THE REGIONAL MUNICIPALITY OF PEEL

COMMUNITY WATER FLUORIDATION COMMITTEE

AGENDA **CWFC - 3/2018**

DATE: **Thursday, September 27, 2018**

TIME: **1:30 PM – 3:00 PM**

LOCATION: **Peel Conference Centre, 1st Floor**
Regional Administrative Headquarters
10 Peel Centre Drive, Suite B
Brampton, Ontario

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

Chaired by Councillor J. Downey or Vice-Chair Councillor J. Sprovieri

1. DECLARATIONS OF CONFLICTS OF INTEREST

2. APPROVAL OF AGENDA

3. DELEGATIONS

3.1. **Liesa Cianchino, Chair, Concerned Residents of Peel to End Fluoridation,** Reading an Affidavit Prepared by John Remington-Graham, Counselor at Law, Regarding Judicial Findings in Three Landmark Cases in Pennsylvania, Illinois and Texas that Artificial Water Fluoridation Causes Cancer and Other Ailments in Man

4. REPORTS

4.1. Community Water Fluoridation - Using Evidence to Inform Public Health Practice (For information)
Presentation by Jessica Hopkins, Medical Officer of Health

4.2. Community Water Fluoridation - Staff Response to Committee Selected Studies (For information)

4.3. Information Regarding Toxicology Reviews (Oral)
Presentation by Jessica Hopkins, Medical Officer of Health

5. COMMUNICATIONS

5.1. **John Sprovieri, Regional Councillor, City of Brampton**, E-mail dated August 22, 2018, Forwarding on an E-mail from Gilles Parent Regarding Canadian Drinking Water Quality: Guideline Technical Document – Fluoride and Toxicological Studies

5.2. **John Sprovieri, Regional Councillor, City of Brampton**, E-mail dated August 22, 2018, Providing a Copy of a Report from the U.S. Environmental Protection Agency, Regarding Toxicological Review of Chlorine Dioxide and Chlorite

5.3. **John Sprovieri, Regional Councillor, City of Brampton**, E-mail dated August 22, 2018, Providing a Copy of the Lancet Neurology Review, Volume 13, March 2014, Regarding Neurobehaviour Effects of Developmental Toxicity

5.4. **John Sprovieri, Regional Councillor, City of Brampton**, E-mail dated August 22, 2018, Providing a Copy of an Article from Environmental Health Perspectives, 2017, Regarding Prenatal Fluoride Exposure and Cognitive Outcomes in Children 4 and 6-12 Years of Age in Mexico

5.5. **Rupinder Kaur on behalf of John Sprovieri, Regional Councillor, City of Brampton**, E-mail dated August 28, 2018, Providing Various Fluoride Attachments

6. IN CAMERA MATTERS

7. OTHER BUSINESS

8. NEXT MEETING

9. ADJOURNMENT

Region of Peel
working with you

Request for Delegation

FOR OFFICE USE ONLY

MEETING DATE YYYY/MM/DD	MEETING NAME
2018/09/27	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
2018/09/19

NAME OF INDIVIDUAL(S)

Liesa Cianchino on behalf of Mr. John Remington Graham

POSITION(S)/TITLE(S)

Chair

NAME OF ORGANIZATION(S)

Concerned Residents of Peel to End Artificial Water Fluoridation

E-MAIL [redacted]

TELEPHONE NUMBER [redacted]

EXTENSION

REASON(S) FOR DELEGATION REQUEST (SUBJECT MATTER TO BE DISCUSSED)
Liesa Cianchino on behalf of John Remington-Graham, Counselor at Law, Regarding Judicial Findings in Three Landmark Cases in Pennsylvania, Illinois and Texas that Artificial Water Fluoridation Causes Cancer and Other Ailments in Man.

Mr. Graham requested that I read a prepared Affidavit in lieu of him presenting in person at the upcoming CWFC meeting on September 27th, 2018.

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.

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.

Please complete and return this form via email to council@peelregion.ca

JOHN REMINGTON GRAHAM

COUNSELOR AT LAW

Important Documents for the Public Records

Community Water Fluoridation Committee Members & Regional Staff

Judicial findings in three landmark cases in Pennsylvania, Illinois and Texas that Artificial Water Fluoridation causes cancer and other ailments in man.

CWFC Meeting Thursday, July 5th, 2018
Peel Region, Ontario Canada

Submitted by Liesa Cianchino, Chair Concerned Residents of Peel to End Artificial Water Fluoridation on behalf of John Remington Graham

SUMMARY OF DOCUMENTS

SHORT CURRICULUM VITAE JOHN REMINGTON GRAHAM

~

LETTER TO DR. DAVID KENNEDY DESCRIBING THE NATURE OF THE EVIDENCE

IN THE PENNSYLVANIA, ILLINOIS AND TEXAS TRIALS

REGARDING ARTIFICIAL WATER FLUORIDATION.

