Mexico City's water supply is not available because fluoride is not reported as part of water quality control programs in Mexico.

Mother–child pairs with at least one archived urine sample from pregnancy and measures of neurocognitive function in the offspring were included in this study. In terms of when the archived samples were collected, the pregnant mothers were invited for assessments with the collection of samples during trimester 1 (13.6 ± 2.1 wk for Cohort 3 and 13.7 ± 3.5 wk for Cohort 2A), trimester 2 (25.1 ± 2.3 wk for Cohort 3 and 24.4 ± 2.9 wk for Cohort 2A), and trimester 3 (33.9 ± 2.2 wk for Cohort 3 and 35.0 ± 1.8 wk for Cohort 2A).

A spot (second morning void) urine sample was targeted for collection during each trimester of pregnancy of ELEMENT mothers as well as the offspring children at the time of their measurements of intelligence at 6–12 y old. The samples were collected into fluoride-free containers and immediately frozen at the field site and shipped and stored at -20°C at the Harvard T. H. Chan School of Public Health (HSPH), and then at -80°C at the University of Michigan School of Public Health (UMSPH).

A procedure for urine analysis of fluoride described elsewhere (Martínez-Mier et al. 2011) was adapted and modified for this study. The fluoride content of the urine samples was measured using ion-selective electrode-based assays. First, 3 M sulfuric acid saturated with hexamethyldisiloxane (HMDS) was added to the sample to allow fluoride to diffuse from the urine for 20–24 hr. The diffused fluoride was allowed to collect in 0.05 M of sodium hydroxide on the interior of the petri dish cover. Once the diffusion was complete, 0.25 M of acetic acid was added to the sodium hydroxide to neutralize the solution and then analyzed directly using a fluoride ion-selective electrode (Thermo Scientific Orion, Cat#13-642-265) and pH/ISE meter (Thermo Scientific Orion, Cat#21-15-001). All electrode readings (in millivolts) were calculated from a standard curve. Analyses were performed in a Class 100/1,000 clean room. Quality control measures included daily instrument calibration, procedural blanks, replicate runs, and the use of certified reference materials (Institut National de Santé Publique du Québec, Cat #s 0910 and 1007; NIST3183, Fluoride Anion Standard). Urinary fluoride concentrations were measured at the UMSPH and the Indiana University Oral Health Research Institute (OHRI) as previously described (Thomas et al. 2016). A validation study comparing measures taken by the two labs in the same samples revealed a between-lab correlation of 0.92 (Thomas et al. 2016).

There were a total of 1,484 prenatal samples measured at the UMSPH lab. All of these samples were measured in duplicate. Of these, 305 (20%) of them did not meet the quality control criteria for ion-selective electrode-based methods (i.e., RSD $<20\%$ for samples with F level <0.2 ppm or RSD $<10\%$ when F level >0.2 ppm) (Martinez-Mier et al. 2011). Of these 305, 108 had a second aliquot available and were successfully measured at the OHRI lab in Indiana (sufficient urine volume was not available for the remaining 197 samples). The OHRI lab in Indiana also measured an additional 289 samples. Of the 397

total samples measured at the OHRI lab in Indiana, 139 (35%) were measured in duplicate, for which >95% complied with the quality control criteria above; thus, all 139 values were retained. The remaining 258 (65%) were not measured in duplicate because of limitations in available urine volume, but were included in the study given the excellent quality control at the OHRI lab. In total, we ended up with 1,576 prenatal urine samples with acceptable measures of fluoride.

Of these 1,576 urine samples, 887 also had data on urinary creatinine and were associated with mother–offspring pairs who had data on the covariates of interest and GCI or IQ in the offspring. The urinary creatinine data were used to correct for variations in urine dilution at the time of measurement (Baez et al. 2014). Creatinine-adjusted urinary fluoride concentrations were obtained for each maternally derived sample by dividing the fluoride concentration (MUF) in the sample by the sample's creatinine concentration (MUC), and multiplying by the average creatinine concentration of samples available at each trimester ($MUC_{average}$) using the formula: $(MUF/MUC) \times MUC_{average}$. The values of average creatinine concentration used for the $MUC_{average}$ at each trimester were derived from the larger pool of trimester-1, -2, and -3 samples from Cohorts 2A and 3 examined in our previous report on maternal fluoride biomarker levels (Thomas et al. 2016): 100.81, 81.60, and 72.41 (mg/L), respectively. For each woman, an average of all her available creatinine-adjusted urinary fluoride concentrations during pregnancy (maximum three samples and minimum one sample) was computed and used as the exposure measure (MUF_{cr}). For children, as creatinine measurements were not available, urinary fluoride values (CUF) were corrected for specific gravity (SG) using the formula $CUFsg = CUF(1.02-1)/(SG-1)$ (Usuda et al. 2007).

After calculating MUF_{cr} for the 887 urine samples noted above, 10 values of MUF_{cr} were identified as extreme outliers (>3.5 SDs) and were dropped, leaving 877 measures of MUF_{cr}. These 877 measures of MUF_{cr} stemmed from 512 unique mothers. Of these 512, 71 participants had measurements from each of the three trimesters; 224 had measurements from two of the three trimesters (74, T1 and T2; 131, T1 and T3; and 19, T2 and T3); and 217 had measurements from only one of the trimesters (159, T1; 34, T2; and 24, T3).

Measurement of Outcomes

At age 4 y, neurocognitive outcomes were measured using a standardized version of McCarthy Scales of Children's Abilities (MSCA) translated into Spanish (McCarthy 1991). MSCA evaluates verbal, perceptual-performance, quantitative, memory, and motor abilities of preschool-aged children, and it has previously been successfully used in translated versions (Braun et al. 2012; Julvez et al. 2007; Kordas et al. 2011; Puertas et al. 2010). For this analysis, we focused on the General Cognitive Index (GCI), which is the standardized composite score produced by the MSCA (McCarthy 1991). For children 6–12 y old a Spanish-version of the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler 1999) was administered. WASI includes four subtests (Vocabulary, Similarities, Block Design, and Matrix Reasoning), which provide estimates of Verbal, Performance, and Full-Scale IQ (Wechsler 1999). Both tests were administered by a team of three psychologists who were trained and supervised by an experienced developmental psychologist (L.S.). This team of three psychologists applied all of the McCarthy tests as well as the WASI-FSIQ tests. At the time of follow-up visits (age 4 and 6–12 y), each child was evaluated by one of the psychologists who was blind to the children's fluoride exposure. The inter-examiner reliability of the psychologists was evaluated by having all three psychologists participate in assessments on a set of 30 individuals. For these 30, the inter-examiner reliability of the psychologists was evaluated by calculating the correlation in GCI scores by two of the psychologists with the scores of a third psychologist whom they observed applying the test in all three possible combinations with 10 participants for each observers–examiner pair (i.e., psychologist A (applicant) was observed by psychologist B and psychologist C; psychologist B (applicant) was observed by psychologist A and psychologist C; and psychologist C (applicant) was observed by psychologist A and psychologist B). The mean observer–examiner correlation was 0.99. All raw scores were standardized for age and sex (McCarthy 1991). Inter-examiner reliability was not examined on the WASI test.

Measurement of Covariates

Data were collected from each subject by questionnaire on maternal age (and date of birth), education, and marital status at the first pregnancy visit; on birth order, birth weight, and gestational age at delivery; and on maternal smoking at every prenatal and postnatal visit. Gestational age was estimated by registered nurses. Maternal IQ was estimated using selected subtests of the Wechsler Adult Intelligence Scale (WAIS)-Spanish (Information, Comprehension, Similarities, and Block Design), which was standardized for Mexican adults (Renteria et al. 2008; Wechsler et al. 1981). Maternal IQ was measured at the study visit 6 mo after birth or at the 12-mo visit if the earlier visit was not completed.

The quality of the children's individual home environments was assessed using an age-appropriate version of the HOME score. However, the measure was not available for all observations because it was only added to on-going cohort evaluation protocols beginning in April 2003, when a version of the HOME score instrument that is age-appropriate for children 0–5 y old was adopted, following which a version of the HOME score instrument that is age-appropriate for children ≥6 y old was adopted in September 2009 (Caldwell and Bradley 2003). Thus, we adjusted for HOME score using the measures for 0- to 5-y-old children in the subset of children who had this data in our analyses of GCI, and we adjusted for HOME score using the measures for >6-y-old children in the subset of children who had this data in our analyses of IQ.

Statistical Analyses

Univariate distributions and descriptive statistics were obtained for all exposure variables, outcome variables, and model covariates. For each variable, observations were classified as outliers if they were outside the bounds of the mean ± 3.5 SDs. Primary analyses were conducted with exposure and outcome outliers excluded. Statistical tests of bivariate associations were conducted using chi-square tests for categorical variables and analysis of variance (ANOVA) to compare the means of the outcomes or exposure within groups defined according to the distribution of each covariate. Spearman correlation coefficients were used to measure the correlation between MUF_{cr} and CUF_{sg}. Regression models were used to assess the adjusted associations between prenatal fluoride and each neurocognitive outcome separately. Generalized additive models (GAMs) were used to visualize the adjusted association between fluoride exposure and measures of intelligence [SAS statistical software (version 9.4; SAS Institute Inc.)]. Because the pattern appeared curvilinear, and because GAMs do not yield exact *p*-values for deviations from linearity, we used a Wald *p*-value of a quadratic term of fluoride exposure to test the null hypothesis that a quadratic model fit the data better

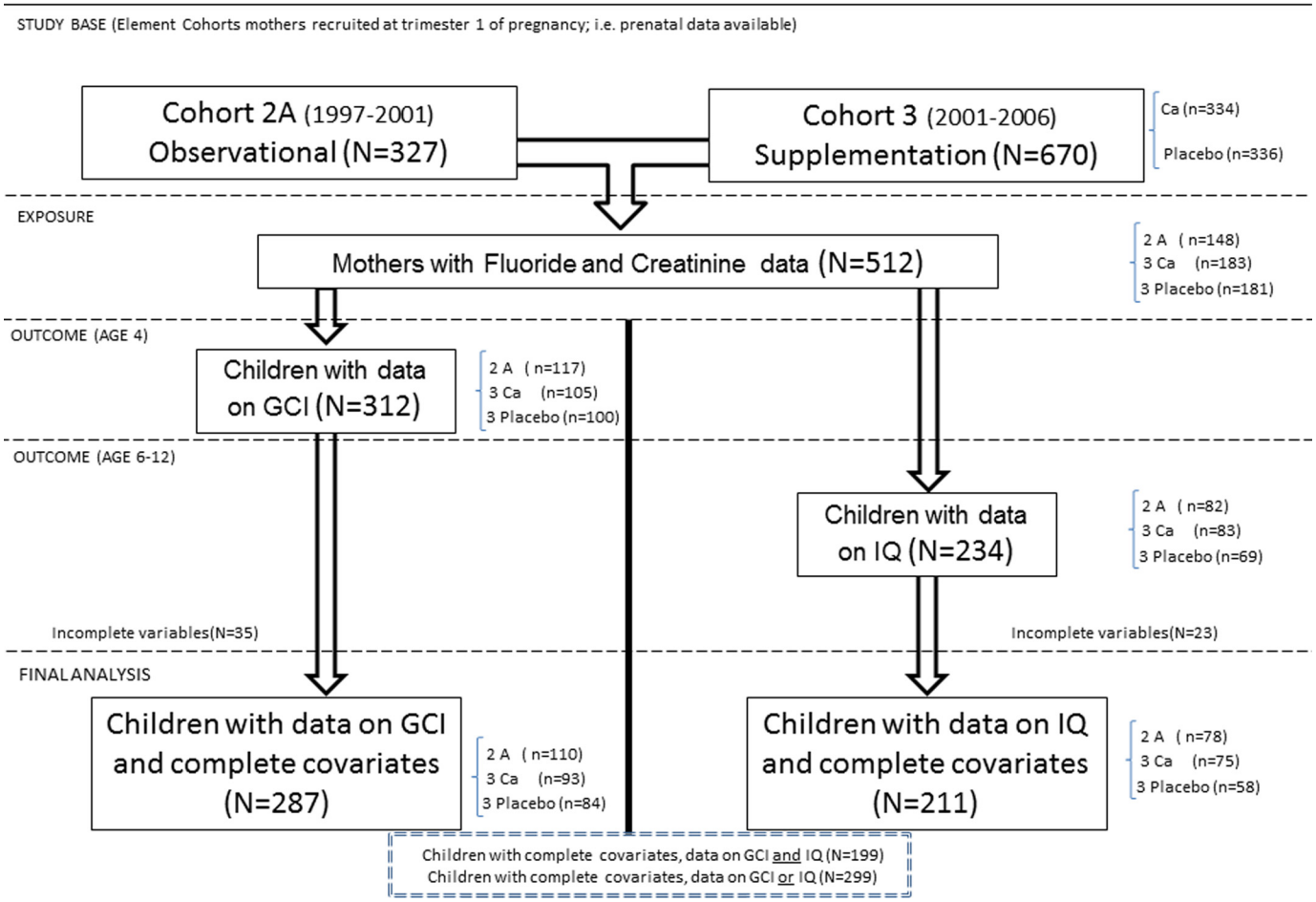

Figure 1. Flowchart describing source of mother–offspring subject pairs, fluoride and cognition study. Cohort 2A was designed as an observational birth cohort of lead toxicodynamics during pregnancy, with mothers recruited early during pregnancy from 1997 to 2001. Cohort 3 was designed as a randomized double-blind placebo-controlled trial of calcium supplements, with mothers recruited early during pregnancy from 2001 to 2006. "Ca" denotes subjects who were randomized to the calcium supplement; "placebo" denotes subjects who were randomized to the placebo. GCI is the McCarthy Scales General Cognitive Index (administered at age 4 y). IQ is the Wechsler Abbreviated Intelligence Scales Intelligence Quotient (administered at age 6–12 y and age-adjusted).

than the model assuming a linear relationship, and thus obtained a *p*-value for deviation from linearity of the fluoride–outcome associations. Residual diagnostics were used to examine other model assumptions and identify any additional potentially influential observations. Visual inspection of default studentized residual versus leverage plot from SAS PROC REG did not identify potential influential observations. Visual inspection of the histogram of the residuals did not indicate lack of normality; however, a fanning pattern in the residual versus predicted value plot indicated lack of constant variance (data not shown). Hence, robust standard errors were obtained using the "empirical" option in SAS PROC GENMOD.

Our overall strategy for selecting covariates for adjustment was to identify those that are well known to have potential associations with either fluoride exposure or cognitive outcomes and/or are typically adjusted for as potential confounders in analyses of environmental toxicants and cognition. All models were adjusted for gestational age at birth (in weeks), birthweight (kilograms), birth order (first born yes vs. no), sex, and child's age at the time of the neurocognitive test (in years). All models were also adjusted for maternal characteristics including marital status (married vs. others), smoking history (ever-smoker vs. never-smoker), age at delivery, IQ, and education (itself also a proxy for socioeconomic status). Finally, all models adjusted for potential cohort effects by including indicator variables denoting from which cohort (Cohort 2A, Cohort 3 + Ca supplement, and Cohort 3 -placebo) the participants came. We used 0.5 mg/L, which was close to the interquartile range of MUF_{cr} for the analyses of both GCI (IQR = 0.45) and IQ (IQR = 0.48), as a standard measure of incremental exposure. SAS statistical software (version 9.4; SAS Institute Inc.) was used for all data analyses described.

Sensitivity Analyses

Models were further adjusted for variables that relate to relatively well-known potential confounders (but for which we were missing a significant amount of data) and variables that were less-well known but possible confounders. The HOME scores were subject to sensitivity analyses because, as noted in the "Methods" section, they were not added to the subject evaluation protocols until 2003, resulting in a significantly smaller subsample of participants with this data. Models of the association between prenatal fluoride exposure (MUF_{cr}) and IQ at 6–12 y old were also adjusted for the child's urine fluoride concentration at 6–12 y of

Table 1. Comparisons across cohorts with respect to the distributions of biomarkers of exposure to prenatal fluoride (MUF_{cr}), prenatal lead (maternal bone Pb), prenatal mercury (maternal blood Hg), and contemporaneous childhood fluoride (CUF_{sg}); and cognitive outcomes (GCI and IQ).

Analysis	Measurement	Cohort	*N*	Mean	SD	Min	Percentiles 25	50	75	Max	*p*-Value[a]
GCI Analysis	GCI	Cohort 3-Ca	84	96.88	14.07	50	88	96	107	124	0.997
		Cohort 3-placebo	93	96.80	13.14	50	89	96	105	125	
		Cohort 2A	110	96.95	15.46	56	88	98	110	125	
		Total[b]	287	96.88	14.28	50	88	96	107	125	
	MUF_{cr} (mg/L)	Cohort 3-Ca	84	0.92	0.41	0.28	0.60	0.84	1.14	2.36	0.57
		Cohort 3-placebo	93	0.87	0.34	0.23	0.62	0.82	1.10	2.01	
		Cohort 2A	110	0.92	0.33	0.23	0.68	0.86	1.11	2.14	
		Total[b]	287	0.90	0.36	0.23	0.65	0.84	1.11	2.36	
	Maternal bone Pb (μg/g)	Cohort 3-Ca	62	7.30	7.37	0.05	0.75	4.40	12.93	26.22	<0.01
		Cohort 3-placebo	43	9.21	7.31	0.11	1.50	8.60	13.97	27.37	
		Cohort 2A	62	13.60	11.36	0.15	5.35	10.52	19.46	47.07	
		Total[c]	167	10.13	9.41	0.05	2.37	8.22	15.37	47.07	
	Maternal blood Hg (μg/L)	Cohort 3-Ca	38	3.32	1.40	0.73	2.40	3.00	4.15	7.06	0.12
		Cohort 3-placebo	28	2.80	1.33	1.27	1.89	2.53	3.40	7.22	
		Cohort 2A	75	4.53	5.61	0.77	2.30	3.24	4.37	35.91	
		Total[c]	141	3.86	4.25	0.73	2.20	3.08	4.15	35.91	
IQ Analysis	IQ	Cohort 3-Ca	58	94.91	9.86	76	87	96	100	120	0.69
		Cohort 3-placebo	75	96.29	9.63	75	89	97	102	124	
		Cohort 2A	78	96.47	13.20	67	87	96	107	131	
		Total[d]	211	95.98	11.11	67	88	96	107	131	
	MUF_{cr} (mg/L)	Cohort 3-Ca	58	0.89	0.38	0.29	0.57	0.84	1.10	1.85	0.86
		Cohort 3-placebo	75	0.87	0.35	0.23	0.61	0.82	1.11	2.01	
		Cohort 2A	78	0.90	0.34	0.23	0.67	0.85	1.09	2.14	
		Total[d]	211	0.89	0.36	0.23	0.64	0.82	1.07	2.14	
	Maternal bone Pb (μg/g)	Cohort 3-Ca	67	6.97	7.20	0.05	0.76	4.36	11.73	26.22	<0.01
		Cohort 3-placebo	48	9.07	7.42	0.11	1.00	8.49	14.41	27.37	
		Cohort 2A	62	13.60	11.36	0.15	5.35	10.52	19.46	47.07	
		Total[e]	177	9.86	9.33	0.05	2.29	7.95	15.22	47.07	
	Maternal blood Hg (μg/L)	Cohort 3-Ca	43	3.25	1.41	0.51	2.43	2.87	4.02	7.06	0.067
		Cohort 3-placebo	31	2.66	1.36	0.78	1.81	2.40	3.26	7.22	
		Cohort 2A	75	4.53	5.61	0.77	2.30	3.24	4.37	35.91	
		Total[e]	149	3.77	4.16	0.51	2.19	2.90	4.11	35.91	
	CUF_{sg} (mg/L)	Cohort 3-Ca	71	0.84	0.4	0.31	0.53	0.78	1.12	2.8	0.29
		Cohort 3-placebo	53	0.85	0.38	0.35	0.57	0.75	1.14	1.85	
		Cohort 2A	65	0.76	0.34	0.18	0.51	0.7	0.89	1.76	
		Total[e]	189	0.82	0.38	0.18	0.54	0.73	1.01	2.8	
All available measurements	GCI	Cohort 3-Ca	133	97.32	13.67	50	88	96	107	124	0.57
		Cohort 3-placebo	149	95.99	13.07	50	88	96	106	125	
		Cohort 2A	150	97.57	14.63	56	88	99	109	131	
		Total[f]	432	96.95	13.80	50	88	96	107	131	
	IQ	Cohort 3-Ca	91	95.92	10.15	76	88	95	103	120	0.92
		Cohort 3-placebo	114	96.56	9.84	75	89	96	102	124	
		Cohort 2A	111	96.25	12.67	67	87	95	105	131	
		Total[f]	316	96.27	10.97	67	88	96	103	131	
	MUF_{cr} (mg/L)	Cohort 3-Ca	181	0.89	0.36	0.28	0.64	0.83	1.09	2.36	0.11
		Cohort 3-placebo	183	0.84	0.31	0.02	0.61	0.81	1.02	2.01	
		Cohort 2A	148	0.91	0.35	0.23	0.67	0.86	1.10	2.15	
		Total[f]	512	0.88	0.34	0.02	0.64	0.82	1.07	2.36	
	Maternal bone Pb (μg/g)	Cohort 3-Ca	97	7.07	7.26	0.01	0.83	4.36	11.78	26.22	<0.01
		Cohort 3-placebo	74	9.15	8.38	0.11	0.85	8.62	13.41	40.8	
		Cohort 2A	86	13.77	11.30	0.15	5.49	10.52	20.58	47.07	
		Total[f]	257	9.91	9.51	0.01	2.01	7.64	15.31	47.07	
	Maternal blood Hg (μg/L)	Cohort 3-Ca	55	3.03	1.41	0.51	2.12	2.77	3.62	7.06	0.09
		Cohort 3-placebo	48	2.87	2.09	0.34	1.82	2.37	3.34	13.47	
		Cohort 2A	104	4.06	4.88	0.77	2.14	3.10	4.16	35.91	
		Total[f]	207	3.51	3.70	0.34	2.07	2.80	3.79	35.91	
	CUF_{sg} (mg/L)	Cohort 3-Ca	104	0.84	0.39	0.31	0.56	0.75	1.07	2.80	0.227
		Cohort 3-placebo	84	0.90	0.46	0.35	0.58	0.75	1.09	2.89	
		Cohort 2A	96	0.79	0.34	0.18	0.53	0.73	0.92	2.11	
		Total[f]	284	0.84	0.40	0.18	0.57	0.74	1.00	2.89	

[a]Analysis of variance across cohorts.
[b]Total number of subjects included in GCI main analysis.
[c]Total number of subjects included in GCI sensitivity analysis.
[d]Total number of subjects included in IQ main analysis.
[e]Total number of subjects included in IQ sensitivity analysis.
[f]Total number of subjects with available measurements, combining Cohort 2A and Cohort 3.