~

HIGHLIGHTS IN NORTH AMERICAN LITIGATION
DURING THE TWENTIETH CENTURY ON
ARTIFICIAL FLUORIDATION OF PUBLIC WATER SUPPLIES

JOHN REMINGTON GRAHAM* AND PIERRE-JEAN MORIN**

~

STATEMENT OF DR. J. WILLIAM HIRZY

NATIONAL TREASURY EMPLOYEES UNION CHAPTER 280 BEFORE THE

SUBCOMMITTEE ON WILDLIFE, FISHERIES AND DRINKING WATER

UNITED STATES SENATE

JUNE 29, 2000

JOHN REMINGTON GRAHAM

COUNSELOR AT LAW

B. A. in philosophy 1963, LL. B. 1966, University of Minnesota; admitted to the Bar of the Minnesota Supreme Court, 1967; admitted to the Bar of the United States Supreme Court, 1971; Public Defender, United States District Court for Minnesota, 1969-1973; Founding professor, teaching common law pleading, judicial writs and remedies, American constitutional law, admiralty, copyrights, legal writing, conflict of laws, legal history, and modern civil procedure, and serving as chairman of the admissions committee, Hamline University School of Law, 1972-1980; Advisor on questions concerning constitutional law and equitable remedies to the Minnesota State Board of Bar Examiners, 1974-1978; Special Counsel for the City of Brainerd, 1974-1980; Crow Wing County Public Defender, 1981-1984; Crow Wing County Attorney, 1991-1995; Occasional lecturer in comparative British, American, and Canadian constitutional law at Laval University, 1989-1991, 1997, and 2000, and in public international law, 2003; and Advisor on British constitutional law and history to the court-appointed Amicus Curiae for Quebec before the Supreme Court of Canada in *Reference on certain Questions concerning the Secession of Quebec from Canada*, [1998] 2 S. C. R. 217.

JOHN REMINGTON GRAHAM

COUNSELOR AT LAW

180 Haut de la Paroisse
St-Agapit (LOTB)
Quebec G0S 1Z0 Canada
TEL-FAX 418-888-5049
jrgraham@novicomfusion.com
January 14, 2015

Dr. David Kennedy
1068 Alexandria Drive
San Diego, California 92107-4115 U. S. A.

Dear Dr. Kennedy, --

You have recently requested that I restate the substance of the evidence presented for the plaintiffs in historic trials in Pennsylvania, Illinois, and Texas in 1978-1982, leading to judicial findings in all three cases, based on at least a fair preponderance of the evidence, that water fluoridation causes cancer and other ailments in man. The underlying forensic evidence, political and legal history, court trials, and the judicial findings have been written up by me and associates in two published works: J. R. Graham and Pierre Morin, *Highlights in North American Litigation During the Twentieth Century on Artificial Fluoridation of Public Water Supplies*, 14 Journal of Land Use and Environmental Law 195-248 (Florida State University, 1999), which is internet accessible, and the chapter on forensic medicine in Pierre Morin, J. R. Graham, and Gilles Parent, *Fluoridation: Autopsy of a Scientific Error*, Éditions Berger, Austin, Qc., 2010, which translates into English and updates an earlier edition of the same work in French, published in 2005.

The key court papers, including transcripts, pleadings, motions, summations of evidence, exhibits, recorded data, judicial findings, and court orders, opinions, and decrees, together with other legal items, and related medico-scientific material in these three cases, and in related litigation, have been archived at the Crow Wing County Historical Society in Brainerd, Minnesota, and by the Geosciences Department at the University of Massachusetts Amherst, and I have much of this material in my own professional records.

It is noteworthy that the union of scientists at the national headquarters of the United States Environmental Protection Agency reviewed the evidence presented during the trials in Pennsylvania, Illinois, and Texas, and pertinent evidence later published. During the review process, I was contacted by the epidemiology section at the national headquarters of the USEPA, because, as a specialist in forensic science and medicine, I appeared for the plaintiffs, conducted direct and cross-examination of all expert witnesses, and wrote summations of evidence in all three cases. Upon my experience and background, I sent a detailed report of the forensic evidence to the epidemiology section at the national headquarters of USEPA. Copies of this report, including appendices, are in the archives in Minnesota and Massachusetts, and in my professional records. The union of scientists at the national headquarters of the USEPA (i. e., the National Treasury

Employees Union, Chapter 280) concluded that the judicial findings were scientifically warranted and correct, as is stated on June 29, 2000, in an internet-accessible report by Dr. J. W. Hirzy, executive vice president of the union, to a subcommittee of the United States Senate.