Table 2. Analysis comparing subjects with and without data of interest [*n* (%) or mean ± SD] with respect to characteristics of mothers and children and sensitivity analysis covariates.

Characteristic	GCI analysis		IQ analysis	
	Included	Excluded	Included	Excluded
Total number[a]	287	710	211	786
Sex				
Female	160 (56%)	244 (47%)	116 (55%)	288 (48%)
Male	127 (44%)	275 (53%)	95 (45%)	307 (52%)
Birth order				
First child	96 (33%)	184 (35%)	93 (32%)	279 (36%)
≥2nd child	191 (67%)	335 (65%)	118 (68%)	507 (65%)
Birth weight (kg)	3.11 ± 0.45	3.11 ± 0.44	3.11 ± 0.46	3.11 ± 0.43
Gestational age (wk)	38.66 ± 1.84	38.58 ± 1.68	38.56 ± 1.80	38.63 ± 1.72
Age at outcome assessment (y)	4.04 ± 0.05	4.05 ± 0.05	8.50 ± 1.31	8.83 ± 1.64
Maternal age at delivery (y)	26.78 ± 5.53	26.49 ± 5.37	27.16 ± 5.61	26.41 ± 5.36
Maternal education (y)[b]	10.63 ± 2.76	10.75 ± 3.08	10.80 ± 2.85	10.69 ± 3.03
Maternal IQ[c]	88.63 ± 12.17	89.27 ± 14.6	89.01 ± 12.45	88.27 ± 13.00
Marital status[d]	3.11 ± 0.45	3.11 ± 0.44	3.11 ± 0.46	3.11 ± 0.43
Married	201 (70%)	493 (70%)	149 (71%)	544 (69%)
Other	86 (30%)	216 (30%)	62 (29%)	240 (31%)
Maternal smoking[e]				
Ever	141 (49%)	335 (51%)	102 (48%)	374 (51%)
Never	146 (51%)	325 (49%)	109 (52%)	362 (49%)
Cohort				
Cohort 3-Ca	93 (32%)	241 (34%)	76 (36%)	259 (33%)
Cohort 3-placebo	84 (29%)	252 (36%)	59 (28%)	278 (35%)
Cohort 2A	110 (38%)	217 (31%)	78 (37%)	249 (32%)
Sensitivity Analyses				
HOME score[f]	$N^{\dagger} = 138$	$N^{\ddagger} = 87$	$N^{\dagger} = 124$	$N^{\ddagger} = 55$
	35.24 ± 6.31	33.23 ± 6.55	35.54 ± 7.46	35.8 ± 7.44
SES[g]	$N^{\dagger} = 188$	$N^{\ddagger} = 110$	$N^{\dagger} = 199$	$N^{\ddagger} = 98$
	6.35 ± 2.43	6.94 ± 2.72	6.36 ± 2.41	6.98 ± 2.79
Maternal Bone Pb (μg/g)[h]	$N^{\dagger} = 167$	$N^{\ddagger} = 91$	$N^{\dagger} = 177$	$N^{\ddagger} = 80$
	9.26 ± 10.55	8.97 ± 10.32	9.02 ± 10.43	9.48 ± 10.55
Maternal Blood Hg (μg/L)[i]	$N^{\dagger} = 141$	$N^{\ddagger} = 67$	$N^{\dagger} = 149$	$N^{\ddagger} = 58$
	3.86 ± 4.25	2.76 ± 1.95	3.77 ± 4.16	2.83 ± 2.01
CUF_{sg}[j] (mg/L)			$N^{\dagger} = 124$	$N^{\ddagger} = 55$
			35.54 ± 7.46	35.8 ± 7.44

[a]The total number of subjects ($n = 997$) are all mother–offspring pairs who participated in the original Cohort 2A and Cohort 3 studies.
[b]Maternal education at the time of the child's birth.
[c]Maternal IQ measured at 6 mo after child's birth.
[d]Mother's marital status at the time of the child's birth.
[e]History of any maternal smoking.
[f]HOME score measured using the separate age-appropriate instruments pertaining to children of ≤5 y old; and children >5 y old.
[g]Family socioeconomic status (SES) measured by questionnaire of family possessions at follow-up.
[h]Maternal patella bone lead measured by KXRF after birth.
[i]Maternal average blood mercury during pregnancy.
[j]Children's specific gravity–corrected urinary fluoride measured at the time of each child's IQ test (6–12 y old).
$N^{\dagger}$ Number of subjects with measurements of MUF_{cr}, cognitive outcome, main covariates, and sensitivity covariates (they are included in the sensitivity model).
$N^{\ddagger}$ Number of subjects with measurements of sensitivity covariates, but missing data on exposure, outcomes, or main covariates (they are excluded from the sensitivity model).

age (CUF_{sg}), a measure that was collected in a significantly smaller subset of individuals, to evaluate the potential role of contemporaneous exposure. Associations between prenatal fluoride exposure (MUF_{cr}) and GCI at 4 y old could not be adjusted for contemporaneous fluoride exposure because urine samples were not collected from children when the MSCA (from which the GCI is derived) was administered. Maternal bone lead measured by a 109-Cd K-X-ray fluorescence (KXRF) instrument at 1 mo postpartum, a proxy for lead exposure from mobilized maternal bone lead stores during pregnancy (Hu et al. 2006), was included in the model to test for the possible confounding effect of lead exposure during pregnancy. We focused on the subset of women who had patella bone lead values because these were found to be most influential on our previous prospective study of offspring cognition (Gomaa et al. 2002). Average maternal mercury level during pregnancy was also tested for being a potential confounder (Grandjean and Herz 2011). Mercury was measured as total mercury content in the subsample of women who had samples of archived whole blood samples taken during pregnancy with sufficient volume to be analyzed using a Direct Mercury Analyzer 80 (DMA-80, Milestone Inc., Shelton, CT, USA) as previously described (Basu et al. 2014).

To address the potential confounding effect of socioeconomic status (SES) we conducted sensitivity analyses that adjusted our model for SES (family possession score). The socioeconomic questionnaire asked about the availability of certain items and assets in the home. Point values were assigned to each item, and SES was calculated based on the sum of the points across all items (Huang et al. 2016). Given that the calcium intervention theoretically could have modified the impact of fluoride, in examining our results, we repeated the analyses with and without the Cohort 3 participants who were randomized to the calcium intervention to omit any potential confounding effect of this intervention. Another sensitivity test was performed to examine the potential effect of the psychologist who performed the WASI test by including tester in the regression model. The information about psychologists who performed the WASI was available for 75% of participants, as recording this data was

Table 3. Distributions of maternal creatinine-adjusted urinary fluoride (MUF_{cr}) and offspring cognitive scores across categories of main covariates.

	GCI Analysis					IQ Analysis				
Covariate	*n*	MUF_{cr}[a]	*p*-Value	GCI (Age 4)	*p*-Value	*n*	MUF_{cr}[a]	*p*-Value	IQ (Age 6–12)	*p*-Value
Mothers										
Age										
≥25 y	123	0.88 ± 0.36	0.45	96.22 ± 14.12	0.50	88	0.89 ± 0.37	0.98	95.75 ± 11.64	0.80
<25 y	164	0.92 ± 0.36		97.37 ± 14.43		123	0.89 ± 0.35		96.15 ± 10.76	
Education										
<12 y	153	0.91 ± 0.4	0.92	94.22 ± 14.23	0.001	111	0.87 ± 0.37	0.53	93.09 ± 10.54	<0.001
12 y	97	0.89 ± 0.34		98.56 ± 14.46		70	0.93 ± 0.35		98.29 ± 10.72	
>12 y	37	0.89 ± 0.42		103.49 ± 11.21		30	0.85 ± 0.31		101.3 ± 11.16	
Marital status										
Married	201	0.90 ± 0.37	0.81	96.40 ± 14.46	0.39	62	0.90 ± 0.35	0.79	96.55 ± 11.06	0.63
Other	86	0.91 ± 0.33		98.00 ± 13.88		149	0.88 ± 0.36		95.74 ± 11.16	
Smoking										
Ever smoker	141	0.90 ± 0.36	0.80	97.77 ± 13.9	0.30	102	0.90 ± 0.36	0.56	97.21 ± 10.7	0.12
Nonsmoker	146	0.91 ± 0.35		96.01 ± 14.63		109	0.87 ± 0.35		94.83 ± 11.41	
HOME score [b]										
Mid-low ≤30	49	0.88 ± 0.37	0.47	90.73 ± 13.36	<0.001	32	0.87 ± 0.36	0.85	89.88 ± 8.45	0.011
High >30	137	0.92 ± 0.38		99.29 ± 14.61		92	0.88 ± 0.38		99.05 ± 11.65	
Maternal IQ										
Mid-low ≤85	116	0.95 ± 0.35	0.09	93.16 ± 15.04	<0.001	86	0.92 ± 0.36	0.23	91.26 ± 9.72	<0.001
High >85	171	0.87 ± 0.36		99.4 ± 13.21		125	0.86 ± 0.35		99.23 ± 10.87	
Children										
Sex										
Boy	127	0.94 ± 0.36	0.09	93.93 ± 13.98	0.002	95	0.96 ± 0.38	0.008	96.82 ± 12.02	0.32
Girl	160	0.87 ± 0.36		99.22 ± 14.12		116	0.83 ± 0.32		95.29 ± 10.31	
Birthweight										
≥3.5 kg	241	0.91 ± 0.36	0.57	96.52 ± 14.36	0.33	201	0.89 ± 0.36	0.88	95.66 ± 11.29	0.58
<3.5 kg	46	0.87 ± 0.35		98.76 ± 13.88		10	0.88 ± 0.34		97.38 ± 9.42	
Gestational age										
≤39 wk	192	0.90 ± 0.35	0.90	96.66 ± 14.23	716	146	0.89 ± 0.36	0.712	95.71 ± 11.62	0.65
>39 wk	95	0.90 ± 0.37		97.32 ± 14.46		65	0.88 ± 0.34		96.58 ± 9.91	
First child										
Yes	96	0.91 ± 0.38	0.75	99.97 ± 12.87	0.009	68	0.88 ± 0.36	0.91	97.00 ± 11.00	0.36
No	191	0.90 ± 0.35		95.32 ± 14.73		143	0.89 ± 0.36		95.50 ± 11.17	
CUF_{sg} [c]										
≥0.80 mg/L						112	0.86 ± 0.32	0.49	96.80 ± 11.16	0.37
<0.80 mg/L						77	0.90 ± 0.38		95.37 ± 10.31	

[a]Maternal creatinine-adjusted urinary fluoride (mg/L).
[b]Home Observation for the Measurement of the Environment (HOME) score, measured using the separate age-appropriate instruments pertaining to children of ≤5 y old; and children >5 y old.
[c]Child contemporaneous specific gravity–adjusted urinary fluoride (available at the time of each child's IQ test).

added later to the study protocol. We also re-ran models with exposure outliers included as a sensitivity step. Finally, we ran models that focused on the cross-sectional relationship between children's exposure to fluoride (reflected by CUF_{sg}) and IQ score, unadjusted; adjusting for the main covariates of interest; and adjusting for prenatal exposure (MUF_{cr}) as well as the covariates of interest.

Results

Flow of Participants

Of the 997 total mothers from two cohorts evaluated, 971 were eligible after removing mothers <18 y old. Of these 971, 825 had enough urine sample volume to measure fluoride in at least one trimester urine sample, and of these 825 participants, 515 participants had urine samples with previously measured creatinine values, enabling calculation of creatinine-adjusted urinary fluoride (MUF_{cr}) concentrations. Of these 515, 3 participants were excluded based on the 10 extreme outlier values identified for MUF_{cr} (see the "Methods" section, "Exposure Assessment" subsection) and not having any other MUF_{cr} values to remain in the analysis. Thus, we had a total of 512 participants (mothers) with at least one value of MUF_{cr} for our analyses (Figure 1).

Of these 512 mothers, 312 had offspring with outcome data at age 4 (i.e., GCI), and 234 had offspring with outcome data at age 6–12 (i.e., IQ). Of these, complete data on all the covariates of main interest (as specified in the "Methods" section) were available on 287 mother–child pairs for the GCI analysis and 211 mother–child pairs for the IQ analysis. A total of 299 mother–child pairs had data on either GCI or IQ, and 199 mother–child pairs had data on both GCI and IQ (Figure 1).

Number of Exposure Measures per Subject

In terms of repeated measures of MUF_{cr} across trimesters, of the 287 participants with data on GCI outcomes; 25 participants had MUF_{cr} data for all three trimesters (11 from Cohort 2A and 14 from Cohort 3), 121 participants had MUF_{cr} data from two trimesters (48 from Cohort 2A and 73 from Cohort 3), and 141 participants had MUF_{cr} data from one trimester (51 from Cohort 2A and 90 from Cohort 3). Of the 211 participants with data on IQ outcomes, 10 participants had MUF_{cr} data for all three trimesters (6 from Cohort 2A and 4 from Cohort 3), 82 participants had data from two trimesters (32 from Cohort 2A and 50 from Cohort 3), and 119 participants had data from one trimester (40 from Cohort 2A and 79 from Cohort 3).

Comparisons across the Cohorts

In terms of the mother–child pairs who had data on all covariates as well as data on either GCI or IQ ($n = 299$), the mean (SD)

Table 4. Multivariate regression models: unadjusted and adjusted differences in GCI and IQ per 0.5 mg/L higher maternal creatinine-adjusted urinary fluoride (MUF_{cr}).

	GCI			IQ		
Estimate	*n*	β (95%CI)	*p*-Value	*n*	β ± S.E (95%CI)	*p*-Value
Unadjusted	287	−3.76 (−6.32, −1.19)	<0.01	211	−2.37 (−4.45, −0.29)	0.03
model A[a]	287	−3.15 (−5.42, −0.87)	0.01	211	−2.50 (−4.12, −0.59)	0.01
Model A −HOME	138	−3.63 (−6.48, −0.78)	<0.01	124	−2.36 (−4.48, −0.24)	0.03
Model A + HOME	138	−3.76 (−7.08, −0.45)	0.03	124	−2.49 (−4.65, −0.33)	0.02
Model A −CUF_{sg}				189	−1.79 (−3.80, 0.22)	0.08
Model A + CUF_{sg}				189	−1.73 (−3.75, 0.29)	0.09
Model A − SES	188	−4.55 (−7.23, −1.88)	0.01	199	−2.10 (−4.02, −0.18)	0.03
Model A + SES	188	−4.45 (−7.08, −1.81)	0.01	199	−2.10 (−4.06, −0.15)	0.04
Model A −Pb	167	−5.57 (−8.48, −2.66)	<0.01	177	−3.21 (−5.17, −1.24)	<0.01
Model A + Pb	167	−5.63 (−8.53, −2.72)	<0.01	177	−3.22 (−5.18, −1.25)	<0.01
Model A −Hg	141	−7.13 (−10.26, −4.01)	<0.01	149	−4.59 (−7.00, −2.17)	<0.01
Model A + Hg	141	−7.03 (−10.19, −3.88)	<0.01	149	−4.58 (−6.99, −2.16)	<0.01
Model A −Ca	194	−3.67 (−6.57, −0.77)	0.01	136	−3.23 (−5.88, −0.57)	0.02

[a]Coefficients from linear regression models adjusted for gestational age, weight at birth, sex, parity (being the first child), age at outcome measurement, and maternal characteristics including smoking history (ever smoked during the pregnancy vs. nonsmoker), marital status (married vs. others), age at delivery, IQ, education, and cohort (Cohort 3-Ca, Cohort 3-placebo and Cohort 2A). Model A–HOME, model A for subset of cases who have data on Home Observation for the Measurement of the Environment (HOME) scores (but the model did not include HOME score). Model A + HOME, model A for subset of cases with HOME score, adjusted for HOME score. Model A −CUF_{sg}, model A for subset of cases who have data on child contemporaneous specific gravity–adjusted urinary fluoride CUF_{sg} (but the model did not include CUF_{sg}). Model A + CUF_{sg}, model A for subset of cases with CUF_{sg}, adjusted for CUF_{sg}. Model A−SES, model A for subset of cases who have data on socioeconomic status (family possession measured by questionnaire of family possessions) (but the model did not include SES). Model A + SES, model A for subset of cases with SES data, adjusted for SES. Model A–Pb, model A for subset of cases who have data on maternal bone lead (but the model did not include maternal bone lead). Model A + Pb, model A for subset of cases with data on maternal bone lead, adjusted for maternal bone lead. Model A−Hg, model A for subset of cases who have data on maternal blood mercury (but the model did not include maternal blood mercury). Model A + Hg, model A for subset of cases who have data on maternal blood mercury, adjusted for maternal blood mercury. Model A − Ca, model A for subset of cases who did not receive the Ca supplement (they received the placebo).

values of creatinine–corrected urinary fluoride for the mothers was 0.90 (0.36) mg/L. The distributions of the urinary fluoride, outcomes (GCI and IQ), and additional exposure variables examined in our sensitivity analyses (maternal bone lead, maternal blood mercury, and children's contemporaneous urinary fluoride) across the three cohort strata (Cohort 3-Calcium, Cohort 3-placebo, and Cohort 2A) and all strata combined are shown in Table 1 for the mother–child pairs who had data for the GCI outcome ($n = 287$) and the IQ outcome ($n = 211$). The distributions showed little variation across the cohort strata except for bone lead and possibly blood mercury, for which, in comparison with Cohort 3, Cohort 2A clearly had higher mean bone lead levels ($p < 0.001$) and possibly higher blood mercury levels ($p = 0.067$). The mean (SD) values of specific gravity–corrected urinary fluoride for the children who had these measures (only available for those children who had IQ; $n = 189$) were 0.82 (0.38) mg/L.

In terms of the comparability of the participants across Cohort 2A and Cohort 3 with respect to our covariates, the distribution of the covariates was very similar with the exception of age of the offspring when IQ was measured, for which the mean ages were 7.6 and 10.0 y, respectively; and birth weight in the GCI analysis, for which Cohort 3 participants were slightly heavier than Cohort 2 participants (see Table S1).

GCI versus IQ Scores

There was a significant correlation between GCI at 4 y and IQ at 6–12 y old (Spearman $r = 0.55$; $p < 0.01$). There was no significant correlation between prenatal MUF_{cr} and offspring CUF_{sg} (Spearman $r = 0.54$, $p = 0.44$).

Comparisons of Participants in Relation to Missing Data

In comparing the participants who were included for the GCI and IQ analyses with the participants who were not included (based on data missing on GCI, IQ or other covariates), the distribution of covariates were similar except for sex, for which the proportion of females was somewhat higher in the included versus excluded group for both the GCI and IQ analyses (Table 2).