The union maintains a website which includes several additional reports in more recent years including material from affiliate unions representing professional staff in USEPA offices across the country, and this material is confirmatory of, and adjunctive to the report of Dr. Hirzy before the United States Senate on June 29, 2000.

My purpose here is to describe for you the evidence presented in the court trials in Pennsylvania, Illinois, and Texas, leading to judicial findings that water fluoridation causes cancer and other ailments in man. It is striking that three veteran trial judges in three different States each heard substantially the same forensic evidence, that each acted independently of the others, and that each reached the same basic conclusion. Each trial had unique features, characterized by differences in civil practice and procedure, not to mention somewhat different political cross-currents, but there was a large overlapping of substantive exhibits and testimony in all three cases. While the trial of each case was unavoidably complex, the main evidence in all three cases followed the same basic pattern:

Our initial evidence in court consisted of expert testimony on large laboratory studies done by Dr. Alfred Taylor, a biochemist at the University of Texas, and by him published in peer-reviewed journals in 1954 (about 600 mice, which is huge by contemporary standards, and important because mice, like man, are mammals) and 1963 (about 900 mice) showing unmistakably that fluoride in drinking water (introduced as NaF, thereby resembling fluoride as artificially introduced in public water supplies) at various concentrations, including 1.0 part per million (the usual target level in water fluoridation), induces cancer-related reactions in laboratory mice. These studies have been directly or indirectly confirmed many times in peer-reviewed articles which have been published in good scientific journals, and which show that fluoride is a carcinogen, a mutagen, and an enzyme inhibiter. We showed that the United States Public Health Service and the American Dental Association had concealed the work of Dr. Taylor, by claiming publicly, contrary to known facts, that Dr. Taylor did not do necessary reruns, that his work was not peer-reviewed, that he never published his work, and that he never observed or reported positive results. This evidence was introductory, but it was impossible for the judges not to notice that pertinent laboratory studies were concealed by promoters of water fluoridation. **The laboratory studies were reinforced by medical evidence to the effect that free fluoride ions in drinking water can be transported by blood to and absorbed in all parts of the human body including soft tissues, are highly reactive, and can cause cancer in all parts of the human body**.

Having laid this foundation of laboratory data and general medical knowledge, our main evidence in all three cases was a huge epidemiological survey conceived and executed by a number of workers under the direction of Dr. Dean Burk, one of the most famous and decorated cancer research scientists in the world during the 20th century. His career at the National Cancer Institute of the United States spanned 35 years. This epidemiological evidence is especially important, because it translates general concern into actual experience of human beings in their natural environment. The survey compared cancer death rates in two large groups of American central cities, both spread out in all parts of the United States (an aggregate population of about 18 million in 1960), including the same size category and density of urban populations in both groups, from 1940 through 1950 during which both groups did not introduce water fluoridation, and

then after 1950 during which ten cities introduced and maintained water fluoridation in 1952-1968 (represented by available data for 1953-1968), and the other ten did not introduce water fluoridation in 1952-1968 (represented by available data for 1953-1968). Before 1950, the cancer death rates remained about the same in both groups for all years observed. After 1950, the cancer death rates the experimental cities introducing water fluoridation in 1952-1968 grew much more rapidly than for the control cities which did not introduce water fluoridation in 1952-1968. **The association shown between water fluoridation and human cancer was slightly more than 300 excess cancer deaths every year per million persons drinking fluoridated water after 15-20 years of exposure.** The 1940-1950 base line served as a control for all known and unknown variables, including socio-economic, environmental, nutritional, and demographic factors. This association between water fluoridation and human cancer works out to about 30,000 excess cancer deaths every year for about 100 million drinking fluoridated water at the time the three cases were tried. At the moment, substantially more Americans are drinking fluoridated water, so the annual casualty is substantially more now. The proper interpretation of the combined impact of laboratory, medical, and epidemiological evidence presented on our side of the case follows basic rules of inductive logic stated by William of Ockham, Sir Francis Bacon, and Sir Isaac Newton.

In these trials, the government of the United States maintained that the data gathered and organized under the direction of Dr. Burk should be adjusted for age, race, and sex. Among our twenty cities, the factors of sex and race proved, upon close examination, not to be important, but age certainly was and is important because cancer has always been an age-prone disease, and there were certain interesting age-related demographic changes within the populations studied between 1940 and 1970. Although we believed that the 1940-1950 base line was a sufficient control for age and all other variables, we agreed that no harm would be done by appropriate demographic adjustments, and that these adjustments might be useful as a precaution. Thus, **in all three cases, the primary point in controversy was not whether, but how and why demographic adjustments should be done**. Statisticians engaged by the government of the United States claimed that, using a textbook procedure in modern applied epidemiology (the indirect method, weighted averages, a national standard, and forty age-race-sex categories), adjusted cancer death rates in 1950-1970 actually grew faster in the control cities that did not introduce water fluoridation, than in the experimental cities which did, -- so they claimed at any rate. Our witnesses then came forth with several alternative age-race-sex adjustments, but they conceded for the sake of discussion that the textbook procedure used by the government justified serious attention. **We proceeded to show, in each of the three trials, that the government workers had left out all or nearly all available and pertinent data in their adjustment, but that, when omitted data are included by standard statistical methods, there remains an enormous association between water fluoridation and human cancer,** -- in light of what is now known, about 200 excess cancer deaths every year per million persons drinking fluoridated water after 15-20 years of exposure, which still translates into a stupefying increase in cancer mortality in the United States, year after year.

In the wake of these court trials, an eminent researcher at an international meeting in 1986 offered plausible evidence to support his contention that changes in population size might explain the huge association between water fluoridation and human cancer displayed by the epidemiological survey carried out under the direction of Dr. Burk. Because of our great respect for this scientist, we reviewed our data once again, and then adjusted for changes in population size among our twenty cities. We discovered that changes in population size are an approximate inverse index of population aging, because a declining population includes fewer people of child-bearing age, and a

population growing larger has more people of child-bearing age. And we discovered, in any event, that a proper adjustment of changes in population size leaves an enormous association between water fluoridation and human cancer, -- an association slightly larger than the association which remains after a correctly executed adjustment for age, or what amounts to the same thing, for age, race, and sex. Our expanded and revised adjustments for age, race, and sex and for changes in population size, drawn from census data and vital statistics of the United States, were published for the record in 1988, with the participation and approval of Dr. Burk, in the proceedings of the Pennsylvania Academy of Science.

Since the cases in Pennsylvania, Illinois, and Texas were tried, new evidence has been generated, including laboratory work showing that there is a statistically significant, dose-dependent trend in fluoride-induced bone cancer in male rats, and this laboratory work has been borne out in several epidemiological studies which show an association between water fluoridation and bone cancer in human males. These studies are important, because they are confirmatory of the laboratory work pioneered by Dr. Taylor and the epidemiological work of Dr. Burk and his associates, with respect to a particular kind of cancer, and include examination of specific cases in clinical setting.

Particularly disturbing to the union of scientists at the national headquarters of the USEPA is the recent emergence of laboratory studies which show that fluoride exposure induces neurological injury in rats, and epidemiological evidence suggesting that fluoride in water may reduce IQ in children. A new report published by the National Institute of Environmental Health Sciences in 2012 concludes, “Our results support the possibility of adverse effects of fluoride exposures on children’s neurodevelopment.” If this suggestion holds up to closer scrutiny in due course, the ramifications for water fluoridation as a disaster in public health administration are almost unthinkable. Yet, if we dump an industrial waste product in public water supplies, and the main ingredient has been identified as a carcinogen, mutagen, and enzyme inhibiter, we should not be surprised to see, as is now sketched out as a concrete possibility from information now available, that the same product is not only associated with large increases in cancer mortality as already established in judicial proceedings, but maybe also lower intelligence in man. With this unhappy note, I remain

Respectfully yours,

Courtesy copies to the Crow Wing County Historical Society, the University of Massachusetts Amherst c/o Professor Michael Dolan, and Dr. J. W. Hirzy

HIGHLIGHTS IN NORTH AMERICAN LITIGATION DURING THE TWENTIETH CENTURY ON ARTIFICIAL FLUORIDATION OF PUBLIC WATER SUPPLIES

JOHN REMINGTON GRAHAM* AND PIERRE-JEAN MORIN**

Table of Contents

I. INTRODUCTION***

Fluoride is an ubiquitous substance in our environment. It is naturally present in public water supplies, bound with calcium, iron, magnesium, or other minerals, usually at a level of around 0.2-0.4 ppm. Except incidentally, this article will not address the natural

---

* B.A., LL.B., of the Minnesota Bar. Federal Public Defender, 1969-1973; Co-Founder, Instructor, Assistant Professor, Associate Professor, Lecturer, Hamline University School of Law, 1972-1980; Special Counsel for the City of Brainerd, 1974-1980; Crow Wing County Public Defender, 1981-1984; Crow Wing County Attorney, 1991-1995; Advisor on British constitutional law and history to the Amicus Curiae for Quebec in the Supreme Court of Canada, 1997-1998. Mr. Graham has served as counsel in major fluoridation litigation in Minnesota, Washington State, Pennsylvania, Illinois, and Texas, 1974-1984.