In terms of the sensitivity analyses, for each sensitivity variable of interest, we compared participants who had data on our exposures, outcomes, covariates, and the sensitivity variable of interest (and were thus included in the sensitivity analysis) versus participants who had data on the sensitivity variable of interest but were missing data on the exposure, outcomes, and/or covariates of interest (and were thus excluded from the sensitivity analysis; Table 2). It can be seen that for each sensitivity analysis, most of the participants with data on the sensitivity variable of interest also had data on the exposures, outcomes, and covariates and were therefore included in the sensitivity analysis. In addition, the distributions appeared to be similar comparing those included with those excluded in each sensitivity analysis (means were within 10% of each other), with the exception of maternal blood Hg, for which the mean levels for those included were 28.5% and 24.9% higher than the mean levels for those excluded in the GCI and IQ analyses, respectively.

Comparisons of GCI and IQ across Covariates

Table 3 shows mean and SD values for MUF_{cr} and offspring cognitive scores across categories of the covariates. In the participants with GCI data, the offspring cognitive scores were higher among mothers with higher levels of education, measured IQ, and HOME scores for both analyses; and scores were higher among first children and girls. In the IQ analysis a statistically significant difference was observed in MUF_{cr} as a function of child sex. No significant differences in MUF_{cr} values across levels of other covariates were observed. A modest difference (not statistically significant), was observed in MUF_{cr} as a function of maternal IQ ($p = 0.09$), and MUF_{cr} as a function of child sex ($p = 0.09$). Among other co-variates there were significant differences in age ($p < 0.01$) in both analyses.

Regression Models of GCI

Before adjustment, a 0.5 mg/L increase in MUF_{cr} was negatively associated with GCI at 4 y old [mean score −3.76; 95% confidence interval (CI): −6.32, −1.19] (Table 4). The association was somewhat attenuated after adjusting for the main covariates

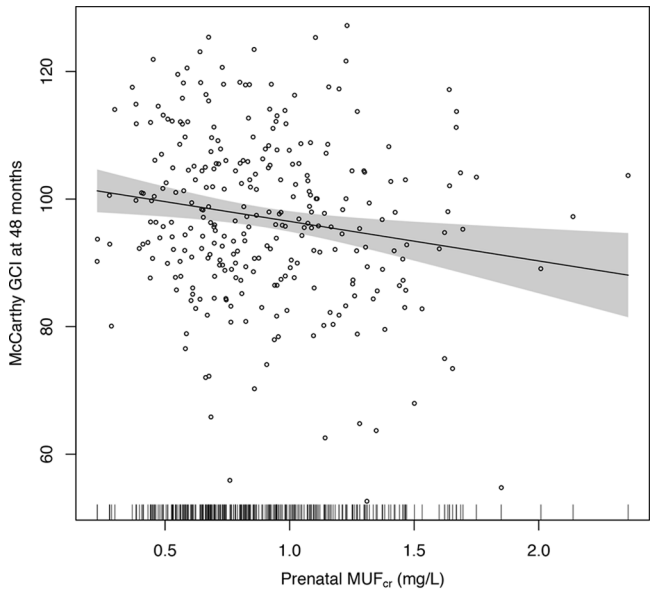

Figure 2. Adjusted association of maternal creatinine-adjusted urinary fluoride (MUF_{cr}) and General Cognitive Index (GCI) scores in children at age 4 y. Adjusted for gestational age, weight at birth, sex, parity (being the first child), age at outcome measurement, and maternal characteristics including smoking history (ever smoked vs. nonsmoker), marital status (married vs. others), age at delivery, IQ, education, and cohort (Cohort 3-Ca, Cohort 3-placebo and Cohort 2A). Shaded area is 95% confidence interval. Short vertical bars on the *x*-axis reflect the density of the urinary fluoride measures. Individual data points are individual observations, $n = 287$.

(model A, −3.15; 95% CI: −5.42, −0.87). The smooth plot of the association between GCI and maternal prenatal urinary fluoride from an adjusted GAM model suggested a linear relation over the exposure distribution (Figure 2).

Regression Models of IQ

A 0.5 mg/L increase in prenatal fluoride was also negatively associated with IQ at age 6–12 y based on both unadjusted (−2.37; 95% CI: −4.45, −0.29) and adjusted models (−2.50; 95% CI: −4.12, −0.59) (Table 4). However, estimates from the adjusted GAM model suggest a nonlinear relation, with no clear association between IQ scores and values below approximately 0.8 mg/L, and a negative association above this value (Figure 3A). There was a nonsignificant improvement in the fit of the model when a quadratic term was added to the linear model ($p = 0.10$).

Sensitivity Analyses

In sensitivity analyses, adjustment for HOME score increased the magnitude of the association between MUF_{cr} and GCI, though the difference was less pronounced when associations with and without adjustment for HOME score were both estimated after restricting the model to the subset of 138 children with HOME score data (Table 4). The association of IQ scores with MUF_{cr} did not substantially change after adding HOME score to the model (Table 4).

The association between MUF_{cr} and IQ was attenuated slightly after adjusting for contemporaneous children's urinary fluoride (CUF_{sg}) and comparing estimates with [−1.73 (95% CI: −3.75, 0.29)] and without [−1.94 (95% CI: −4.15, 0.26)] adjustment for CUF_{sg} among the 189 children with this data (Table 4). In addition, the evidence of nonlinearity was more pronounced, with no clear evidence of an association for MUF_{cr} <1.0 mg/L

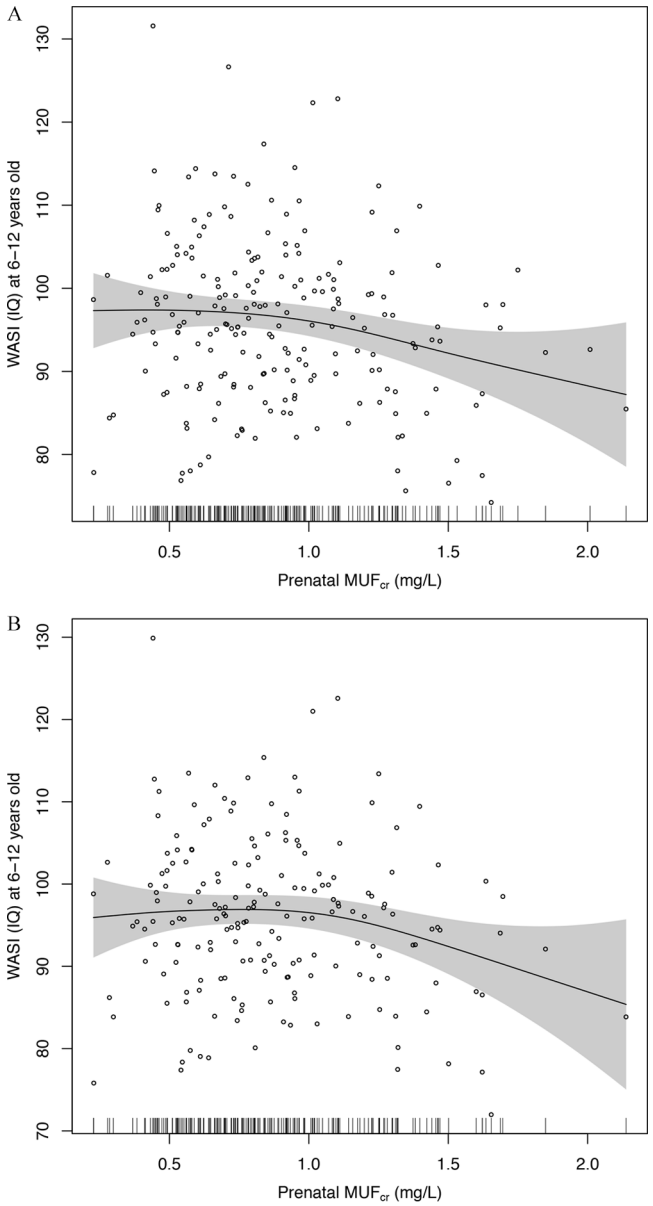

Figure 3. (A) Adjusted association of maternal creatinine-adjusted urinary fluoride (MUF_{cr}) and children's IQ at age 6–12 y. Adjusted for gestational age, weight at birth, sex, parity (being the first child), age at outcome measurement, and maternal characteristics including smoking history (ever smoked vs. nonsmoker), marital status (married vs. others), age at delivery, IQ, education, and cohort (Cohort 3-Ca, Cohort 3-placebo and Cohort 2A). Short vertical bars on the *x*-axis reflect the density of the urinary fluoride measures. Individual data points are individual observation, $n = 211$. (B) Association of maternal creatinine-adjusted urinary fluoride ($MUFU_{cr}$) and children's IQ at age 6–12 y, adjusted for specific gravity–adjusted child urinary fluoride (CUF_{sg}). Adjusted for gestational age, weight at birth, sex, parity (being the first child), age and CUF_{sg} at outcome measurement, and maternal characteristics including smoking history (ever smoked vs. nonsmoker), marital status (married vs. others), age at delivery, IQ, education. and cohort (Cohort 3-Ca, Cohort 3-placebo and Cohort 2A). Shaded area is 95% confidence interval. Short vertical bars on the *x*-axis reflect the density of the urinary fluoride measures. Individual data points are individual observation, $n = 189$.

based on the GAM model (Figure 3B), and a significant improvement in model fit when a quadratic term was added to the linear regression model ($p = 0.01$).

When we restricted models to subsets of children with available data for each additional covariate, there was little difference

between adjusted and unadjusted associations between MUF_{cr} and GCI or IQ when socioeconomic status (family possession), maternal bone lead, and blood mercury, were added to models (Table 4). However, the effect estimates associated with MUF_{cr} for these analyses appear to be higher in the subsets with available data for these variables.

Adding tester (psychologist who performed WASI) in the model did not substantially change the results (data not shown). In the sensitivity analyses in which we excluded Cohort 3 participants who received the calcium supplement, we continued to observe a negative association between MUF_{cr} and GCI [0.5 mg/L increase in MUF_{cr} associated with 3.67 lower GCI (95% CI: −6.57, −0.77), $n = 194$]; and between MUF_{cr} and IQ [0.5 mg/L increase in MUF_{cr} associated with 3.23-lower IQ (95% CI: −5.88, −0.57), $n = 136$].

In sensitivity analyses in which we re-ran models that included the 10 outliers with respect to fluoride exposure (for each of seven participants already in our models, an additional value of MUF_{cr} [from a different trimester]; for three participants, a value of MUF_{cr} that then allowed the participants to be added to our models), the results did not change in any meaningful way (data not shown). There were no outliers with respect to cognitive outcomes.

Independent Influence of Child Fluoride Exposure

Finally, in models that focused on the cross-sectional relationship between children's exposure to fluoride (reflected by their specific gravity–adjusted urinary fluoride levels) and IQ score and that contained the main covariates of interest, there was not a clear, statistically significant association between contemporaneous children's urinary fluoride (CUF_{sg}) and IQ either unadjusted or adjusting for MUF_{cr}. A 0.5 mg/L increase in CUF_{sg} was associated with a 0.89 lower IQ (95% CI: −2.63, 0.85) when not adjusting for MUF_{cr}; and 0.77-lower IQ (95% CI: −2.53, 0.99), adjusting for MUF_{cr} ($n = 189$).

Discussion

In our study population of Mexican women and children, which accounted for two of the three cohorts included in the ELEMENT study, higher prenatal exposure to fluoride (as indicated by average creatinine-adjusted maternal urinary fluoride concentrations during pregnancy) was associated with lower GCI scores in children at approximately 4 y old, and with lower Full-Scale IQ scores at 6–12 y old. Estimates from adjusted linear regression models suggest that mean GCI and IQ scores were about 3 and 2.5 points lower in association with a 0.5 mg/L increase in prenatal exposure, respectively. The associations with GCI appeared to be linear across the range of prenatal exposures, but there was some evidence that associations with IQ may have been limited to exposures above 0.8 mg/L. In general, the negative associations persisted in sensitivity analyses with further adjustment for other potential confounders, though the results of sensitivity analyses were based on subsets of the population with available data.

Overall, our results are somewhat consistent with the ecological studies suggesting children who live in areas with high fluoride exposure (ranging from 0.88 to 11.0 mg/L fluoride in water, when reported) have lower IQ scores than those who live in low-exposure or control areas (ranging from 0.20 to 1.0 mg/L fluoride in water) (Choi et al. 2012) and with results of a pilot study of 51 children (mean age 7 y) from southern Sichuan, China, that reported that children with moderate or severe dental fluorosis (60% of the study population) had lower WISC-IV digit span scores than other children (Choi et al. 2015). A distinction is that our study, which was longitudinal with repeated measures of exposure beginning in the prenatal period, found associations with respect to prenatal fluoride exposures.

To our knowledge, the only other study that is similar to ours was only recently published. Valdez Jiménez et al. (2017) studied the association of prenatal maternal urinary fluoride levels (not corrected for dilution) and scores on the Bayley Scales of Infant Development II among 65 children evaluated at age 3–15 mo (average of 8 mo). The mothers in their study had urinary fluoride levels of which the means at each of the three trimesters of pregnancy (1.9, 2.0, 2.7 mg/L) were higher than the mean MUF_{cr} in our participants (0.88 mg/L) (Valdez Jiménez et al. 2017). These levels of exposure were found to be associated with statistically significantly lower scores on the Bayley Scales' Mental Development Index (MDI) score after adjusting for gestational age, age of child, a marginality index, and type of drinking water (Valdez Jiménez et al. 2017). By comparison, our study had much longer periods of follow-up and larger sample sizes, controlled for a much larger set of covariates and sensitivity variables, and used creatinine–corrected urinary fluoride measures (which, by adjusting for urinary dilution effects, provides a more reliable measure of internal fluoride exposure).

With respect to understanding the generalizability of our findings to other populations, there are very few studies that measured prenatal fluoride levels among women derived from population-based samples. Gedalia et al. (1959) measured urinary fluoride in multiple samples collected from each of 117 healthy pregnant women living in Jerusalem, where fluoride in the water was approximate 0.50 mg/L, and reported mean levels per person that ranged from 0.29 to 0.53 mg/L. However, these analysis were not conducted utilizing modern analytical techniques. In a study of 31 pregnant women living in Poland, Opydo-Szymaczek and Borysewicz-Lewicka (2005) measured urinary fluoride in healthy pregnant women patients of a maternity hospital in Poland, where fluoride in the water ranged from 0.4 to 0.8 mg/L, and found a mean level of 0.65 mg/L for women in their 28th week of pregnancy, 0.84 mg/L in their 33rd week, and 1.30 mg/L in healthy non-pregnant women of similar age. This would suggest that the mothers in our study, who had a mean MUF_{cr} value of 0.90 mg/L, had fluoride exposures slightly higher than prior-mentioned populations.

In terms of comparing our findings with other studies of fluoride (using urinary fluoride as a biomarkers of exposure) and intelligence (i.e., those not involving prenatal exposures), of the 27 epidemiologic studies on fluoride and IQ reviewed by Choi et al. in their 2012 meta-analysis, only 2 had measures of urinary fluoride. Both were of urinary fluoride measures in children (not pregnant mothers), and neither corrected for dilution (either by correcting for urinary creatinine or specific gravity). Of these two, in comparison with the urinary fluoride levels of both our mothers (0.88 mg/L) and our children (0.82 mg/L), the mean levels of children's urinary fluoride were higher in the non-fluorosis (1.02 mg/L) and high-fluorosis (2.69 mg/L) groups found by Li et al. (1995) as well as the control (1.5 mg/L) and high-fluorosis (5.1 mg/L) groups described by Wang et al. (2007).

Among the limitations of our study are that we measured fluoride in spot (second morning void) urine samples instead of 24-hr urine collections. However, others have noted a close relationship between the fluoride concentrations of early morning samples and 24-hr specimens (Watanabe et al. 1994; Zohouri et al. 2006). Another limitation relates to the potential differences in the distribution of covariates over our study cohorts, raising the issue of potential bias. In the analyses we conducted across cohorts, we saw that, in comparison with Cohort 3, Cohort 2A clearly had

higher mean bone lead levels ($p < 0.001$) and possibly higher blood mercury levels ($p = 0.067$). However, we saw no other differences and the differences in these measures have a clear likely explanation: Cohort 2A had bone lead levels measured in 1997–2001 and Cohort 3 had bone lead levels measured in 2001–2005. Given that environmental lead and mercury exposures were steadily decreasing during this time interval (due to the phase-out of lead from gasoline), this difference likely relates to an exposure–time–cohort effect. We do not anticipate that this phenomenon would have introduced a bias in our analyses of fluoride and cognition controlling for bone lead.

Another limitation relates to the missing data that pertain to our covariate and sensitivity variables. In the comparisons of participants in relation to missing data (Table 2A,B), the proportion of females was somewhat higher in the included versus excluded group for both the GCI and IQ analyses, and the mean levels of maternal blood Hg for those included were 28.5% and 24.9% higher than the mean levels for those excluded in the GCI and IQ analyses, respectively. We also note that the coefficients for the associations between fluoride on cognition varied substantially in some of the sensitivity analyses, particularly with respect to the subgroups of participants who have data on SES, lead exposure, and mercury exposure (of which, for the latter, the effect estimates almost doubled). We do not have a ready explanation for this phenomenon, given that there is no obvious way that each of the selection factors governing which mothers had these measurements (discussed above) could have influenced the fluoride–cognition relationship. Nevertheless, it is not possible to entirely rule out residual confounding or in the population as a whole (that might have been detected had we had full data on larger sample sizes) or bias (should the subpopulations that had the data for analysis have a different fluoride–cognition relationship than those participants who were excluded from the analyses).

Other limitations include the lack of information about iodine in salt, which could modify associations between fluoride and cognition; the lack of data on fluoride content in water given that determination of fluoride content is not reported as part of the water quality monitoring programs in Mexico; and the lack of information on other environmental neurotoxicants such as arsenic. We are not aware of evidence suggesting our populations are exposed to significant levels of arsenic or other known neurotoxicants; nevertheless, we cannot rule out the potential for uncontrolled confounding due to other factors, including diet, that may affect urinary fluoride excretion and that may be related to cognition.

Another potential limitation is that we adjusted maternal urinary fluoride levels based on urinary creatinine, whereas we adjusted children's urinary fluoride levels based on urinary specific gravity; however, these two methods are almost equivalent in their ability to account for urinary dilution. We also had no data to assess the inter-examiner reliability of the testers administering the WASI test; however, the excellent reliability of these same testers in administering the McCarthy tests provides some reassurance that the WASI tests were conducted in a consistent manner.

Finally, our ability to extrapolate our results to how exposures may impact on the general population is limited given the lack of data on fluoride pharmacokinetics during pregnancy. There are no reference values for urinary fluoride in pregnant women in the United States. The Centers for Disease Control and Prevention has not included fluoride as one of the population exposures measured in urine or blood samples in its nationally representative sampling. The WHO suggests a reference value of 1 mg/L for healthy adults when monitoring renal fluoride excretion in community preventive programs (Marthaler 1999). As part of the NRC's review of the fluoride drinking-water standard, it was noted that healthy adults exposed to optimally fluoridated water had urinary fluoride concentrations ranging from 0.62 to 1.5 mg/L.

Conclusion

In this study, higher levels of maternal urinary fluoride during pregnancy (a proxy for prenatal fluoride exposure) that are in the range of levels of exposure in other general population samples of pregnant women as well as nonpregnant adults were associated with lower scores on tests of cognitive function in the offspring at 4 and 6–12 y old.

Community water and salt fluoridation, and fluoride toothpaste use, substantially reduces the prevalence and incidence of dental caries (Jones et al. 2005) and is acknowledged as a public health success story (Easley 1995). Our findings must be confirmed in other study populations, and additional research is needed to determine how the urine fluoride concentrations measured in our study population are related to fluoride exposures resulting from both intentional supplementation and environmental contamination. However, our findings, combined with evidence from existing animal and human studies, reinforce the need for additional research on potential adverse effects of fluoride, particularly in pregnant women and children, and to ensure that the benefits of population-level fluoride supplementation outweigh any potential risks.

Acknowledgments

This study was supported by the U.S. National Institutes of Health (NIH; grants R01ES021446 and R01-ES007821); the National Institute of Environmental Health Sciences/the U.S. Environmental Protection Agency (NIEHS/EPA; grant P01ES022844), the NIEHS (grant P42-ES05947 and NIEHS Center Grant P30ES017885), and by the National Institute of Public Health/Ministry of Health of Mexico. The American British Cowdray Hospital provided facilities used for this research. The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the NIEHS, NIH, or the U.S. EPA. David Bellinger collaborated on the design and execution of this study's cognitive testing.