** Ph.D. in Experimental Medicine. Chief Profusionist, Royal Victoria Hospital in Montreal, 1957-1967; Coordinator for Research in the Heart Institute and Artificial Organs Group, and Lecturer in Medicine, Laval University, 1967-1979; Director of Medical Research, Laval University Hospital, 1973-1979; Senior Scientific Advisor to the Environment Minister and the Prime Minister of Quebec, 1976-l985; Director, Local Community Services Center, Lotbiniere West, 1979-1990. Dr. Morin was scientific advisor to counsel for the plaintiffs in major fluoridation litigation in Texas in 1982.

*** The authors wish to express their gratitude to J. William Hirzy, Ph.D., Senior Vice President of the National Treasury Employees Union, Chapter 280, at the National Headquarters of the United States Environmental Protection Agency (EPA) for documentation concerning developments at EPA from 1986 through 1998, and also to Rt. Hon. Edward Baldwin, Earl of Bewdley, for his assistance in securing records of important debates on fluoridation in the British House of Lords.

presence of fluoride in drinking water, which is a distinct question. The focus of this article will be the artificial fluoridation of public water supplies which occurs when the fluoride content of drinking water is artificially adjusted from its natural level to a desired level of 0.9-l.2 ppm. This change is effected by adding sodium silicofluoride, hydrofluosilicic acid, or some such industrial waste product, which releases free fluoride ions into water consumed by human beings.[1]

The theory behind this practice, which now affects about 130 million people in the United States, is that the ingestion of fluoride will harden the surfaces of teeth and make them less susceptible to dental caries. The literature is extensive on whether this practice does or does not reduce tooth decay, and whether it is or is not safe.[2] The standard work, done under auspices of the American Dental Association (ADA) and the United States Public Health Service (USPHS), is the *Newburgh-Kingston Caries-Fluorine Study: Final Report*.[3] Published over forty years ago, it proudly concluded that artificial fluoridation of public water supplies dramatically reduces tooth decay in humans, at no risk to human health.[4] In language tinged with contemporary fanaticism, the *Final Report* announced, "The opposition stems from several sources, chiefly food faddists, cultists, chiropractors, misguided and misinformed persons who are ignorant of the scientific facts on the ingestion of water fluorides, and, strange as it may seem, even among a few uninformed physicians and dentists."[5]

---

1. See GEORGE L. WALDBOTT, M.D. ET AL., FLUORIDATION: THE GREAT DILEMMA 47-54, 148-74 (1978) for a detailed discussion of the absorption of fluoride, mainly as free ions, into the soft tissues of the human body. On the other hand, when fluoride is naturally present in public water supplies, it is generally bound with calcium and other minerals and, in such form, it does not readily dissociate and so is more readily excreted. Experiments with trout indicate that fluoride in water so bound tends to be less toxic. *See* Joseph W. Angelovic et al., *Temperature and Fluorosis in Rainbow Trout*, 33 J. WATER POLLUTION CONTROL FED'N 371 (1961). Hence, the artificial presence of fluoride in drinking water should be considered separately from its natural presence, at least in connection with questions about whether or not fluoride in drinking water produces harmful side effects.

2. The most respected scientific works, published during the twentieth century in support of artificial fluoridation of public water supplies, are WORLD HEALTH ORGANIZATION, FLUORIDES AND HUMAN HEALTH (1970), and FRANK J. MCCLURE, U.S. DEP'T OF HEALTH, EDUCATION, AND WELFARE, WATER FLUORIDATION: THE SEARCH AND THE VICTORY (1970). The work of WALDBOTT ET AL., *supra* note l, is a comprehensive and powerful rebuttal. Considerable research has been done since these classic treatises were published.

3. Herman E. Hilleboe et al., *Newburgh-Kingston Caries Fluorine Study: Final Report*, 52 J. AM. DENTAL ASS'N 290 (1956).

4. *See id.* at 313-14, 316-19 (1956).

5. *Id.* at 294.

From the beginning, this ostentatious pronouncement has set the tone of ADA and USPHS activists and others promoting this practice in the face of growing opposition from eminent scientists and physicians. The ultimate merits of the issues in science and medicine aside, there has always been learned and respectable opposition to artificial fluoridation of public water supplies,[6] and all attempts to deny it can only be characterised as irresponsible.

A few preliminary questions need to be asked. The first is whether the natural or artificial level of fluoride in public water supplies really has any beneficial effect in reducing tooth decay. The main difficulty with the experimental runs at Newburgh and Kingston in New York and elsewhere is that tooth decay is enhanced or diminished by innumerable factors including dietary, socio-economic, environmental, hygienic, and many others. Thus, criticism was voiced, initially in a doctoral dissertation,[7] that there was no control for known and unknown variables and, consequently, the conclusions on the reduction of tooth decay associated with fluoridation were invalid.