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From: Christine Massey [redacted]
Sent: October 11, 2017 12:11 PM
To: Thompson, Allan; Downey, Johanna; Groves, Annette; Innis, Jennifer; Shaughnessy, Barb; Jeffrey, Linda Mayor; Gibson, Grant; Medeiros, Martin; Miles, Gael; Moore, Elaine; Palleschi, Michael; Crombie, Bonnie; Carlson, George; Fonseca, Chris; Iannicca, Nando; Kovac, John; Mahoney, Matt; McFadden, Sue; Parrish, Carolyn; Ras, Karen; Saito, Pat; Starr, Ron; Tovey, Jim; Loh, Lawrence; Polsinelli, Nancy; Szwarc, David; Smith, Janette; Hennings, Jeff; Jim Nardi; ZZG-RegionalClerk; O'Connor, Patrick; Burkiewicz, Justyna; ZZG-WaterQualityInquiries; Sprovieri, John; Hau, Monica; Ward, Megan; Bingham, Kate; Hopkins, Jessica
Subject: tooth decay rates did not increase faster after fluoridation stopped in Calgary

Dear Peel Council / CWFC Members, Dr. Hopkins, Commissioner Polsinelli, Mr. Hennings, Commissioner Smith, CAO Szwarc, Regional Clerk Lockyer and Mr. Nardi,
FYI:

NEW YORK, Oct. 11, 2017 /PRNewswire-USNewswire/

http://www.prnewswire.com/news-releases/report-reveals-flaws-in-calgary-study-that-claimed-fluoridation-cessation-increased-tooth-decay-it-didnt-300534808.html

*"A commentary in yesterday's Community Dentistry and Oral Epidemiology reveals tooth decay rates **did not** increase faster after fluoridation stopped in Calgary as claimed in a previously published study (McLaren, et al 2016). Chris Neurath led the team that reports McLaren's study is scientifically inaccurate, uses incomplete data, and relies on two populations that are not similar, reports the Fluoride Action Network (FAN).*

McLaren used older survey data from 6.5 years before Calgary stopped fluoridation and excluded more relevant data from 1.5 years before cessation. Including the more current data revealed that tooth decay rose in Calgary at the same rate both before and after fluoridation was stopped. Factors other than fluoridation must account for the steady increase in decay. This is confirmed by a large increase in decay in the "control" city of Edmonton, which had long-standing continuous fluoridation. Fluoridation was unable to prevent that increase in decay.

"These findings negate McLaren's conclusion that fluoridation cessation caused an increase in decay," says Neurath.

Additional problems with the McLaren study were noted:

- *The study design is vulnerable to confounding by caries risk factors other than fluoridation.*
- *Baseline decay rates for the two cities differed substantially.*
- *Other risk factors for decay were not controlled for in either Calgary or Edmonton.*
- *There was low participation in the dental surveys and inadequate analysis to check whether this may have skewed results.*

"Our commentary shows that McLaren's study design is too weak to meet minimum quality criteria set up by the prestigious Cochrane Collaborative in their recent review of fluoridation effectiveness," says Neurath.

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McLaren has heavily promoted her work throughout Canada, and especially in Calgary where there have been efforts to reverse the city council's 11 to 3 vote that stopped fluoridation in 2011.

FAN Senior Advisor Paul Connett, PhD noted "McLaren received over a million dollars in grant funding and salary from federal and provincial public health organizations whose policy is to promote fluoridation."

Commentary co-author James Beck, MD PhD, who lives in Calgary, said "As a scientist, the seriously flawed science in the McLaren study disturbs me. Citizens should be concerned that their tax dollars have funded this biased work."

Paper available here: http://onlinelibrary.wiley.com/doi/10.1111/cdoe.12329/abstract"

Notice: I do not consent to anyone adding fluoride, in any form or any amount, to my drinking water. Cease and desist.

Christine Massey, M. Sc.

From: Christine Massey [redacted]
Sent: January 26, 2018 12:07 PM
To: ZZG-ConnectToPeel
Subject: Re: Connect to Peel

Hello,

I cannot find hydrofluorosilicic acid (water fluoridation chemical) listed in the budget. How much will be spent on it?

Also, it doesn't seem appropriate to use the budget as a vehicle for false reassurances regarding the safety of our neurotoxic, endocrine disrupting, enzyme inhibiting, mitochondrial poisoning, bone and tooth damaging drinking water. Is this not consumer fraud?

Thank you,
Christine

On Fri, Jan 26, 2018 at 11:01 AM, Region of Peel <connecttopeel@peelregion.ca> wrote:

January 26, 2018

Region of Peel
working with you

Connect2Peel

If your waste collection is delayed, leave your carts at the curb. If collection hasn't happened by 8 p.m., tell us. Your waste will be collected as a priority the next day.

Report Online

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In memoriam

Peel recognizes the contributions of Regional Councillor Jim Tovey for his 8 years of dedicated support to the citizens of Peel. He will be greatly missed.

How the Region is spending your tax dollars

Watch how the 2018 Regional Budget is supporting our vision to improve residents' lives in their time of need; build integrated, safe communities; and ensure that Peel stays future-oriented and accountable.

Unthaw frozen pipes in 3 easy steps

Icy winter temperatures can cause water pipes to freeze, leaving your household without water. Follow these simple steps to get your water flowing again.

Should Peel stores stay open on stat holidays?

We're considering a 'made-in-Peel' approach to shopping on statutory holidays in Peel, and we need your opinion. Help influence shopping activity in Peel by taking our 5-minute online survey.

From: Christine Massey [redacted]
Sent: February 22, 2018 4:26 PM
To: Thompson, Allan; Downey, Johanna; Groves, Annette; Innis, Jennifer; Shaughnessy, Barb; Jeffrey, Linda Mayor; Gibson, Grant; Medeiros, Martin; Miles, Gael; Moore, Elaine; Palleschi, Michael; Crombie, Bonnie; Carlson, George; Fonseca, Chris; Iannicca, Nando; Kovac, John; Mahoney, Matt; McFadden, Sue; Parrish, Carolyn; Ras, Karen; Saito, Pat; Starr, Ron; Dale, Frank; Loh, Lawrence; Polsinelli, Nancy; Szwarc, David; Smith, Janette; Hennings, Jeff; Jim Nardi; Burkiewicz, Justyna; ZZG-WaterQualityInquiries; Hau, Monica; Ward, Megan; Bingham, Kate; Hopkins, Jessica; ehoskins.mpp@liberal.ola.org; premier@ontario.ca; ZZG-CDIP-Oral Health; ZZG-PeelHealth; Farr, Andrew
Cc: O'Connor, Patrick; Sprovieri, John; pam douglas; newsroom@bramptonguardian.com; Vic Dhillon; Dbhat; Criscione, Peter; Belgrave, Roger; editor@caledoncitizen.com; ZZG-RegionalClerk
Subject: Re agenda item: SLEEP & WELL- BEING AMONG CHILDREN AND YOUTH

Feb. 22, 2018

Dear Council, Chair, Commissioners, CAO, Medical Officers, General Manager of Water & Wastewater, Water-related Staff, Premier and Provincial Health Minister,

(Please add this letter to Council's next agenda.)

Re today's agenda item 12.1 "SLEEP AND WELL - BEING AMONG CHILDREN AND YOUTH", from Nancy Polsinelli, Commissioner of Health Services and Dr. Jessica Hopkins, Medical Officer of Health (both of whom are well aware that 385 ml of Peel's fluoridated drinking water contains the same 0.25 mg fluoride that everyone agrees must be spit out by young children when brushing their teeth, and 2.5 times more fluoride than the 0.10 mg that children up to age 3 must spit out according to Health Canada).

As kindly summarized **here** by the Fluoride Action Network (and attached in pdf):

> "In the 1990s, a British scientist, Jennifer Luke, discovered that fluoride accumulates to strikingly high levels in the pineal gland. (Luke 2001). The pineal gland is located between the two hemispheres of the brain and is responsible for the synthesis and secretion of the hormone melatonin. Melatonin maintains the body's circadian rhythm (sleep-wake cycle), regulates the onset of puberty in females, and helps protect the body from cell damage caused by free radicals.
>
> While it is not yet known if fluoride accumulation affects pineal gland function, preliminary animal experiments found that fluoride reduced melatonin levels and shortened the time to puberty. (Luke, 1997). Based on this and other evidence, the National Research Council has stated that "fluoride is likely to cause decreased melatonin production and to have other effects on normal pineal function, which in turn could contribute to a variety of effects in humans" (NRC, 2006, p. 256).
>
> **The Pineal Gland Has Highest Levels of Fluoride in Body**
>
> As a calcifying tissue that is exposed to a high volume of blood flow, the pineal gland is a major target for fluoride accumulation in humans. In fact, the calcified parts of the pineal gland (hydroxyapatite crystals) contain the highest fluoride concentrations in the human

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body (up to 21,000 ppm F), higher than either bone or teeth. (Luke 1997; 2001). Although the soft tissue of the pineal does not accumulate fluoride to the same extent as the calcified part, it does contain higher levels of fluoride than found than in other types of soft tissue in the body — with concentrations (~300 ppm F) that are known in other contexts to inhibit enzymes. While the impacts of these fluoride concentrations in the pineal are not yet fully understood, studies have found that calcified deposits in the pineal are associated with decreased numbers of functioning pinealocytes and reduced melatonin production (Kunz et al., 1999) as well as impairments in the sleep-wake cycle. (Mahlberg 2009).

Fluoride and Earlier Puberty in Girls

In the United States, children are reaching the age of puberty at earlier ages than in the past — a trend that carries health consequences, including a heightened risk for breast cancer. Some evidence indicates that fluoride, via its effect on the pineal, could be a contributing cause to this trend. In animal studies, for example, fluoride exposure has been found to cause a decrease in the amount of circulating melatonin and lead to an accelerated sexual maturation in females. (Luke 1997). Similar findings have been reported in two epidemiological studies of human populations drinking fluoridated water. In the first published fluoridation safety experiment in Newburgh, New York, the authors found that girls living in a fluoridated community reached puberty five months earlier than girls living in a non-fluoridated community. (Schlesinger 1956) Later, in 1983, Farkas reported that postmenarcheal girls were “present at younger ages in the higher fluoride town than in the low-fluoride town, although the reported median ages were the same.”

References:

- Farkas G, et al. (1983). The fluoride content of drinking water and menarcheal age. Acta Univ Szeged Acta Biol. 29(1-4):159-168.
- Kunz D, et al. (1999). A new concept for melatonin deficit: on pineal calcification and melatonin excretion. Neuropsychopharmacology 21(6):765-72.
- Luke J. (2001). Fluoride deposition in the aged human pineal gland. Caries Res. 35(2):125-128.
- Luke J. (1997). The Effect of Fluoride on the Physiology of the Pineal Gland. Ph.D. Thesis. University of Surrey, Guildford.
- Mahlberg R, et al. (2009). Degree of pineal calcification (DOC) is associated with polysomnographic sleep measures in primary insomnia patients. Sleep Med. 10(4):439-45.
- National Research Council. (2006). Fluoride in Drinking Water: A Scientific Review of EPA’s Standards. National Academies Press, Washington D.C.
- Schlesinger ER, et al. (1956). Newburgh-Kingston caries fluorine study. XIII. Pediatric findings after ten years. J Am Dent Assoc. 52(3):296-306."

The following is Dr. de Villa's dismissive summary of the NRC's (2006) comments re: fluoride and the pineal gland (see page 21: http://www.peelregion.ca/council/agendas/2016/2016-11-24-cwfc-agenda.pdf):

"Pineal gland: One animal study reported high doses of fluoride have some effects on melatonin production and sexual maturation. The human studies showed no effect."

However, here is an excerpt from the NRC's actual report, specifically on the human studies (page 255, emphasis is mine: https://www.nap.edu/read/11571/chapter/10#254):

"Although **no studies are available that specifically address the effect of fluoride exposure on pineal function or melatonin production in humans**, two studies have examined the age of onset of menstruation (age of menarche) in girls in fluoridated areas (Schlesinger et al. 1956; Farkas et al. 1983; for details, see Appendix E, Table E-15);12 the earlier study was discussed by Luke (1997) as part of the basis for her research. **No comparable information on sexual maturation in boys is available.**

In girls examined approximately 10 years after the onset of fluoridation (1.2 mg/L, in 1945) in Newburgh, New York, the average age at menarche was 12 years, versus 12 years 5 months among girls in unfluoridated Kingston (Schlesinger et al. 1956). The authors stated that this difference was not statistically significant. "

[They went on to critique the methodology used in both studies.]

The following is an excerpt from Dr. John Colquhoun, Former Principal Dental Officer of Auckland, NZ, in Why I Changed my Mind about Water Fluoridation (*Perspect Biol Med. 1997 Autumn;41(1):29-44.https://www.ncbi.nlm.nih.gov/pubmed/9394474)*

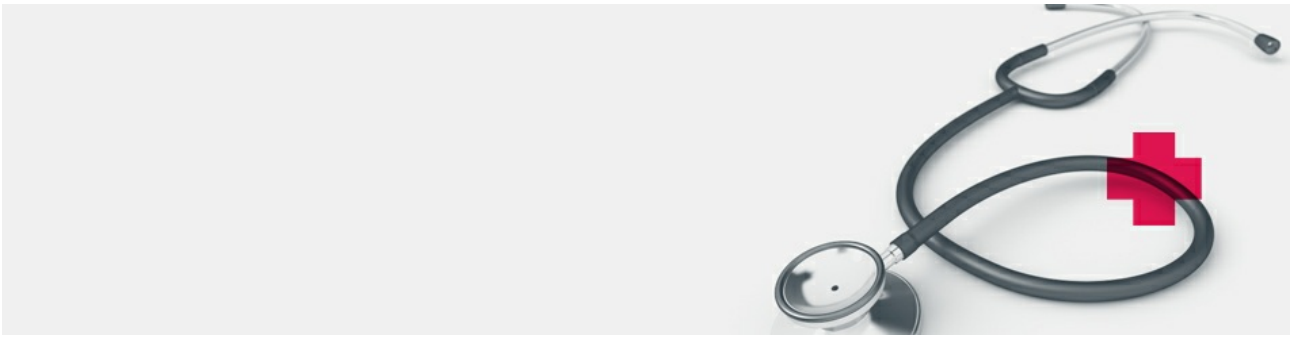
When I re-examined the classic fluoridation studies, which had been presented to me in the text books during my training, I found, as others had before me, that they also contained serious flaws [28-30]. The earliest set, which purported to show an inverse relationship between tooth decay prevalence and naturally occurring water fluoride concentrations, are flawed mainly by their nonrandom methods of selecting data. The later set, the "fluoridation trials" at Newburgh, Grand Rapids, Evanston, and Brantford, display inadequate baselines, negligible statistical analysis, and especially a failure to recognize large variations in tooth decay prevalence in the control communities. We really cannot know whether or not some of the tooth decay reductions reported in those early studies were due to water fluoride.

Best regards,
Christine Massey, M.Sc.
Fluoride Free Peel
http://www.fluoridefreepeel.ca/same-dose-of-fluoride/

fluoridealert.org

Fluoride Action Network

fluoridealert.org/issues/health/pineal-gland/



In the 1990s, a British scientist, Jennifer Luke, discovered that fluoride accumulates to strikingly high levels in the pineal gland. (Luke 2001). The pineal gland is located between the two hemispheres of the brain and is responsible for the synthesis and secretion of the hormone melatonin. Melatonin maintains the body's circadian rhythm (sleep-wake cycle), regulates the onset of puberty in females, and helps protect the body from cell damage caused by free radicals.

While it is not yet known if fluoride accumulation affects pineal gland function, preliminary animal experiments found that fluoride reduced melatonin levels and shortened the time to puberty. (Luke, 1997). Based on this and other evidence, the National Research Council has stated that "fluoride is likely to cause decreased melatonin production and to have other effects on normal pineal function, which in turn could contribute to a variety of effects in humans" (NRC, 2006, p. 256).

The Pineal Gland Has Highest Levels of Fluoride in Body

As a calcifying tissue that is exposed to a high volume of blood flow, the pineal gland is a major target for fluoride accumulation in humans. In fact, the calcified parts of the pineal gland (hydroxyapatite crystals) contain the highest fluoride concentrations in the human body (up to 21,000 ppm F), higher than either bone or teeth. (Luke 1997; 2001). Although the soft tissue of the pineal does not accumulate fluoride to the same extent as the calcified part, it does contain higher levels of fluoride than found than in other types of soft tissue in the body — with concentrations (~300 ppm F) that are known in other contexts to inhibit enzymes. While the impacts of these fluoride concentrations in the pineal are not yet fully understood, studies have found that calcified deposits in the pineal are associated with decreased numbers of functioning pinealocytes and reduced melatonin production (Kunz et al., 1999) as well as impairments in the sleep-wake cycle. (Mahlberg 2009).

Fluoride and Earlier Puberty in Girls

In the United States, children are reaching the age of puberty at earlier ages than in the past — a trend that carries health consequences, including a heightened risk for breast cancer. Some evidence indicates that fluoride, via its effect on the pineal, could be a contributing cause to this trend. In animal studies, for example, fluoride exposure has been found to cause a decrease in the amount of circulating melatonin and lead to an accelerated sexual maturation in females. (Luke 1997). Similar findings have been reported in two epidemiological studies of human populations drinking fluoridated water. In the first published fluoridation safety experiment in Newburgh, New York, the authors found that girls living in a fluoridated community reached puberty five months earlier than girls living in a non-fluoridated community. (Schlesinger 1956) Later, in 1983, Farkas reported that postmenarcheal girls were "present at younger ages in the higher fluoride town than in the low-fluoride town, although the reported median ages were the same."

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- Kunz D, et al. (1999). A new concept for melatonin deficit: on pineal calcification and melatonin excretion. Neuropsychopharmacology 21(6):765-72.
- Luke J. (2001). Fluoride deposition in the aged human pineal gland. Caries Res. 35(2):125-128.
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- National Research Council. (2006). Fluoride in Drinking Water: A Scientific Review of EPA's Standards. National Academies Press, Washington D.C.
- Schlesinger ER, et al. (1956). Newburgh-Kingston caries fluorine study. XIII. Pediatric findings after ten years. J Am Dent Assoc. 52(3):296-306.

From: Sprovieri, John Councillor [mailto:John.Sprovieri@brampton.ca]
Sent: February 8, 2018 7:34 PM
To: Christine Massey; Thompson, Allan; Downey, Johanna; Groves, Annette; Innis, Jennifer; Shaughnessy, Barb; Jeffrey, Linda Mayor; Gibson, Grant; Medeiros, Martin; Miles, Gael; Moore, Elaine; Palleschi, Michael; Crombie, Bonnie; Carlson, George; Fonseca, Chris; Iannicca, Nando; Kovac, John; Mahoney, Matt; McFadden, Sue; Parrish, Carolyn; Ras, Karen; Saito, Pat; Starr, Ron; Dale, Frank
Cc: Loh, Lawrence; Polsinelli, Nancy; Szwarc, David; Smith, Janette; Hennings, Jeff; Jim Nardi; ZZG-RegionalClerk; O'Connor, Patrick; Burkiewicz, Justyna; ZZG-WaterQualityInquiries; Hau, Monica; Ward, Megan; Bingham, Kate; Hopkins, Jessica; ehoskins.mpp@liberal.ola.org; pam douglas; newsroom@bramptonguardian.com; Vic Dhillon; Dbhat; premier@ontario.ca; Criscione, Peter; ZZG-CDIP-Oral Health; ZZG-PeelHealth; rbelgrave@thebramptonguardian.com; editor@caledoncitizen.com
Subject: RE: NEW study: fluoride concentrations lower than Peel's contribute to hypothyroidism.

Thank you for the information Christine.
I am certain that the chair of the community water fluoridation committee will appreciate this information.
John.

Sent from Mail for Windows 10

From: Christine Massey
Sent: February 8, 2018 4:50 PM
To: Thompson, Allan; Johanna Downey; Annette Groves; Jennifer Innis; Barb Shaughnessy; Jeffrey, Linda Mayor; Gibson, Grant - Councillor; Medeiros, Martin - Councillor; Miles, Gael - Councillor; Moore, Elaine - Councillor; Palleschi, Michael - Councillor; Crombie, Bonnie; George Carlson; Chris Fonseca; Iannicca, Nando; John Kovac; Matt Mahoney; McFadden, Sue; Carolyn Parrish; Karen Ras; Saito, Pat; Starr, Ron; Dale, Frank
Cc: Lawrence; Nancy Polsinelli; Szwarc, David; Smith, Janette; jeff.hennings@peelregion.ca; Jim Nardi; ZZG-Regionalclerk@peelregion.ca; patrick.o'connor@peelregion.ca; Burkiewicz, Justyna; ZZG-WaterQualityInquiries; Sprovieri, John Councillor; Monica.hau@peelregion.ca; Megan.ward@peelregion.ca; Kate Bingham; Hopkins, Jessica; ehoskins.mpp@liberal.ola.org; pam douglas; newsroom@bramptonguardian.com; Vic Dhillon; Dbhat; premier@ontario.ca; Criscione, Peter; ZZG-CDIP-Oral Health; ZZG-PeelHealth; rbelgrave@thebramptonguardian.com; editor@caledoncitizen.com
Subject: NEW study: fluoride concentrations lower than Peel's contribute to hypothyroidism.