Subsequent research, involving vastly more data and sophistication, has entirely upset the Newburgh-Kingston orthodoxy.[8] It has since been persuasively demonstrated that the lowest rates of tooth decay in children occur in areas where the fluoride level is about 0.2-0.4 ppm, which is the normal level in most parts of the world.[9] From

---

6. *See, e.g., Hearings on H.R. 2341 Before the House Comm. on Interstate and Foreign Commerce*, 83d Cong. 62-86 (1954) (statement of Frederick Exner, M.D.). In his time, George Waldbott, M.D., was the dean of physicians against fluoridation. His pioneering book, A STRUGGLE WITH TITANS (1965), is bound to be of great interest to scientific historians in future years. He was a founder of the International Society for Fluoride Research, a learned society of about five hundred scientists who specialize in the field, publishing a quarterly journal entitled *Fluoride*.

7. *See* Edward S. Groth III, Two Issues of Science and Public Policy: Air Pollution Control in the San Francisco Bay Area and Fluoridation of Community Water Supplies 146-462 (1973) (unpublished Ph.D. dissertation, Stanford University) (on file with University Microfilms in Ann Arbor, Michigan).

8. *See, e.g.,* H. Kalsbeek & G.H.W. Verrips, *Dental Caries Prevalence and the Use of Fluorides in Different European Countries*, 69 J. DENTAL RES. 728 (1990); Rudolph Ziegelbecker, *WHO Data on Dental Caries and Natural Water Fluoride Levels*, 26 FLUORIDE 263 (1993) (setting forth impressive analyses of data published by the World Health Organization). Trends now evident in Newburgh and Kingston indicate no significant differences in tooth decay rates between the two cities, although dental mottling is somewhat higher in fluoridated Newburgh. *See, e.g.*, Jayanth V. Kumer et al., *Trends in Dental Fluorosis and Dental Caries Prevalences in Newburgh and Kingston, NY*, 79 AM. J. PUB. HEALTH 565 (1989); Jayanth V. Kumer et al., *Changes in Dental Fluorosis and Dental Caries in Newburgh and Kingston, New York*, 88 AM. J. PUB. HEALTH 1866 (1998); Jayanth V. Kumer et al., *Recommendations for Fluoride Use in Children*, N.Y.S. DENTAL J., Feb. 1998, at 40.

9. *See, e.g.,* Yoshitsugu Imai, *Relationship Between Fluoride Concentration in Drinking Water and Dental Caries in Japan*, 6 FLUORIDE 248 (1973).

all published studies on the question in Europe and North America, it has been shown that, while there is a strong positive relationship between dental mottling and the natural level of fluoride in drinking water, there is no statistical relationship between the extent of tooth decay and the natural level of fluoride in drinking water.[10] In more recent years, it has been observed that tooth decay rates have decreased as fast in unfluoridated areas as in fluoridated areas.[11] From massive data gathered by the government of the United States, it has been revealed that there is no statistical relationship between rates of tooth decay in children and the extent or duration of artificial fluoridation of public water supplies.[12]

Another question is whether public officials of the United States have been honest in levelling with the American people about the potential harmful effects of artificially releasing fluoride into the environment. In this regard, some attention needs to be given to the seminal work of Dr. Alfred Taylor, a biochemist at the University of Texas. The facts have been written up by reputable scholars[13] and make up an important episode in scientific history.

In the early 1950s, Dr. Taylor undertook a series of preliminary experiments by which it appeared that cancer-prone mice consuming water treated with sodium fluoride had shorter life spans than mice drinking distilled water.[14] Because the mice in both the control and experimental groups ate chow containing measurable fluoride, probably as CaF, as he learned after his initial runs, Dr. Taylor replicated his earlier work, but used chow containing negligible fluoride. He ran twelve experiments using 645 cancer-prone mice. He found that, as measured for statistical significance, cancer-prone mice drinking water containing fluoride, introduced as NaF, had shorter life spans than mice drinking distilled water.[15] In 1954, the results of Dr. Taylor's reruns were published in a refereed journal.[16]

Dr. Taylor's work was published at a politically sensitive time, because the last stages of the much-boasted surveys at Newburgh

---

10. Rudolph Ziegelbecker, *Natürlicher Fluoridgehalt des Trinkwassers und Karies* [*Natural Fluoridation of Drinking Water and Caries*], 122 GWF WASSER/ABWASSER 495 (1981), translated in 14 FLUORIDE 123 (1981).

11. John Colquhuon, *Child Dental Health Differences in New Zealand*, 9 COMM. HEALTH STUD. 85 (1987).

12. John Yiamouyiannis, *Water Fluoridation and Tooth Decay: Results from the 1986-1987 National Survey of U.S. Schoolchildren*, 23 FLUORIDE 55 (1990)

13. *See, e.g.*, WALDBOTT ET AL., *supra* note l, at 222-25.

14. *See id.* at 222.

15. *See id.* at 222-23.