[Peel's F'd water has 0.5 - 0.8 mg/L fluoride.]

Published online 08 February 2018 in Nature, one of the world's top academic journals:

Impact of Drinking Water Fluoride on Human Thyroid Hormones: A Case- Control Study

Authors: Zohreh Kheradpisheh, Masoud Mirzaei, Amir Hossein Mahvi, Mehdi Mokhtari, Reyhane Azizi, Hossein Fallahzadeh & Mohammad Hassan Ehrampoush

https://www.nature.com/articles/s41598-018-20696-4

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RECOMMENDED
DIRECTION REQUIRED _____
RECEIPT RECOMMENDED ✓ _____

...It was found that fluoride has impacts on TSH, T_3 hormones even in the standard concentration of less than 0.5 mg/L. ***Application of standard household water purification devices was recommended for hypothyroidism....***

Conclusion and Recommendation

This paper compares measurements of the average amount of thyroid hormones (T3, T4, and TSH) in people with thyroid disease (specifically, hypothyroidism) and people without thyroid disease, with respect to fluoride concentrations in two levels 0–0.29 and 0.3–0.5 (mg/L) in drinking water and several other variables (gender, family history, water consumption, exercise, other disease conditions).

The major finding of this study is that TSH values are higher with a higher fluoride concentration in the drinking water, even for generally low fluoride concentrations. This is seen both in cases of untreated hypothyroidism and in controls. *In multivariate regression logistic analysis, the independent variables associated with hypothyroidism were: gender (odds ratio: 2.5, CI 95%: 1.6–3.9), family history of thyroid disease (odds ratio: 2.7, CI 95%: 1.6–4.6), exercise (odds ratio: 5.34, CI 95%: 3.2–9), diabetes (odds ratio: 3.7, CI 95%: 1.7–8), hypertension (odds ratio: 3.2, CI 95%:1.3–8.2), amount of water consumed per day (odds ratio: 4, CI 95%: 1.2–14).*

In other words, cases tend to have higher TSH values (greater impairment of thyroid function) with higher fluoride concentrations in the water. Controls, with normal thyroid function, also have higher TSH values with higher fluoride concentrations, even though their TSH values are still within the normal range. TSH values are higher (in both cases and controls) with higher levels of water consumption. This is consistent with an association between increased fluoride intake (due to increased water consumption) and increased TSH. It was found that F impacts human thyroid hormones, especially TSH and T3 even in the standard concentration of less than 0.5 mg/L.

Even after the addition of iodine to salt by the integrated program in Iran more than 27 years ago, this study showed that the problem remains unsolved. The results showed that those who consume larger amounts of water per day have an adjusted OR of 4.1 (1.2–14). ***Hence, the application of standard household water purification (such as reversed osmosis, electro dialysis, activated carbon filter, and other adsorption/ion-exchange methods) is recommended for patients with hypothyroidism since they have a higher consumption of drinking water. The purification systems can help remove fluoride that interferes with thyroid functions.***

RECEIVED
November 16, 2017
REGION OF PEEL
OFFICE OF THE REGIONAL CLERK

Gurpreet SIngh Dhillon
City Councillor, City of Brampton

Why is Council spending $500,000.00 on Water Fluoridation when:

#1, Municipal Councillors do not have the detailed familiarity to interpret data regarding the efficacy of Hydrofluorosilicic Acid in water fluoridation treatments and are struggling with a range of conflicting and public concerns on the matter of fluoridation.

#2, On February 2017 Regional Council acknowledged that Water Fluoridation is a Provincial responsibility.

#3, On January 7, 2016 The Minister of Health and long term care issued a memo to all Provincial heads of Council indicating the importance of water fluoridation. He indicated that Water Fluoridation prevents dental cavities, various diseases and benefits all residents in a community, regardless of age, socioeconomic statue, education or employment.

#4, 30% of Ontario Towns and Cities have discontinued water fluoridation and the Province has failed to take responsibility and stop the continuous defection of water fluoridation across the Province.

#5, In 2016 the Province failed to approve MPP Delaney's private members bill in legislation, that all the provincial parties supported unanimously.

#6, Dr. Cooney the former Canadian Chief Dental officer of Health conceded that Water Fluoridation reduces cavity rates by LESS than HALF CAVITY PER CHILD.

#7, The FDA has never approved Fluoride supplements as safe and effective for preventing cavities.

#8, Most European countries do not fluoridate their water, because such Medication is considered Ineffective and Unethical.

REFERRAL TO _____
RECOMMENDED
DIRECTION REQUIRED _____
RECEIPT RECOMMENDED ✓ _____

From: Sprovieri, John Councillor [mailto:John.Sprovieri@brampton.ca]
Sent: February 27, 2018 8:18 AM
To: 'Christine Massey'; Thompson, Allan; Downey, Johanna; Groves, Annette; Innis, Jennifer; Shaughnessy, Barb; Jeffrey, Linda Mayor; Gibson, Grant; Medeiros, Martin; Miles, Gael; Moore, Elaine; Palleschi, Michael; Crombie, Bonnie; Carlson, George; Fonseca, Chris; Iannicca, Nando; Kovac, John; Mahoney, Matt; McFadden, Sue; Parrish, Carolyn; Ras, Karen; Saito, Pat; Starr, Ron; Dale, Frank; Loh, Lawrence; Polsinelli, Nancy; Szwarc, David; Smith, Janette; Hennings, Jeff; Jim Nardi; Burkiewicz, Justyna; ZZG-WaterQualityInquiries; Hau, Monica; Ward, Megan; Bingham, Kate; Hopkins, Jessica; ehoskins.mpp@liberal.ola.org; premier@ontario.ca; ZZG-CDIP-Oral Health; ZZG-PeelHealth; Farr, Andrew
Cc: O'Connor, Patrick; pam douglas; newsroom@bramptonguardian.com; Vic Dhillon; Sprovieri, John; Dbhat; Criscione, Peter; Belgrave, Roger; editor@caledoncitizen.com; ZZG-RegionalClerk; igheorghiu@rnao.ca; atsangsit@rnao.ca; cbintakies@rnao.ca; mtandoc@rnao.ca; snoronha@rnao.ca; tshelvey@rnao.ca; vboscart@rnao.ca; jenny.yuen@sunmedia.ca; Amanda.Ferguson@citynews.rogers.com; de Villa, Eileen; dr.david.williams@ontario.ca; laura.seeds@ontario.ca; Catherine.Fraser@ontario.ca; sarah.cox@ontario.ca; gillian.macdonald2@ontario.ca; Mikayla.Wicks@ontario.ca; Derrick.Araneda@ontario.ca; catharine.gapp@ontario.ca; Alyson.Rowe@ontario.ca; Dara.McLeod@ontario.ca; maria.babbage@ontario.ca; Holly.burke@ontario.ca; vivian.w.ng@ontario.ca; Saurabh.Popat@ontario.ca; olivia.nero@ontario.ca; ian.chesney@ontario.ca; joshua.McLarnon@ontario.ca; beth.mackinnon@ontario.ca; Mark.Tishman@ontario.ca; carley.lennox@ontario.ca; rachel.levy@ontario.ca; jelena.rakovac@ontario.ca; Katie.Heelis@ontario.ca; shae.greenfield@ontario.ca; Diana.Egbe@ontario.ca; info@wellfort.ca; Edesiri Udoh
Subject: RE: Health Minister RESIGNS

Thank you for letting us know Christine.
Perhaps the Health Minister has a conscience and could no longer tolerate Government nonsense.
John.

John Sprovieri
Regional Councillor for wards 9 & 10
City of Brampton
(905) 874-2610

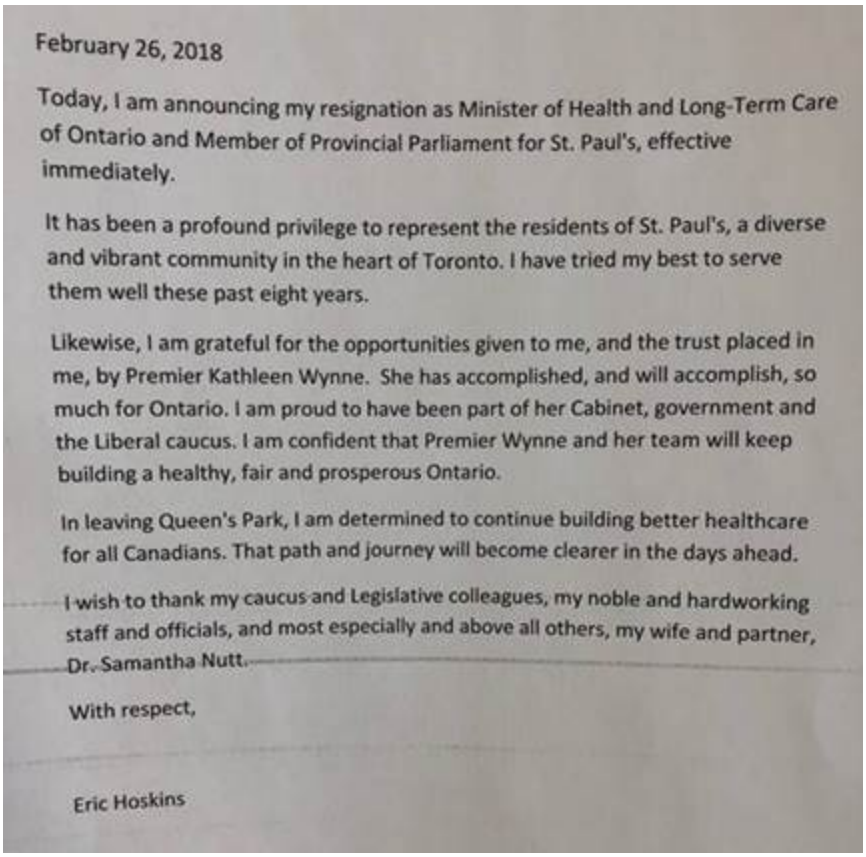
From: Christine Massey [redacted]
Sent: 2018/02/26 7:01 PM
To: Thompson, Allan <Allan.Thompson@caledon.ca>; Johanna Downey <Johanna.Downey@caledon.ca>; Annette Groves <Annette.Groves@caledon.ca>; Jennifer Innis <Jennifer.Innis@caledon.ca>; Barb Shaughnessy <Barb.Shaughnessy@caledon.ca>; Jeffrey, Linda Mayor <Linda.Jeffrey@brampton.ca>; Gibson, Grant - Councillor <Grant.Gibson@brampton.ca>; Medeiros, Martin - Councillor <Martin.Medeiros@brampton.ca>; Miles, Gael - Councillor <Gael.Miles@brampton.ca>; Moore, Elaine - Councillor <Elaine.Moore@brampton.ca>; Palleschi, Michael - Councillor <Michael.Palleschi@brampton.ca>; Crombie, Bonnie <Bonnie.Crombie@mississauga.ca>; George Carlson <George.Carlson@mississauga.ca>; Chris Fonseca <Chris.Fonseca@mississauga.ca>; Iannicca, Nando <Nando.Iannicca@mississauga.ca>; John Kovac <John.Kovac@mississauga.ca>; Matt Mahoney <Matt.Mahoney@mississauga.ca>; McFadden, Sue <Sue.McFadden@mississauga.ca>; Carolyn Parrish <carolyn.parrish@mississauga.ca>; Karen Ras <Karen.Ras@mississauga.ca>; Saito, Pat

REFERRAL TO _____
RECOMMENDED
DIRECTION REQUIRED _____
RECEIPT RECOMMENDED ✓

<Pat.Saito@mississauga.ca>; Starr, Ron <Ron.Starr@mississauga.ca>; Dale, Frank <frank.dale@mississauga.ca>; Lawrence <lawrence.loh@peelregion.ca>; Nancy Polsinelli <nancy.polsinelli@peelregion.ca>; Szwarc, David <David.Szwarc@peelregion.ca>; Smith, Janette <Janette.Smith@peelregion.ca>; jeff.hennings@peelregion.ca; Jim Nardi <JNardi@ocwa.com>; Burkiewicz, Justyna <justyna.burkiewicz@peelregion.ca>; ZZG-WaterQualityInquiries <ZZG-WaterQualityInquiries@peelregion.ca>; Monica.hau@peelregion.ca; Megan.ward@peelregion.ca; Kate Bingham <Kate.bingham@peelregion.ca>; Hopkins, Jessica <Jessica.hopkins@peelregion.ca>; ehoskins.mpp@liberal.ola.org; premier@ontario.ca; ZZG-CDIP-Oral Health <zzg-cdip-oralhealth@peelregion.ca>; ZZG-PeelHealth <ZZG-PeelHealth@peelregion.ca>; andrew.farr@peelregion.ca
Cc: patrick.o'connor@peelregion.ca; Sprovieri, John Councillor <John.Sprovieri@brampton.ca>; pam douglas <pdouglas@thebramptonguardian.com>; newsroom@bramptonguardian.com; Vic Dhillon <vdhillon.mpp.co@liberal.ola.org>; Dbhat <dbhat@liberal.ola.org>; Criscione, Peter <pcriscione@thebramptonguardian.com>; Belgrave, Roger <rbelgrave@thebramptonguardian.com>; editor@caledoncitizen.com; ZZG-Regionalclerk@peelregion.ca; igheorghiu@rnao.ca; atsangsit@rnao.ca; cbintakies@rnao.ca; mtandoc@rnao.ca; snoronha@rnao.ca; tshelvey@rnao.ca; vboscart@rnao.ca; jenny.yuen@sunmedia.ca; Amanda.Ferguson@citynews.rogers.com; de Villa, Eileen <Eileen.deVilla@peelregion.ca>; dr.david.williams@ontario.ca; laura.seeds@ontario.ca; Catherine.Fraser@ontario.ca; sarah.cox@ontario.ca; gillian.macdonald2@ontario.ca; Mikayla.Wicks@ontario.ca; Derrick.Araneda@ontario.ca; catharine.gapp@ontario.ca; Alyson.Rowe@ontario.ca; Dara.McLeod@ontario.ca; maria.babbage@ontario.ca; Holly.burke@ontario.ca; vivian.w.ng@ontario.ca; Saurabh.Popat@ontario.ca; olivia.nero@ontario.ca; ian.chesney@ontario.ca; joshua.McLarnon@ontario.ca; beth.mackinnon@ontario.ca; Mark.Tishman@ontario.ca; carley.lennox@ontario.ca; rachel.levy@ontario.ca; jelena.rakovac@ontario.ca; Katie.Heelis@ontario.ca; shae.greenfield@ontario.ca; Diana.Egbe@ontario.ca; info@wellfort.ca; Edesiri Udoh <Edesiri.Udoh@wellfort.ca>
Subject: Health Minister RESIGNS

Byyyyyeeeee!

Who's next?



February 26, 2018

Today, I am announcing my resignation as Minister of Health and Long-Term Care of Ontario and Member of Provincial Parliament for St. Paul's, effective immediately.

It has been a profound privilege to represent the residents of St. Paul's, a diverse and vibrant community in the heart of Toronto. I have tried my best to serve them well these past eight years.

Likewise, I am grateful for the opportunities given to me, and the trust placed in me, by Premier Kathleen Wynne. She has accomplished, and will accomplish, so much for Ontario. I am proud to have been part of her Cabinet, government and the Liberal caucus. I am confident that Premier Wynne and her team will keep building a healthy, fair and prosperous Ontario.

In leaving Queen's Park, I am determined to continue building better healthcare for all Canadians. That path and journey will become clearer in the days ahead.

I wish to thank my caucus and Legislative colleagues, my noble and hardworking staff and officials, and most especially and above all others, my wife and partner, Dr. Samantha Nutt.

With respect,

Eric Hoskins

On Fri, Feb 23, 2018 at 11:34 AM, Christine Massey [redacted] wrote:
Dear Peel Council, Chair, Commissioners, CAO, Medical Officers, General Manager of Water & Wastewater, Water-related Staff, Premier and Provincial Health Minister,

According to Health Canada, fluoridated toothpaste is a drug, even though you're supposed to spit it out.

150 ml of our fluoridated drinking water has the same 0.1 mg fluoride that Health Canada says children under 3 must spit out when brushing with a rice-sized bit of fluoridated toothpaste.

.15 L x .65 mg / L = .10 mg

Parents are advised to call poison control if a child under 3 swallows more than 0.1 mg fluoride in toothpaste.

385ml of our fluoridated drinking water has the same 0.25 mg fluoride that Health Canada says children age 3 to 6 must spit out when brushing with a pea-sized bit of fluoridated toothpaste .

.385 L x .65 mg / L = .25 mg

Parents are advised to call poison control if a child age 3 to 6 swallows more than 0.25 mg fluoride in toothpaste.

Health Canada:

Toothpastes (dentifrice) with fluoride are drugs since fluoride prevents caries, but toothpastes without fluoride are cosmetics...

https://www.canada.ca/en/health-canada/services/consumer-product-safety/reports-publications/industry-professionals/labelling-cosmetics.html

Health Canada:

Dentifrice products that do not contain Potassium nitrate

- *Keep out of reach of children under 6 years of age.*
- *If a quantity greater than the dose used for brushing is accidentally swallowed, get medical help or contact a Poison Control Centre right away (FDA 1995).*

  http://webprod.hc-sc.gc.ca/nhpid-bdipsn/atReg.do?atid=oral.health.sante.bucco.dentaire

FDA:

Warning. The labeling of the product contains the following warning under the heading "Warning":

(1) For all fluoride dentifrice (gel, paste, and powder) products. "Keep out of reach of children under 6 years of age. [highlighted in bold type] If more than used for brushing is accidentally swallowed, get medical help or contact a Poison Control Center right away."

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=355.50

CDC:

...each gram of fluoride toothpaste, as formulated in the United States, contains approximately 1.0 mg of fluoride.

...a pea-sized amount (approximately 0.25 g) of fluoride toothpaste...

...Counsel Parents and Caregivers Regarding Use of Fluoride Toothpaste by Young Children, Especially Those Aged <2 Years

Fluoride toothpaste is a cost-effective way to reduce the prevalence of dental caries. However, for children aged <6 years, especially those aged <2 years, an increased risk for enamel fluorosis exists because of inadequately developed control of the swallowing reflex.

https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5014a1.htm

Health Canada:

> *Fluoride is good for your teeth, but having too much fluoride can cause two potential effects on health:*
>
> - *dental fluorosis*
> - *skeletal fluorosis*

Because very young children may not have developed the ability to spit, they may swallow toothpaste when brushing. We recommend using the right amount of toothpaste for your child's age.

If your child is under 3 years old (0 to 36 months)... is at risk of developing tooth decay, then they should have their teeth brushed by an adult using a minimal amount (rice-sized grain) of fluoridated toothpaste.

An adult should always help children under age 6 brush their teeth and use only a small amount (small green pea-sized or 5 mm maximum) of fluoridated toothpaste.

https://www.canada.ca/en/health-canada/services/healthy-living/your-health/environment/fluorides-human-health.html

Canadian Dental Association:

The use of fluoridated toothpaste in this age group is determined by the level of risk. Parents should consult a health professional to determine whether a child up to 3 years of age is at risk of developing tooth decay. If such a risk exists, the child's teeth should be brushed by an adult using a minimal amount (a portion the size of a grain of rice – see figure 1) of fluoridated toothpaste.

Children from 3 to 6 years of age should be assisted by an adult in brushing their teeth. Only a small amount (a portion the size of a green pea – see figure 1) of fluoridated toothpaste should be used.

https://www.cda-adc.ca/_files/position_statements/fluoride.pdf

American Dental Association Council on Scientific Affairs*:*

The results of the review demonstrated that for children younger than 6 years, fluoride toothpaste use is effective in reducing caries. The evidence also showed that ingesting pea-sized amounts or more can lead to mild fluorosis.

...no more than a smear or the size of a grain of rice...

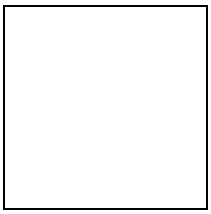


Figure 1

The toothbrush on the left shows a smear of toothpaste (0.1 milligram of fluoride) and the one on the right a pea-sized amount (0.25 mg of fluoride).

Supervise children's brushing to minimize swallowing of toothpaste.

http://jada.ada.org/article/S0002-8177(14)60226-9/fulltext

Best regards,

Christine Massey
Fluoride Free Peel
http://www.fluoridefreepeel.ca/same-dose-of-fluoride/

From: Sprovieri, John Councillor [mailto:John.Sprovieri@brampton.ca]
Sent: March 2, 2018 9:57 AM
To: Lockyer, Kathryn
Cc: Bonnie Crombie; Jeffrey, Linda Mayor; O'Connor, Patrick; Thompson, Allan; Gibson, Grant; Medeiros, Martin; Miles, Gael; Moore, Elaine; Palleschi, Michael; Parrish, Carolyn; Carlson, George; Fonseca, Chris; Iannicca, Nando; Kovac, John; Mahoney, Matt; McFadden, Sue; Ras, Karen; Saito, Pat; Starr, Ron; Downey, Johanna; Groves, Annette; Innis, Jennifer; Shaughnessy, Barb; mistma.consulting@live.com; 'Christine Massey'; 'Kerr, John'; 'Gilles Parent, ND'; 'Councillor Augimeri'; torontotips@cbc.ca; Szwarc, David; Lockyer, Kathryn; Dale, Frank; Polsinelli, Nancy; Hopkins, Jessica; ehoskins.mpp@liberal.ola.org
Subject: RE: Dianne Saxe Blog

Hi Kathryn,
Can you provide me the list of items that have been referred to the suspended Community Water Fluoridation Committee.
John.

John Sprovieri
Regional Councillor for wards 9 & 10
City of Brampton
(905) 874-2610

From: O'Connor, Patrick [mailto:patrick.oconnor@peelregion.ca]
Sent: 2018/03/01 11:37 AM
To: Sprovieri, John Councillor <John.Sprovieri@brampton.ca>
Cc: Bonnie Crombie <bonnie.crombie@mississauga.ca>; Jeffrey, Linda Mayor <Linda.Jeffrey@brampton.ca>; Thompson, Allan <allan.thompson@caledon.ca>; Gibson, Grant - Councillor <Grant.Gibson@brampton.ca>; Medeiros, Martin - Councillor <Martin.Medeiros@brampton.ca>; Miles, Gael - Councillor <Gael.Miles@brampton.ca>; Moore, Elaine - Councillor <Elaine.Moore@brampton.ca>; Palleschi, Michael - Councillor <Michael.Palleschi@brampton.ca>; Sprovieri, John Councillor <John.Sprovieri@brampton.ca>; Parrish, Carolyn <carolyn.parrish@mississauga.ca>; Carlson, George <george.carlson@mississauga.ca>; Fonseca, Chris <chris.fonseca@mississauga.ca>; Iannicca, Nando <nando.iannicca@mississauga.ca>; Kovac, John <john.kovac@mississauga.ca>; Mahoney, Matt <matt.mahoney@mississauga.ca>; McFadden, Sue <sue.mcfadden@mississauga.ca>; Ras, Karen <karen.ras@mississauga.ca>; Saito, Pat <pat.saito@mississauga.ca>; Starr, Ron <ron.starr@mississauga.ca>; Downey, Johanna <johanna.downey@caledon.ca>; Groves, Annette <annette.groves@caledon.ca>; Innis, Jennifer <jennifer.innis@caledon.ca>; Shaughnessy, Barb <barb.shaughnessy@caledon.ca>; mistma.consulting@live.com; 'Christine Massey' <cmssyc@gmail.com>; 'Kerr, John' <john.kerr@peelsb.com>; 'Gilles Parent, ND' <gilles.parent-nd@bellnet.ca>; 'Councillor Augimeri' <Councillor_Augimeri@toronto.ca>; torontotips@cbc.ca; Szwarc, David <david.szwarc@peelregion.ca>; Lockyer, Kathryn <kathryn.lockyer@peelregion.ca>; Dale, Frank <frank.dale@peelregion.ca>; Polsinelli, Nancy <nancy.polsinelli@peelregion.ca>; Hopkins, Jessica <jessica.hopkins@peelregion.ca>; ehoskins.mpp@liberal.ola.org
Subject: RE: Dianne Saxe Blog

Councillor Sprovieri

You have posed below a number of questions touching upon the issue of drinking water fluoridation, some from a legal and some from a political perspective.

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DIRECTION REQUIRED _____
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As you know, like other staff of the Region, I have Council's instructions (Resolution 2017-234) to refer such requests to the Community Water Fluoridation Committee for determination upon the reconvening of the Committee from its suspension under Council resolution 2017-185. As a practical matter, responsibility for undertaking the referral of such matters has been assumed by the Regional Clerk who is also in receipt of your message and is copied here.

I understand your view to be that this is an unsatisfactory state of affairs and that the Committee should be reconvened. That as you know is a matter for Council to determine.

You have provided links to two web postings from a respected environmental law firm. I will be pleased to provide my interpretation of their relevance to Peel if asked by the Committee, under the framework established by Council's resolutions.

Regards

Patrick

Patrick O'Connor

Regional Solicitor

Region of Peel

((905) 791-7800 ex. 4319
: Patrick.O'Connor@PeelRegion.ca

From: Sprovieri, John Councillor [mailto:John.Sprovieri@brampton.ca]
Sent: February 24, 2018 3:24 PM
To: O'Connor, Patrick; Szwarc, David; Lockyer, Kathryn; Dale, Frank; Polsinelli, Nancy; Hopkins, Jessica; ehoskins.mpp@liberal.ola.org
Cc: Bonnie Crombie; Jeffrey, Linda Mayor; Thompson, Allan; Gibson, Grant; Medeiros, Martin; Miles, Gael; Moore, Elaine; Palleschi, Michael; Sprovieri, John; Parrish, Carolyn; Carlson, George; Fonseca, Chris; Iannicca, Nando; Kovac, John; Mahoney, Matt; McFadden, Sue; Ras, Karen; Saito, Pat; Starr, Ron; Tovey, Jim; Downey, Johanna; Groves, Annette; Innis, Jennifer; Shaughnessy, Barb; mistma.consulting@live.com; 'Christine Massey'; 'Kerr, John'; 'Gilles Parent, ND'; 'Councillor Augimeri'; torontotips@cbc.ca
Subject: Dianne Saxe Blob.

Hi Patrick,
Are Municipal Councillors at Risk for approving Water Fluoridation and are you responsible to protect the Councillors or the Corporation?
Below you will see Diane Saxe's comments when she worded at Siskinds Environmental Law.
Have you seen her Blog that she posted after the residents of Peel lodged the lawsuit against the Region for artificially Fluoridating the Drinking water Supply?
As you can see on the link below, Diane believes that section 19 of the Safe Drinking Water Act Poses a Legal Risk to Municipal Councillors and that the Province should have fixed the risk. As you are well aware, the Statutory Standard of Care was put in place to ensure that Municipal

Councillors [the decision makers] are doing their Due Diligence to protect public health when making decisions about drinking water safety and providing oversight of the accredited operation authority.

As you are aware, the Standard of care is all about ensuring responsible actions are taken to protect human health. Given the seriousness of this duty to the community, those whose actions fall below the standard of care, fail to protect the public and cause harm to human health could face significant penalties, including fines and imprisonment. Although Regional Councillors qualify for legal cost coverage from the Region, Councillors are not protected from fines and imprisonment. According to the Standard of care provisions, Councillors are at risk of being fines and of imprisonment, if the courts find that Water Fluoridation is unsafe and residents may have been harmed over the past years by the chemicals that make up Hydrofluorosilicic Acid [HFSA]. As you are well aware HFSA is made up of, Silica, Fluoride, Arsenic, Lead, Radium, and traces of other toxic substances all known to be harmful to Humans and the Environment.

Keeping in mind that the US EPA has classified Fluoride as a Neuro Toxin, same as Lead and Arsenic which have similar Toxicity, the EPA and Health Canada allows 4000 ppb [parts per billion] of Fluoride, 1.5 ppb of lead and 1.0 ppb Arsenic in our drinking water.
Since the "Public Health Goal"/ Maximum Contaminant Level Goal" [MCLG] for both Arsenic and Lead is ZERO, how will any lawyer be able to defend Councillors when it has been well established by recent Scientific studies that Fluoride is connected to numerous Health related problems?

As you may recall, in February 2017 Regional Council passed a resolution requesting the Province to take back the responsibility for approving water fluoridation and do the Health Canada required Toxicology studies to asure the public that Water Fluoridation is safe. As you know, one year has gone by and the Province has neither acknowledged receipt of the Council resolution nor responded to Councils request.

Questions that need to be addressed by Legal.

- #1: One year has gone by. Why hasn't the Province acknowledged or responded to the Council Resolution?

- #2 Water Fluoridation has been called one of the greatest public health achievements of the 20th. Century by the CDC. 70% of Canadian towns and Cities have discontinued Water Fluoridation. Why has Health Canada and the Provincial Health Ministers of Health turned their backs on 70% of Canadians?

- #3: Why didn't the Province enact PPM Delaney's 2015 proposed private members bill into legislation and make Water Fluoridation available to all the residents of Ontario?

- #4: Who is responsible to do the Health Canada required Toxicology Reviews on the Fluoridation product [Hydrofluorosilicic Acid] to ensure it's safe for Human Consumption?

- #5: Why is the Province allowing the Municipalities to add a Toxic and dangerous substance to the drinking water without the required Toxicology Studies?

- #6: The Supreme Court of Canada ruled that Water Fluoridation is a Medication, the Charter of Rights and Freedoms protects Canadians from forced medication. Why is

the Provincial Minister of Health allowing Municipalities to add an untested and medication to the peoples drinking water?

- #7: Health Canada and the Provinces have provided no Scientific Evidence that Water Fluoridation is Safe and Effective to Peel Region. Why does Health Canada, the Provincial Ministry of Health and Municipal Medical Officers of Health recommend adding a Toxic and Harmful
Chemical to the peoples drinking water supply?

Patrick, as the Regional Solicitor, if you are responsible to protect Regional Councillors from a lawsuit, you should have answers to the questions and if you don't have the answers, you should get the answers for the sake of Council.
Regards, John.

Here's the Diane Saxe blog link:

https://www.siskinds.com/envirolaw/personal-liability-water-fluoridation/

https://www.siskinds.com/envirolaw/fluoride-litigation-update/

From: Sprovieri, John Councillor [mailto:John.Sprovieri@brampton.ca]
Sent: March 10, 2018 1:27 PM
To: 'Christine Massey'
Cc: Thompson, Allan; Sprovieri, John; Downey, Johanna; Groves, Annette; Innis, Jennifer; Shaughnessy, Barb; Jeffrey, Linda Mayor; Gibson, Grant; Medeiros, Martin; Miles, Gael; Moore, Elaine; Palleschi, Michael; Crombie, Bonnie; Carlson, George; Fonseca, Chris; Iannicca, Nando; Kovac, John; Mahoney, Matt; McFadden, Sue; Parrish, Carolyn; Ras, Karen; Saito, Pat; Starr, Ron; Dale, Frank; Loh, Lawrence; Polsinelli, Nancy; Szwarc, David; Smith, Janette; Hennings, Jeff; Jim Nardi; Burkiewicz, Justyna; ZZG-WaterQualityInquiries; Hau, Monica; Ward, Megan; Bingham, Kate; Hopkins, Jessica; ehoskins.mpp@liberal.ola.org; premier@ontario.ca; ZZG-CDIP-Oral Health; ZZG-PeelHealth; Farr, Andrew; O'Connor, Patrick; pam douglas; newsroom@bramptonguardian.com; Vic Dhillon; Dbhat; Criscione, Peter; Belgrave, Roger; editor@caledoncitizen.com; ZZG-RegionalClerk; igheorghiu@rnao.ca; atsangsit@rnao.ca; cbintakies@rnao.ca; mtandoc@rnao.ca; snoronha@rnao.ca; tshelvey@rnao.ca; vboscart@rnao.ca; de Villa, Eileen; dr.david.williams@ontario.ca; info@wellfort.ca; Edesiri Udoh
Subject: RE: Medical officer of health declines fluoridation debate in Parry Sound

Thank you for your comments Christine.
I am certain that the day of reckoning will soon come and all these supposedly reputable world organizations will be exposed that they have endorsed Artificial Water Fluoridation without doing their own due diligence.
John.

John Sprovieri
Regional Councillor for wards 9 & 10
City of Brampton
(905) 874-2610

From: Christine Massey [redacted]
Sent: 2018/03/09 2:10 PM
To: Sprovieri, John Councillor <John.Sprovieri@brampton.ca>
Cc: Thompson, Allan <Allan.Thompson@caledon.ca>; Johanna Downey <Johanna.Downey@caledon.ca>; Annette Groves <Annette.Groves@caledon.ca>; Jennifer Innis <Jennifer.Innis@caledon.ca>; Barb Shaughnessy <Barb.Shaughnessy@caledon.ca>; Jeffrey, Linda Mayor <Linda.Jeffrey@brampton.ca>; Gibson, Grant - Councillor <Grant.Gibson@brampton.ca>; Medeiros, Martin - Councillor <Martin.Medeiros@brampton.ca>; Miles, Gael - Councillor <Gael.Miles@brampton.ca>; Moore, Elaine - Councillor <Elaine.Moore@brampton.ca>; Palleschi, Michael - Councillor <Michael.Palleschi@brampton.ca>; Crombie, Bonnie <Bonnie.Crombie@mississauga.ca>; George Carlson <George.Carlson@mississauga.ca>; Chris Fonseca <Chris.Fonseca@mississauga.ca>; Iannicca, Nando <Nando.Iannicca@mississauga.ca>; John Kovac <John.Kovac@mississauga.ca>; Matt Mahoney <Matt.Mahoney@mississauga.ca>; McFadden, Sue <Sue.McFadden@mississauga.ca>; Carolyn Parrish <carolyn.parrish@mississauga.ca>; Karen Ras <Karen.Ras@mississauga.ca>; Saito, Pat <Pat.Saito@mississauga.ca>; Starr, Ron <Ron.Starr@mississauga.ca>; Dale, Frank <frank.dale@mississauga.ca>; Lawrence <lawrence.loh@peelregion.ca>; Nancy Polsinelli <nancy.polsinelli@peelregion.ca>; Szwarc, David <David.Szwarc@peelregion.ca>; Smith, Janette <Janette.Smith@peelregion.ca>; jeff.hennings@peelregion.ca; Jim Nardi <JNardi@ocwa.com>; Burkiewicz, Justyna <justyna.burkiewicz@peelregion.ca>; ZZG-WaterQualityInquiries <ZZG-WaterQualityInquiries@peelregion.ca>; Monica.hau@peelregion.ca; Megan.ward@peelregion.ca; Kate Bingham <Kate.bingham@peelregion.ca>; Hopkins, Jessica <Jessica.hopkins@peelregion.ca>; ehoskins.mpp@liberal.ola.org; premier@ontario.ca; ZZG-CDIP-Oral Health <zzg-cdip-

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oralhealth@peelregion.ca>; ZZG-PeelHealth <ZZG-PeelHealth@peelregion.ca>; andrew.farr@peelregion.ca; patrick.o'connor@peelregion.ca; pam douglas <pdouglas@thebramptonguardian.com>; newsroom@bramptonguardian.com; Vic Dhillon <vdhillon.mpp.co@liberal.ola.org>; Dbhat <dbhat@liberal.ola.org>; Criscione, Peter <pcriscione@thebramptonguardian.com>; Belgrave, Roger <rbelgrave@thebramptonguardian.com>; editor@caledoncitizen.com; ZZG-Regionalclerk@peelregion.ca; igheorghiu@rnao.ca; atsangsit@rnao.ca; cbintakies@rnao.ca; mtandoc@rnao.ca; snoronha@rnao.ca; tshelvey@rnao.ca; vboscart@rnao.ca; de Villa, Eileen <Eileen.deVilla@peelregion.ca>; dr.david.williams@ontario.ca; info@wellfort.ca; Edesiri Udoh <Edesiri.Udoh@wellfort.ca>
Subject: Re: Medical officer of health declines fluoridation debate in Parry Sound

Hi John,

Those bizarre organizations, like Ontario's math-challenged Medical Officers, will happily lie to hundreds of school children at a time, but come up empty when asked for the required toxicology studies on HFSA... or randomized controlled studies on water fluoridation, or even observational studies that control for all the potential confounding variables.

If they do have any, they aren't sharing them with the public.

Christine
http://www.fluoridefreepeel.ca/same-dose-of-fluoride/

On Fri, Mar 9, 2018 at 1:54 PM, Sprovieri, John Councillor <John.Sprovieri@brampton.ca> wrote:

Hi Christine,

Thank you for sharing the information. Would you know if any of the 90 National and International organizations undertake the Toxicology studies that would determine if the Fluoridation product [HFSA] used to artificially fluoridate the water supply is safe?

John.

Sent from Mail for Windows 10

From: Christine Massey
Sent: March 9, 2018 12:28 PM
To: Thompson, Allan; Johanna Downey; Annette Groves; Jennifer Innis; Barb Shaughnessy; Jeffrey, Linda Mayor; Gibson, Grant - Councillor; Medeiros, Martin - Councillor; Miles, Gael - Councillor; Moore, Elaine - Councillor; Palleschi, Michael - Councillor; Crombie, Bonnie; George Carlson; Chris Fonseca; Iannicca, Nando; John Kovac; Matt Mahoney; McFadden, Sue; Carolyn Parrish; Karen Ras; Saito, Pat; Starr, Ron; Dale, Frank; Lawrence; Nancy Polsinelli; Szwarc, David; Smith, Janette; jeff.hennings@peelregion.ca; Jim Nardi; Burkiewicz, Justyna; ZZG-WaterQualityInquiries; Monica.hau@peelregion.ca; Megan.ward@peelregion.ca; Kate Bingham; Hopkins, Jessica; ehoskins.mpp@liberal.ola.org; premier@ontario.ca; ZZG-CDIP-Oral Health; ZZG-PeelHealth; andrew.farr@peelregion.ca
Cc: patrick.o'connor@peelregion.ca; Sprovieri, John Councillor; pam douglas; newsroom@bramptonguardian.com; Vic Dhillon; Dbhat; Criscione, Peter; Belgrave, Roger; editor@caledoncitizen.com; ZZG-Regionalclerk@peelregion.ca; igheorghiu@rnao.ca; atsangsit@rnao.ca; cbintakies@rnao.ca; mtandoc@rnao.ca; snoronha@rnao.ca; tshelvey@rnao.ca; vboscart@rnao.ca; de Villa, Eileen; dr.david.williams@ontario.ca; info@wellfort.ca; Edesiri Udoh
Subject: Medical officer of health declines fluoridation debate in Parry Sound

Typical!

Medical officer of health declines fluoridation debate in Parry Sound *Group plans to inform residents ahead of the October municipal election*

> *PARRY SOUND — The invitation to debate fluoridation was declined.*
>
> *On Oct. 28, 2017, Joe Moloney, chair of Parry Sounders for Progressive Water Management wrote to North Bay Parry Sound District Health Unit medical officer of*

health/executive director Dr. Jim Chirico, asking if he would participate in a public debate with Dr. Hardy Limeback on fluoridation.

The McKellar resident, Limeback, is former dentist and professor. He has written peer-reviewed papers on the dangers and long- term effects of hydrofluorosilicic acid (fluoride).

"In order for the electorate to have a well-informed opinion before the vote, we invite you to have a public debate with Dr. Hardy Limeback on the issues related to fluoridation," wrote Moloney. "Such a debate is timely in light of new research and warnings issued by the International Academy of Oral Medicine and Toxicology."

Chircio responded to Parry Sounders for Progressive Water Management just days later, saying he has already made two deputations to Town of Parry Sound council and has no intentions in participating in a debate.

"After careful review of the science by panels of skilled experts from many disciplines looking at all of the evidence, over the years and recent years — both positive and negative studies — the same conclusion has been reached by over 90 national and international organizations," responded Chirico. "Fluoridation of community water systems is safe and effective in reducing cavities for the young and old."

Speaking on behalf of the group on Feb. 20, Moloney said the medical officer of health's response was expected.

"It didn't surprise us," Moloney said. "This is not a dental issue; this is a health issue. However, because he's not going to debate Hardy Limeback, we're going to arrange some public information sessions with several public health officials speaking about fluoridation so the residents are well informed ahead of the October municipal election. In Parry Sound, I think people are progressive enough to say, we don't want this chemical in our water."

At its Feb. 20 meeting, Parry Sound council approved a bylaw, allowing the question, "Are you in favour of the fluoridation of the public water supply of this municipality?" on the Oct. 22 municipal election ballot.