16. *See* Alfred Taylor, *Sodium Fluoride in the Drinking Water of Mice*, 60 DENTAL Dig. 170 (1954).

and Kingston were underway. The obvious meaning of Dr. Taylor's results was that a possible danger to public health had been overlooked, and that widespread fluoridation should be delayed until the situation had been clarified. However, the ADA and the USPHS had already endorsed and begun the drive to promote fluoridation.

The embarrassment, therefore, had to be addressed. In the *Final Report*, reference was made to Dr. Taylor's original tests two years after the positive results of his reruns had been peer-reviewed and published. Then it was said, contrary to the known state of world literature:

> The reports by Alfred Taylor, a biochemist at the University of Texas, on the increased incidence of cancer in mice drinking fluoride-treated water have been shown to be unfounded, since the food that he was giving the mice had many times the fluoride content of the drinking water, and the food was supplied both to the control and experimental groups. Subsequent tests did not confirm the differences.[17]

Ever since, USPHS officials have insisted, contrary to known facts, that Dr. Taylor's reruns were never done and never published, and that no work supporting Taylor's results exists or has ever been published. For example, in a standard history of the National Institute of Dental Health, published thirty-five years after Dr. Taylor's work first appeared in a refereed journal, Ruth Roy Harris said, "Alfred Taylor, an investigator with a doctorate in biochemistry, indicated that he would not publish his findings because he was unable to confirm those results in a second experiment."[18] Harris added still another misrepresentation, also contrary to known facts, "A literature search of scientific journals failed to show any publication of this work by Taylor -- an indication that it was not subjected to review by his peers."[19] The importance of Dr. Taylor's work is revealed by what USPHS officials have done to conceal it.

After his first study, Dr. Taylor and his wife, also a Ph.D. biochemist, published the results of yet another large-scale study, in which fluoride in water, introduced as NaF, was shown to induce growth in implanted tumors in mice.[20] Dr. Taylor's pioneering work

---

17. Hilleboe et al., *supra* note 4, at 313.

18. RUTH ROY HARRIS, DENTAL SCIENCE IN A NEW AGE, HISTORY OF THE NATIONAL INSTITUTE OF DENTAL RESEARCH 112 (1989).

19. *Id.* at 396 n.33.

20. *See* Alfred Taylor & Nell Carmichael Taylor, *Effect of Sodium Fluoride on Tumor Growth*, 119 PROC. OF SOC'Y FOR EXPERIMENTAL BIOLOGY AND MED. 252 (1965).

has been confirmed and reconfirmed by a considerable multitude of laboratory studies done by world class scientists, all published in peer-reviewed journals.[21] Meanwhile, it has been held in some environmental litigation during the twentieth century that, if laboratory tests indicate the capacity of a certain substance to produce harmful side effects in laboratory animals, the same substance may also be presumed deleterious to man in the environment.[22]

The main inquiry of this article will be whether the several States have constitutional authority to impose artificial fluoridation of public water supplies. The question depends in part on scientific and medical facts. As we shall relate in detail, trial judges over the past twenty years have repeatedly found, after hearing experts, that fluoridation is injurious to public health. We proceed, first, to review the legal fundamentals.

II. THE NATURE OF POLICE POWER

The first clause of Article I, Section 8 of the United States Constitution states that Congress shall have the power to "provide for the common Defence and general Welfare." James Madison showed that this provision was intended to define the objects of federal spending, not to confer a general legislative authority upon