Best regards,
Christine Massey
Fluoride Free Peel
http://www.fluoridefreepeel.ca/

-----Original Message-----
From: Raymond Ray [redacted]
Sent: March 12, 2018 1:47 PM
To: ZZG-RegionalClerk
Subject: Water fluoridation

Web Form Title :: Director of Clerks and Regional Clerk

This email was sent by the following person. Please reply to them:

Sender's Name: Raymond Ray
Sender's Email: [redacted]

The message was submitted through an Automated Email Service on Peel's Website Mon Mar 12 13:47:20 2018:

Mar. 12. 2018
Dear Madam, Sir.
I am writing you this letter hoping you will understand my feeling why I am so concerned about the poison without knowing the truth you are adding into the drinking water that the children drinks every day.
Just a few days ago I know a little girl who lost her life in brain cancer who used to live where water is highly fluoridated. It broke my heart and I cry in the night when I went to bed. Just think if you would have lost someone you love very much because you are forced to believe water fluoridation is good for them it does not herm.
Our health officers telling you how important to have this hydrofluorosilicic acid into our water. They are sending city to city, town to town and region to region Health Canada's representatives to market this poisonous dirty by-product of fertilizer industry. They are warning you that failure to continue this water fluoridation will cause increase in dental cavity. Please think why it is so important a non-life-threatening dental cavity when there are so many life-threatening diseases don't concern them at all?
It is obvious that those marketers are receiving their money into a foreign bank account so that this can be kept secret. I believe this matter should be investigated by our authorities and bring those law breakers criminals to the justice. Not just that, we all pay our income tax but those marketers are not paying any income tax on their illegal income. Our Prime Minister Justin Trudeau recently said that Canada losing as much as 7 Billion dollars tax revenue to those who hide their money in to foreign bank.
Few years ago I went to Panama City to visit few bank to find out the name of the Canadian who is hiding their money illegally into their bank. The bank officer told me if I want to open an account into their bank they will help me to register a Panama Corporation and this Corporation shall open a bank account into their bank. The shareholder of the Corporation will be an invisible person living in Dubai. A 16 digit pin number I shall create to transfer or withdrawal money from this bank account. My money will be safe and no one will be able to find out about it except myself. When I asked them if they have any Canadian has their account into their bank, they told me they have already over 50 Canadian enjoying their bank account with close to $1billion into their account but they refused to give their name.
You know well recently the largest hydrofluorosilicic acid producers MOSAIC FERTILIZER LLC fined by US government 2 billion dollars and now Middle District of Florida and the Eastern

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District of Louisiana, also filed legal action against MOSAIC for environmental damage. I have over 1500 pages the original court document if you want I can provide you in a CD.
Water fluoridation violates many Canadian environmental protection acts. Therefore without knowing the fact you are violating those acts.
If you look in the chemical dictionary hydrofluorosilicic acid is written as an unstable poisonous corrosive acid but not as fluoride.
Some our highly paid and highly educated senior health officers when they come to you and tell you fluoride protect teeth. They tell you fluoride is a natural product and it is harmless. They do not tell you that fluoride in nature is calcium fluoride (CaF_2) and the fluoride added to our drinking water is Hydrofluorosilicic acid (H_2SiF_6). There is a big difference between those two chemical compounds. They use you for their personal benefit.
At present, 97% of the western European population drinks non-fluoridated water. This includes: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Iceland, Italy, Luxembourg, Netherlands, Northern Ireland, Norway, Portugal, Scotland, Sweden, Switzerland, and approximately 90% of both the United Kingdom and Spain. Some of these countries have fluoridated and non-fluoridated salt in the market so that citizen can make their own choice as they want. The only western European countries allow salt fluoridation are Austria, France, Germany, Spain, and Switzerland.
The white fluorosis on child's teeth it may not bother too much because our health officers telling us it is harmless. But they do not tell us it is the sign of damage already happening inside that little body. There bones, organs, immune system and the brain are already under attack. They will not be able to prevent any bacterial disease once their immune system is destroyed and therefore they may end up in hospital bed. God forbid someday there little life may end.
Tap water supplied by the Metro Vancouver Water District is not fluoridated. In Quebec only 4% water is fluoridated but they have less cavity then Ontario has where 78% population drinks fluoridated water. Now look at European countries. Almost all European countries do not fluoridate their water nor they consume fluoride in different sources but according to World Health Organization they have fewer cavities less cancer and no fluorosis into their teeth then we have in Ontario. Does it ever come to your mind why so many civilized countries ban water fluoridation? Are they all wrong and our North American health officers especially health Canada is right?
U.S. Environmental Protection Agency says hydrofluorosilicic acid's inorganic silicofluoride, lead, arsenic, mercury, and radionuclides pose environmental harm to living things when diluted into the atmosphere and into natural waterways then how do they not pose a threat when diluted in our drinking water?
There for the "addition of Hydrofluorosilicic acid in drinking water is clearly a method of recycling or disposing this hazardous waste," according to Deputy Assistant Administrator for Water at the United States, Environmental Protection Agency.
It is obvious that our health organizations prefer to have water fluoridation to continue so that the flow of millions of dollars donation for research (that never done or needed) from the Fluoride producers can keep coming. Therefor it is very clear that fluoride in our water is not for tooth decay prevention.
We spend billions of dollars to have our health Canada the counterpart of American FDA and CDC so that our health will be protected. Unfortunately those senior officers actually destroying our health by poisoning us slowly. Here is one example will make you surprise.
Monsanto an American Corporation manufacturer of rBGH hormone came to Canada and mate senior health officer of health Canada in a closed-door meeting for their approval of this hormone so that it can be marketed in Canada.
This hormone when injected to the cows' body artificiality their body and breast get unnaturally big. Because of that reason they will be producing more meat and milk. It is one of the most

painful cruel treatments to an animal and it is also extremely unhealthy for our children especially young girls when they consume milk and meat contain this hormone.
Our senior health officers after the closed-door meeting with Monsanto order three highly educated senior scientist of health Canada to write a false report that they have tested studied and researched this hormone and found no negative affect on human health. Those three scientists to protect Canadian refused to do so unless a proper study and work done. Because of this refusal, those Health Canada's senior officers lost their millions of dollars backdoor deal with Monsanto. The angry officers immediately fire those three scientist and the reason was given is confidential. After that one of those scientists was offered by Monsanto large sum of money to approve this product. But instead of taking the money this honest scientist brought this matter to the Canadian Senate committee and that is why today because of those three scientist our children our drinking milk and eating hamburger that free of this rBGH hormone.
I'm asking you before you approve water fluoridation any more please think seriously if this acid really helps? If it does then why European Union ban water fluoridation? Why World Health Organization telling us not to fluoridated our water why it is legislated in the UK as type II poison and why FDA telling the mothers not to use fluoridated water to make baby formula.
Do you know our Health Canada and Health Ontario very cleverly transfer all legal responsibilities to the City councillors those who voted in favor of water fluoridation? You are the one making them very rich and getting nothing for yourself except taking the risk being sued.
When you add hydrofluorosilicic acid to water people only drink 1% or 2% of this water and the rest 98% to 99% end up into our environment. Our lakes rivers soil are polluted with this acid. Our sewage system cannot remove the hydrofluorosilicic acid from the waist therefore they dump this waste into our Lake or in the river killing all the aquatic life.
Every square inch of surface soil contained millions of bacteria that revitalize our soil so we can produce our food again. But when we dump water that contain hydrofluorosilicic acid into the soil we kill all those bacteria those are so important for our food production. Therefore slowly and steadily we are destroying our land and this planet just because you believe those criminal senior officers. .
The pesticide, insecticide that contain sodium fluoride we spray on our firm land that killing bees in millions in every day. Just think without bees there will be no pollination and there will be no food. Those chemicals are now prohibited use in France.
Albert Einstein once said "when the bees' population will end the human population also will end too".
Let me tell you what hydrofluorosilicic acid do to your health. What I am writing you is not something I am creating but it is the result of thousands of research made by many qualified organisations and scientist around the globe.
1. Fluoride is a developmental neurotoxin.
A neurotoxin is a substance that's poisonous or destructive to the tissues in the brain, spinal cord, and nervous system. A developmental neurotoxin is one that affects the brain during the most susceptible stages of life — before birth and during early childhood.
Developmental neurotoxins are linked to increases in autism, attention deficit hyperactivity disorder (ADHD), dyslexia, loss of IQ points, disruptive behavior, and other cognitive impairments.
2. Fluoride increases risk of low thyroid.
When you cannot sleep in the night and feel next morning very tired and weak because of sleepless night. You go to the medical pharmacy and buy sleeping tablet or liquid so you can sleep. You never ask why it is so. Please allow me to explain you about it.
In the centre your brain there is a tiny little gland is called Pineal Gland. It is no bigger than size of a pea and pinecone-shaped.
How you think and feel every day depends on the pineal gland. As the producer of the hormone melatonin, the quality and duration of your sleep relies on how well it produces this hormone.

This tiny organ regulates your daily and seasonal circadian rhythms, the sleep-wake patterns that determine your hormone levels, stress levels, and physical performance.
Melatonin is known mainly as a sleep hormone, but it's much more than that. Melatonin is a potent antioxidant that is especially protective of the brain. It can offset the damage of serious brain disorders including dementia and Alzheimer's. It may even help you live longer.
When you consume fluoride it causes Pineal Gland hardening as it consumes more fluoride than your bone can do. This affects melatonin production contributing to insomnia, depression, and accelerated brain aging.
3. Fluoride lowers IQ.
Harvard School of Public Health and China Medical University did a joint analysis of 27 studies on the effects of fluoride and found a strong correlation between fluoride and adverse effects on brain development.
Children in high-fluoride areas had significantly lower IQ scores than those living in low-fluoride areas.
This is not the only study that supports these findings.
As of September 2017 a total of 58 studies has been conducted around the globe and found fluoride effects especially on the Yonge brain strongly.
4. Fluoride causes Alzheimer
In the year 1970 research found Alzheimer patients have more aluminium into their brain than normal people has.
In the University of Harvard, researcher and more than 30 studies around the globe found that fluoride play a big role in the aluminium concentration in the brain of Alzheimer patients.
The blood-brain barrier is a semi-permeable membrane designed to keep foreign substances out of the brain.
When aluminum comes into contact with fluoride, it hitches a ride into the brain as aluminum fluoride which can bypass this barrier.
This aluminum compound found in the brains of all Alzheimer's patients.
5. Fluoride causes nervous system degeneration.
Once fluoride crosses the blood-brain barrier, it causes degeneration to specific parts of the brain — the hippocampus, the neocortex, and the cerebellum.
The hippocampus is considered the seat of memory and is critical for learning, emotional regulation, and shutting off the stress response.
The neocortex is considered the most evolved area of the brain where sensory perception, conscious thought, and language skills largely take place.
The cerebellum is responsible for coordination and balance.
The damage from fluoride doesn't stop at your brain — it continues on to your spinal cord and sciatic nerve.
6. Fluoridated water increases risk of lead ingestion.
If you are as old as I am you'll remember when paint, gasoline, and water pipes regularly contained lead.
Lead is another neurotoxin that posed a serious health threat which led to a series of bans.
Lead has been banned from paint since 1978, phased out of gasoline in the 1990s, and outlawed in the manufacture of water pipes since 1986.
But if you live in a house built before 1986 you may still have lead water pipes.
Even new brass or chrome-plated faucets contain some lead.
If you have fluoridated water coming through lead pipes and chrome faucets you have the "perfect neurotoxin storm" since fluoridated water leaches lead and greatly increases the amount in your water up to 9-fold more.
Young brains are most at risk but brains of all ages can suffer from lead exposure that can manifest as memory loss, mood disorders, lower IQ, and learning disabilities.
8. Fluoride linked to ADHD.

Rates of ADHD skyrocketed in the 1990s, about the same time that fluoridation of water supplies was also on the rise in the United States. (28) This may not be a coincidence since researchers have found a correlation between water fluoridation and ADHD.
States with the largest number of ADHD cases also have the greatest proportion of people drinking fluoridated water.
According to the Centers for Disease Control, over 67% of the US population receives fluoridated water but the numbers vary greatly by state.
If you live in Washington DC, the chances of fluoridated water coming out of your tap are 100%.
States with the lowest levels of fluoridated water are Montana at 32% and Hawaii at 10%.
9. Fluoride is found in antidepressants (and causes depression).
If you are one of the millions of people taking Prozac you may have noticed that the generic name for Prozac is fluoxetine.
It's not a coincidence that the name sounds a lot like fluoride.
Some of the most commonly prescribed drugs contain significant amounts of fluoride, including antidepressants and anti-anxiety drugs.
This is disturbing since fluoride can cause depression.
Besides Prozac, other antidepressants that contain fluoride include Paxil, Zoloft, and Lexapro. (31) If you currently take one of these medications you may want to discuss switching to a fluoride-free antidepressant or try some natural ways to relieve depression instead.
But do not stop taking any medication before talking to your health care professional.
Some our highly paid and highly educated senior health officers when they come to you and tell you fluoride protect teeth. They tell you fluoride is a natural product and it is harmless. They do not tell you that fluoride in nature is calcium fluoride (CaF_2) and the fluoride added to our drinking water is Hydrofluorosilicic acid (H_2SiF_6). There is a big difference between those two chemical compounds. Calcium fluoride available in nature and not as poisonous as hydrofluorosilicic acid. Just look how they use you to make their foreign bank account fatter.
Here is what Health Canada saying to us.
"Fluoride is a natural element that is found in soil, water (both fresh and salt) and in various foods. Fluorides are released into the environment by weathering processes and by volcanic activity. They may also be released by the production of phosphate fertilizers, by aluminum smelting and by chemical manufacturing. Most Canadians are exposed to fluorides on a daily basis, through the trace amounts that are found in almost all foods and through those that are added to some drinking water supplies to prevent tooth decay."
"Fluorides protect tooth enamel against the acids that cause tooth decay. The use of fluoride for the prevention of dental cavities is endorsed by over 90 national and international professional health organizations including Health Canada, Canadian Public Health Association, Canadian Dental Association, Canadian Medical Association, I thank you for your time. Please stop killing our children and bring those criminals to the justice.
Yours truly
Dr. Raymond Ray D.Sc.
[redacted]

Ministry of Health and Long-Term Care

Assistant Deputy Minister's Office

Population and Public Health Division
777 Bay Street, 19th Floor
Toronto ON M7A 1S5

Telephone: (416) 212-8119
Facsimile: (416) 212-2200

Ministère de la Santé et des Soins de longue durée

Bureau du sous-ministre adjoint

Division de la santé de la population et de la santé publique
777, rue Bay, 19e étage
Toronto ON M7A 1S5

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Ontario

March 23, 2018

HLTC2966MC-2017-1929

Mr. Frank Dale
Regional Chair and Chief Executive Officer
The Regional Municipality of Peel
10 Peel Centre Drive, Suite A
Brampton ON L6T 4B9

Dear Mr. Dale:

I am writing to you in response to correspondence received by the Ministry of Health and Long-Term Care advising of the Regional Municipality of Peel Council Resolution (number 2017-68) regarding regional drinking water fluoridation in Ontario.

The Ministry of Health and Long-Term Care ("the ministry") appreciates you bringing forward this resolution to reassure the public that the use of hydrofluorosilicic acid (HFSA) in water fluoridation treatments is safe.

Drinking water must meet Ontario's strict health-based standards for microbiological organisms and chemical substances which are prescribed under the *Safe Drinking Water Act* (SDWA). As a condition of a municipal licence under the SDWA, any chemical additives used by municipal drinking water treatment plants must meet all applicable standards set by the American Water Works Association (AWWA) and be tested and certified to National Sanitation Foundation/American National Standards Institute (NSF/ ANSI) Standard 60: Drinking Water Treatment Chemicals – Health Effects.

Public Health Ontario has reviewed NSF/ANSI 60 on behalf of the ministry. NSF/ANSI 60 establishes requirements to be protective of human health for products and their impurities that may be added directly during drinking water treatment, storage and distribution. This standard is reviewed and maintained annually by the NSF Joint Committee on Drinking Water Additives.

The NSF certifies three products for use in water fluoridation and the manner in which they may be used. They are: (i) hydrofluosilicic acid, (ii) sodium fluorosilicate, and (iii) sodium fluoride.

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The established safeguards noted above continue to be used to ensure the safety of fluoridated drinking water in Ontario. The ministry will also continue to monitor and review new research.

The ministry urges all municipalities to continue to protect their communities from avoidable health issues by maintaining fluoride in their drinking water, to promote the health of all residents.

Sincerely,

Roselle Martino
Assistant Deputy Minister
Population and Public Health Division

Office of the Chair

February 22, 2017

Resolution Number 2017-68

The Honourable Dr. Eric Hoskins
Minister of Health and Long-Term Care
10th Floor, Hepburn Block, 80 Grosvenor Street
Toronto, ON M7A 2C4

Dear Minister:

Subject: **Motion of the Community Water Fluoridation Committee (CWFC-1/2017) Regarding Regional Fluoridation**

I am writing to advise that Regional Council approved the following resolution at its meeting held on Thursday, February 9, 2017:

Resolution 2017-68:

Whereas the Minister of Health and Long Term Care is working to establish a health system in Ontario that is based on helping people stay healthy, delivering good care when people need it, and protecting the health system for future generations;

And whereas, the Ministry of Health and Long Term Care has changed its focus to work towards better health care for Ontarians, and stewardship has become its mission and mandate;

And whereas, this new stewardship role will mean that the Ministry will provide overall direction and leadership for the system, developing legislation, regulations, standards, policies and directives to support the health of Ontarians;

And whereas, on January 7, 2016 the Region of Peel received a letter from the Minister of Health and Long Term Care, Dr. Eric Hoskins, supporting the benefits of water fluoridation as an important measure to protect the health of Ontarians;

And whereas, the Province of Ontario is responsible for *The Safe Drinking Water Act*, the purposes of which include (i) recognizing that the people of Ontario are entitled to expect their drinking water be safe and (ii) providing for the protection of human health and the prevention of drinking water health hazards through the control and regulation of drinking water systems and drinking water testing;

And whereas, Municipal Councillors do not have the detailed familiarity to interpret data regarding the efficacy of Hydrofluorosilicic Acid [HFSA] in water

fluoridation treatments and are struggling with a range of conflicting reports and public concern on the matter of fluoridation;

Therefore be it resolved, that Regional of Peel Council request the Premier of Ontario, and the Minister of Health and Long Term Care, whose mandate it is to protect the health of Ontarians, (i) to undertake appropriate and comprehensive toxicity testing necessary to reassure the public that the use of HFSA in water fluoridation treatments is safe; and (ii) take legislative responsibility for the regulation and administration of HFSA in water fluoridation treatments across the province relieving local governments from what is a provincial responsibility;

And further, that copies of this resolution be circulated to MPPs, the Association of Municipalities of Ontario and municipalities across Ontario.

On behalf of Regional Council, I request that you give consideration to the above resolution.

Frank Dale
Regional Chair and Chief Executive Officer

FD:sm

c: Ontario MPP's
Pat Vanini, Executive Director, Association of Municipalities of Ontario
Ontario Municipalities
Nancy Polsinelli, Commissioner, Health Services, Region of Peel
Dr. Eileen de Villa, Medical Officer of Health, Region of Peel

From: Christine Massey [redacted]
Sent: April 2, 2018 1:43 PM
To: Sharma, Paul
Cc: O'Connor, Patrick; Sprovieri, John; pam douglas; newsroom@bramptonguardian.com; Vic Dhillon; Dbhat; Criscione, Peter; Belgrave, Roger; editor@caledoncitizen.com; ZZG-RegionalClerk; igheorghiu@rnao.ca; atsangsit@rnao.ca; cbintakies@rnao.ca; mtandoc@rnao.ca; snoronha@rnao.ca; tshelvey@rnao.ca; jenny.yuen@sunmedia.ca; Amanda.Ferguson@citynews.rogers.com; de Villa, Eileen; dr.david.williams@ontario.ca; laura.seeds@ontario.ca; Catherine.Fraser@ontario.ca; sarah.cox@ontario.ca; gillian.macdonald2@ontario.ca; Mikayla.Wicks@ontario.ca; Derrick.Araneda@ontario.ca; catharine.gapp@ontario.ca; Alyson.Rowe@ontario.ca; Dara.McLeod@ontario.ca; maria.babbage@ontario.ca; Holly.burke@ontario.ca; vivian.w.ng@ontario.ca; Saurabh.Popat@ontario.ca; olivia.nero@ontario.ca; ian.chesney@ontario.ca; joshua.McLarnon@ontario.ca; beth.mackinnon@ontario.ca; Mark.Tishman@ontario.ca; carley.lennox@ontario.ca; rachel.levy@ontario.ca; jelena.rakovac@ontario.ca; Katie.Heelis@ontario.ca; shae.greenfield@ontario.ca; Diana.Egbe@ontario.ca; info@wellfort.ca; Edesiri Udoh; Sanjukta Mohanta; Thompson, Allan; Downey, Johanna; Groves, Annette; Innis, Jennifer; Shaughnessy, Barb; Jeffrey, Linda Mayor; Gibson, Grant; Medeiros, Martin; Miles, Gael; Moore, Elaine; Palleschi, Michael; Crombie, Bonnie; Carlson, George; Fonseca, Chris; Iannicca, Nando; Kovac, John; Mahoney, Matt; McFadden, Sue; Parrish, Carolyn; Ras, Karen; Saito, Pat; Starr, Ron; Dale, Frank; Loh, Lawrence; Polsinelli, Nancy; Szwarc, David; Smith, Janette; Hennings, Jeff; Jim Nardi; Burkiewicz, Justyna; ZZG-WaterQualityInquiries; Hau, Monica; Ward, Megan; Bingham, Kate; Hopkins, Jessica; Eric MPP; premier@ontario.ca; ZZG-CDIP-Oral Health; ZZG-PeelHealth; Farr, Andrew; Helena MPP; +Andrea+Horwath+; 21div.communitystation@peelpolice.ca; 22div.communitystation@peelpolice.ca
Subject: Re: question re: fluoride intake for children

Dear Mr. Sharma, Director of Chronic Disease and Injury Prevention, Region of Peel,

Just a friend reminder of my question sent to you on March 20th, below.

In your (or, the Region's) opinion, is it advisable, or acceptable, for young children to swallow 0.25+ milligrams of fluoride each and every day, year after year?

Health Canada and the FDA warn parents to call poison control or seek medical attention right away if their child swallows more than 0.25 mg (the typical amount in a pea-sized bit of fluoridated toothpaste, according to the CDC) when brushing. Dentists insist that children be taught to spit out the pea-sized bit of toothpaste and not swallow it. But every 385 ml of Peel's fluoridated tap water (used plain and to mix juices and powdered drinks, in cooking rice, pasta, etc.) contains 0.25 mg.

Under exactly which conditions is it advisable, or acceptable, for them to swallow 0.25 mg or more fluoride, and when should parents/caregivers seek medical attention?

If you will not advise on this, to whom should I address my query? The Regional Staff I have contacted in recent months do not answer any of my emails, and Council has referred all fluoridation-related queries to the the Community Water Fluoridation Committee but the Committee was suspended over a year ago.

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Best regards,
Christine Massey
Fluoride Free Peel
http://www.fluoridefreepeel.ca/same-dose-of-fluoride/

On Tue, Mar 20, 2018 at 4:39 PM, Christine Massey [redacted] wrote:
Dear Mr. Sharma, BSc, RDH, MSc, Director, Chronic Disease and Injury Prevention, Region of Peel; former Manager, Oral Health Section, Chronic Disease and Injury Prevention Division, Region of Peel; Adjunct Professor, Faculty of Dentistry, University of Toronto; current President of Ontario Association of Public Health Dentistry, Affiliate Representative, Association of Local Public Health Associations,

Should children up to age 5 swallow or spit out 0.25 mg of fluoride throughout each day, day after day, year after year?

I cannot find a pro-fluoridation dentist or dental association willing to answer this question, even though the public clearly needs an answer.

Even Health n' Smiles dentist Sanjukta Mohanta, who delegated so passionately to Council last year, will not respond to my queries. I hope you will provide a response.

Best regards,

Christine Massey
Fluoride Free Peel
http://www.fluoridefreepeel.ca/same-dose-of-fluoride/

From: Christine Massey [redacted]
Sent: April 4, 2018 5:21 PM
To: Sharma, Paul; O'Connor, Patrick; Sprovieri, John; pam douglas; newsroom@bramptonguardian.com; Vic Dhillon; Dbhat; Criscione, Peter; Belgrave, Roger; editor@caledoncitizen.com; ZZG-RegionalClerk; igheorghiu@rnao.ca; atsangsit@rnao.ca; cbintakies@rnao.ca; mtandoc@rnao.ca; snoronha@rnao.ca; tshelvey@rnao.ca; jenny.yuen@sunmedia.ca; Amanda.Ferguson@citynews.rogers.com; de Villa, Eileen; dr.david.williams@ontario.ca; laura.seeds@ontario.ca; Catherine.Fraser@ontario.ca; sarah.cox@ontario.ca; gillian.macdonald2@ontario.ca; Mikayla.Wicks@ontario.ca; Derrick.Araneda@ontario.ca; catharine.gapp@ontario.ca; Alyson.Rowe@ontario.ca; Dara.McLeod@ontario.ca; maria.babbage@ontario.ca; Holly.burke@ontario.ca; vivian.w.ng@ontario.ca; Saurabh.Popat@ontario.ca; olivia.nero@ontario.ca; ian.chesney@ontario.ca; joshua.McLarnon@ontario.ca; beth.mackinnon@ontario.ca; Mark.Tishman@ontario.ca; carley.lennox@ontario.ca; rachel.levy@ontario.ca; jelena.rakovac@ontario.ca; Katie.Heelis@ontario.ca; shae.greenfield@ontario.ca; Diana.Eqbe@ontario.ca; info@wellfort.ca; Edesiri Udoh; Sanjukta Mohanta; Thompson, Allan; Downey, Johanna; Groves, Annette; Innis, Jennifer; Shaughnessy, Barb; Jeffrey, Linda Mayor; Gibson, Grant; Medeiros, Martin; Miles, Gael; Moore, Elaine; Palleschi, Michael; Crombie, Bonnie; Carlson, George; Fonseca, Chris; Iannicca, Nando; Kovac, John; Mahoney, Matt; McFadden, Sue; Parrish, Carolyn; Ras, Karen; Saito, Pat; Starr, Ron; Dale, Frank; Loh, Lawrence; Polsinelli, Nancy; Szwarc, David; Smith, Janette; Hennings, Jeff; Jim Nardi; Burkiewicz, Justyna; ZZG-WaterQualityInquiries; Hau, Monica; Ward, Megan; Bingham, Kate; Hopkins, Jessica; premier@ontario.ca; ZZG-CDIP-Oral Health; ZZG-PeelHealth; Farr, Andrew; Helena MPP; +Andrea+Horwath+; 21div.communitystation@peelpolice.ca; 22div.communitystation@peelpolice.ca; Bill MPP CO; Bob MPP CO; Brad MPP; Charles MPP; Dave MPP; dorazietti.mpp@liberal.ola.org; David MPP; Deborah MPP; Dipika MPP CO; Eric MPP; gmurray.mpp@liberal.ola.org; James MPP; Jeff MPP CO; Kevin MPP CO; Liz MPP; mmeilleur.mpp@liberal.ola.org; Mario MPP; Michael MPP; Michael MPP CO; Michael MPP; Mitzie-MPP-CO; Reza MPP; Steven MPP CO; Ted MPP; Tracy MPP CO; Yasir MPP CO; Amrit MPP CO; Ann MPP CO; Arthur MPP CO; Bas Balkissoon; bill.walker@pc.ola.org; BobDelaneyMPP .; cfife-qp@ndp.on.ca; dinovoc-qp@ndp.on.ca; cballard.mpp.co@liberal.ola.org; cforster-qp@ndp.on.ca; Cristina MPP CO; Daiene MPP CO; Eleanor MPP CO; ernie.hardeman@pc.ola.org; fgelinas-qp@ndp.on.ca; gila.martowco@pc.ola.org; gbisson@ndp.on.ca; Glenn MPP CO; Grant (Rockland); Granville MPP CO; Han MPP CO; Harinder MPP CO; Harinder MPP; Indira MPP CO; jack.maclarenco@pc.ola.org; jsingh-qp@ndp.on.ca; Jeff Yurek; JFrench-QP@ndp.on.ca; jim.mcdonellco@pc.ola.org; Jim WilsonMPP; JCimino-QP@ndp.on.ca; Joe MPP; John Fraser, MPP (Constituency Office); jvanthof-qp@ndp.on.ca; john.yakabuski@pc.ola.org; julia.munro@pc.ola.org; Kathryn MPP CO; Laura MPP; Laurie Scott; LGretzky-QP@ndp.on.ca; lisa.thompson@pc.ola.org; Lisa MacLeod; Lorenzo MPP; Lou MPP CO; Marie-France MPP CO; michael.harris@pc.ola.org; mmantha-qp@ndp.on.ca; Mike MPP; mtaylor-qp@ndp.on.ca; Monte MPP; Monte McNaughton, MPP; norm.miller@pc.ola.org; patrick.brown@pc.ola.org; pmiller-qp@ndp.on.ca; Psattler-qp@ndp.on.ca; phatfield-co@ndp.on.ca; tabunsp-qp@ndp.on.ca; Peter MPP CO; randy.hillierco@pc.ola.org; randy.pettapiececo@pc.ola.org; rick.nicholllsco@pc.ola.org; bob.baileyco@pc.ola.org; scmpp@ndp.on.ca; Shafiq MPP; Soo MPP CO; Sophie MPP CO; steve.clark@pc.ola.org; sylvia.jones@pc.ola.org; tnatyshak-qp@ndp.on.ca; ted.arnott@pc.ola.org; tarmstrong-qp@ndp.on.ca; tim.hudakco@pc.ola.org; toby.barrettco@pc.ola.org; Todd Smith MPP; Vic+Fedeli+; wgates-qp@ndp.on.ca; Yvan MPP CO; Kathleen MPP; loretta@alphaweb.org; Gordon Fleming; susan@alphaweb.org; karen@alphaweb.org; dave.cook@mississauga.ca; alane@ocwa.com; ocwa@ocwa.com; Aimee Hennessy; nbaker@ocwa.com; tsmider@ocwa.com; jmuller@ocwa.com; Canadian

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Waterman; MPontone@ocwa.com; sbudden@ocwa.com; anthony.hylton@ontario.ca; vania.cecchin@ontario.ca; robin.rix@ontario.ca; Elizabeth.Dowdeswell@ontario.ca
Subject: News: Fluoride Exposure in Utero ALSO Linked to Lower IQ in Children Aged 1-3

Dear Peel Council, Chair, Commissioners, CAO, Medical Officers, Director of Chronic Disease and Injury Prevention, General Manager of Water & Wastewater, Water-related Staff, Ontario Premier, Lieutenant Governor, Ontario Health Minister, OCWA Staff, ALPHA Board, ON MPPs,

March 2018, international team of leading experts funded by U.S. government:

Conclusion: Our findings add to our team's recently published report on prenatal fluoride and cognition at ages 4 and 6–12 years by suggesting that higher in utero exposure to F has an adverse impact on offspring cognitive development that can be detected earlier, in the first three years of life.

Abstract: http://oem.bmj.com/content/75/Suppl_1/A10.1

Health Canada:

"*The action of fluoride is topical. No fluoride should be given before the teeth have erupted. Supplemental fluoride should be given only after 6 months of age*"
https://www.canada.ca/en/health-canada/services/first-nations-inuit-health/health-care-services/nursing/clinical-practice-guidelines-nurses-primary-care/pediatric-adolescent-care/chapter-7-nutrition.html

2012, CDC director:

zero data suggesting benefits for infants <6 months from water fluoridation (letter attached; NB: bottle-fed infants in fluoridated areas receive far more than .01 milligrams of fluoride per day)

All risk, no benefit for the most vulnerable.

Best regards,

Christine Massey
Fluoride Free Peel
http://www.FluorideFreePeel.ca/Poisoning-Babies-with-Fluoride/

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Centers for Disease Control
and Prevention (CDC)
Atlanta GA 30333

May 15, 2012

The Honorable Barbara Boxer
United States Senator
70 Washington Street, Suite 203
Oakland, California 94607

Attn: Kathleen Brennan

Dear Senator Boxer:

Thank you for your inquiry on behalf of your constituent, Mr. Doug Cragoe, regarding potential benefits and adverse health effects related to fluoride intake in infants 0 to 6 months of age.

In January 2011, the Department of Health and Human Services (HHS) and the United States Environmental Protection Agency (EPA) announced important actions to ensure that recommendations and standards on fluoride in drinking water continue to provide the health benefits of water fluoridation while lessening the chance that children are taking in too much fluoride. Both actions are based on recent HHS and EPA scientific assessments and a shared understanding of the latest science by HHS and EPA investigators. These actions do not change the longstanding consensus among panels of experts from different health and scientific fields that have provided strong evidence that water fluoridation is safe and effective.

Based on the most up-to-date available evidence, HHS has proposed to modify the recommended level of fluoride in drinking water. In a Federal Register Notice issued January 13, 2011, HHS sought public comments on a proposal that community water systems adjust the amount of fluoride to 0.7 mg/L. This new proposed guidance, which is advisory rather than regulatory, would update and replace the current recommended range of 0.7 to 1.2 mg/L. The proposed recommendation is intended to provide the best balance of protection from dental caries while limiting the risk of dental fluorosis.

The public comment period for the HHS announcement ended on April 15, 2011. HHS is currently reviewing the proposed guidance in light of the public comments and will soon submit the guidance document to an external scientific review panel. In the coming months, HHS expects to incorporate the external review panel's input and issue final non-regulatory guidance.

At the same time, EPA announced that it would initiate a review of the maximum amount of naturally occurring fluoride allowed in drinking water, a level set to prevent adverse health effects. Currently, the maximum amount of fluoride allowed in public drinking water is 4 mg/L.

For more information on this review, please visit the EPA website at http://water.epa.gov/action/advisories/drinking/fluoride_index.cfm.

EPA also has a secondary standard for fluoride in public drinking water of 2.0 mg/L to reduce the chance of dental fluorosis in its moderate and severe forms. A secondary standard is a non-enforceable guideline. Although water systems are not required to comply with secondary standards, for fluoride, EPA does require that water systems notify customers if the fluoride concentrations exceed the secondary standard. In areas where community water systems contain more than 2 ppm fluoride, but less than 4 ppm fluoride, EPA requires that each household be notified annually of the desirability of using an alternative water source for children less than 9 years old. Parents of children with developing teeth are strongly encouraged to use an alternative source of water if their water system contains 2 ppm fluoride or greater.

We have enclosed information addressing the specific questions posed by Mr. Cragoe. Thank you again for your interest in this matter. I hope this information is helpful to you and your constituent.

Sincerely,

Thomas R. Frieden, M.D., M.P.H.
Director, CDC

Enclosure

Answers to Mr. Cragoe's Specific Questions

1. *Since .01 mg/d is the optimal amount of total dietary fluoride intake for infants 0 to 6 months of age, would an infant with a much larger daily fluoride intake be expected to have additional protection against tooth decay?*
2. *Would infants 0 to 6 months of age with a much larger daily fluoride intake be expected to have less tooth decay than infants who got the optimal amount of fluoride intake?*
3. *For the 0 to 6 month age group only, if additional fluoride intake above the optimal amount provides additional protection against tooth decay, how much less tooth decay would be expected for these infants?*

The Institute of Medicine (IOM) has concluded that fluoride intake from human milk (0.01 mg/d) is adequate for infants aged 0–6 months because risk of tooth decay does not appear to be significantly increased.[1] We are unaware of data that directly answers your questions about the additional protection from tooth decay that could result from greater daily fluoride intake by infants, 0–6 months of age.

4. *If infants 0 to 6 months of age exceed the tolerable upper intake level of .7 mg/day, what are the adverse health effects that might be expected for these infants?*

The IOM established the tolerable upper limit to reduce risk of moderate and severe dental fluorosis, which generally present with aesthetically objectionable changes in tooth color when the permanent teeth erupt beginning at age six years. Severe forms include pitting of the tooth surface. The IOM also noted that the developing enamel of the permanent teeth in children older than 6 months of age—for example, in the second and third year of life—is probably most susceptible to fluorosis. Among adolescents 12–15 years in the United States, the prevalence of moderate and severe dental fluorosis in the permanent teeth, combined, is 3.6 percent. The prevalence of the severe form alone could not be estimated because there were so few cases www.cdc.gov/nchs/data/databriefs/db53.htm. The severe form is rare in the United States, especially in communities where the level of fluoride in water is less than 2 mg per liter.

[1] Institute of Medicine, Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. DRI, dietary reference intakes: for calcium, phosphorus, magnesium, vitamin D, and fluoride. Washington, DC: National Academy Press, 1997.

From: Karen Ras [mailto:Karen.Ras@mississauga.ca]
Sent: April 5, 2018 1:04 PM
To: Lockyer, Kathryn
Cc: Ras, Karen
Subject: Fluoride Committee

Good afternoon Kathryn,

At this time, please accept my resignation from the Fluoride Committee.

Given that Councillor Kovac has stepped forward, quorum should not be an issue.

Kind regards

Karen Ras

Councillor, Ward 2

300 City Centre Drive

Mississauga, ON L5B 3C1

905-896-5200

www.karenras.ca

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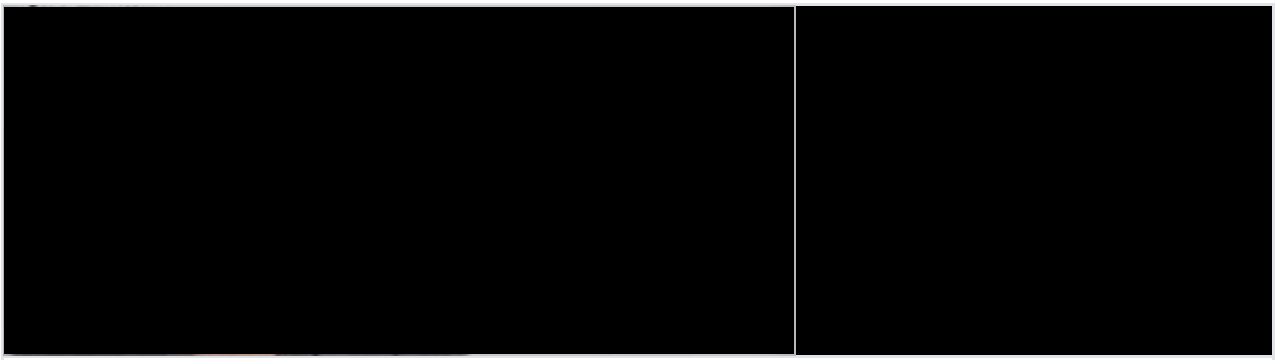
RECOMMENDED
DIRECTION REQUIRED _____
RECEIPT RECOMMENDED ✓_____

From: Sprovieri, John Councillor [mailto:John.Sprovieri@brampton.ca]
Sent: April 6, 2018 10:17 AM
To: Lockyer, Kathryn; Palleschi, Michael; Kovac, John; Dale, Frank; 'annette.groves@peelregion.ca'; Downey, Johanna
Cc: Gibson, Grant; Medeiros, Martin; Miles, Gael; elaine.moore@brampton.ca; john.sprovieri@brampton.ca; Carlson, George; Fonseca, Chris; Iannicca, Nando; Mahoney, Matt; McFadden, Sue; Parrish, Carolyn; Ras, Karen; Saito, Pat; Starr, Ron; Innis, Jennifer; Shaughnessy, Barb; Thompson, Allan; Hopkins, Jessica
Subject: FW:

Hi Kathryn,
Can you place this video from Simon Fraser University on the next Community Water Fluoridation Committee Meeting.
Also, can you make all the received correspondence that was referred to the Fluoridation committee to members of the committee before next meeting.
John.

The Impact of Toxins on the Developing Brain: Video 1



The Impact of Toxins on the Developing Brain: Video 1

A video from the 2015 review by Bruce P. Lanphear, "The Impact of Toxins on the Developing Brain," from the Annu...

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RECEIPT RECOMMENDED ✓_____

From: Annette Groves [mailto:Annette.Groves@caledon.ca]
Sent: April 11, 2018 7:08 AM
To: West, Helena
Subject: Re: Proposed Date for Community Water Fluoridation Committee (CWFC) Meeting

Hi Helena

I would like it effective immediately please

Annette Groves
Regional Councillor
Ward 5, Bolton
Cell: 416-434-3256

On Apr 10, 2018, at 3:25 PM, West, Helena <helena.west@peelregion.ca> wrote:

Hi Councillor Groves. When would you like your resignation to be effective? We have a meeting scheduled for April 19, 2018 at 9:00 AM and we have not confirmed a meeting for May 31st. Is it your intent to resign from the Committee effective April 19th.

Thank you

Helena West
Legislative Specialist
Clerk's Division
905-791-7800 ext. 4697
helena.west@peelregion.ca

<image001.gif>

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RECOMMENDED
DIRECTION REQUIRED _____
RECEIPT RECOMMENDED ✓_____

From: Annette Groves [mailto:Annette.Groves@caledon.ca]
Sent: April 10, 2018 2:59 PM
To: West, Helena
Subject: Re: Proposed Date for Community Water Fluoridation Committee (CWFC) Meeting

Hi Helena

I'm available on May 31st. I would like to remove my name from the Committee please.

Thanks very much

Annette Groves
Regional Councillor
Ward 5, Bolton
Cell: 416-434-3256