---

21. *See, e.g.*, Irwin H. Herskowitz & Isabel L. Norton, *Increased Incidence of Melanotic Tumors in Two Strains of Drosophila Melanogaster Following Treatment with Sodium Fluoride*, 48 GENETICS 307 (1963); Chong Chang, *Effect of Fluoride on Nucleotides and Ribonucleic Acid in Germinating Corn Seedling Roots*, 43 PLANT PHYSIOLOGY 669 (1968); Danuta Jachimczak & Bogumila Skotarczak, *The Effect of Fluorine and Lead Ions on the Chromosomes of Human Leucocytes in Vitro*, 19 GENETICA POLONCIA 353 (1978); John Emsley et al., *An Unexpectedly Strong Hydrogen Bond: Ab Initio Calculations and Spectroscopic Studies of Amide-Fluoride Systems*, 103 J. AM. CHEM. SOC'Y 24 (1981); John Emsley et al., *The Uracil-Fluoride Interaction: Ab Initio Calculations including Solvation*, 8 J. CHEMICAL SOC'Y CHEMICAL COMMUN. 476 (1982); A.H. Mohamed & M.E. Chandler, *Cytological Effects of Sodium Fluoride on Mice*, 15 FLUORIDE 110 (1982); Toshio Imai et al., *The Effects of Fluoride on Cell Growth of Two Human Cell Lines and on DNA and Protein Synthesis in HeLa Cells*, 52 ACTA PHARMACOLOGICA ET TOXICOLOGICA 8 (1983); Takeki Tsutsui et al., *Cytotoxicity, Chromosome Aberrations and Unscheduled DNA Synthesis in Cultured Human Diploid Fibroblasts Induced by Sodium Fluoride*, 139 MUTATION RES. 193 (1984); Takeki Tsutsui et al., *Induction of Unscheduled DNA Synthesis in Cultured Human Oral Keratinocytes by Sodium Fluoride*, 140 MUTATION RES. 43 (1984); Takeki Tsutsui et al., *Sodium Fluoride-induced Morphological and Neoplastic Transformation, Chromosome Aberrations, Sister Chromatid Exchanges, and Unscheduled DNA Synthesis in Cultured Syrian Hamster Embryo Cells*, 44 CANCER RES. 938 (1984); Carol A. Jones et al., *Sodium Fluoride Promotes Morphological Transformation of Syrian Hamster Embryo Cells*, 9 CARCINOGENESIS 2279 (1988); Marilyn J. Aardema et al., *Sodium Fluoride-induced Chromosome Aberrations in Different Stages of the Cell Cycle: A Proposed Mechanism*, 223 MUTATION RES. 191 (1989); Takeki Tsutsui et al., *Cytotoxicity and Chromosome Aberrations in Normal Human Oral Keratinocytes Induced by Chemical Carcinogens: Comparison of Inter-Individual Variations*, 5 TOXICOLOGY IN VITRO 353 (1991).

22. *See e.g.*, Environmental Defense Fund v. Environmental Protection Agency, 548 F.2d 998, 1006 (D.C. Cir. 1976).

Congress, because, if this clause conferred such a general legislative authority, it would render the enumeration of specific legislative powers redundant and pointless.[23]

Madison's observation was important because he showed that, if Congress had a general legislative authority as such, it would be nothing other than a power to provide for the common defense and the general welfare. It would be a power, subject to the limitations inherent and implied in every republican form of government,[24] to enact only by laws necessary and proper or, in other words, laws fairly proportioned to and consistent with the common defense and general welfare, in keeping with legal custom and tradition.[25] Alexander Hamilton made unmistakably clear that a bill of rights, including all essential privileges and immunities of a free people, is always implied, if not expressed, in every republican form of government.[26] And every republican form of government, as an outgrowth of the American Revolution, necessarily presupposes the essential truths of the Declaration of Independence, which begins, before all else, with a tribute to the "Laws of Nature and Nature's God."[27]

So it was that Justice Samuel Chase of the United States Supreme Court, one of the signers of the Declaration of Independence, thus

---

23. *See* THE FEDERALIST NO. 41, at 276-77 (Clinton Rossiter ed., 1961). In reaching this conclusion, Madison applied the rule of construction from the common law that clauses dealing with the same general subject or question should be construed together, if possible, to give every distinct provision some useful purpose and to coalesce into a harmonious whole with the others. *See* THE FEDERALIST NO. 40, at 260 (Clinton Rossiter ed., 1961). The same idea is advanced in the 7th of the Kentucky Resolutions of 1798, authored by Thomas Jefferson. *See* 4 DEBATES ON THE FEDERAL CONSTITUTION 542 (Elliot ed., Lippencott & Co., Philadelphia) (2d ed. 1859).

24. James Madison emphasized that the government of the Union, like the government of every State, is a republican form of government which has its origin in the people and features distinctive of the American Revolution. *See* THE FEDERALIST NO. 39, at 240-42 (Clinton Rossiter ed., 1961). The first mature prototype of such a republican form of government, see the Virginia Bill of Rights and Constitution of 1776, reprinted in 9 Hening's Statutes at Large, at 109-19.

25. *See* THE FEDERALIST NO. 33, at 203-04 (Alexander Hamilton) (Clinton Rossiter ed., 1961); THE FEDERALIST NO. 44, at 285 (James Madison) (Clinton Rossiter ed., 1961). Both Hamilton and Madison agreed that the eighteenth clause of Article I, Section 8, of the United States Constitution, granting Congress the power to enact necessary and proper laws, would have been implied if it had not been expressed. Also, while it allows implied powers, it also imposes implied limits on powers of just legislation. The standard judicial definition of necessary and proper laws is found in *M'Colloch v. Maryland*, 17 U.S. (4 Wheat.) 3l6, 421 (1819).

26. *See* THE FEDERALIST NO. 84, at 512-14 (Clinton Rossiter ed., 1961).

27. THE DECLARATION OF INDEPENDENCE para. 1 (U.S. 1776). Sir William Blackstone gave incomparable exposition to the meaning of natural law as the foundation of constitutional government in 1 COMMENTARIES ON THE LAWS OF ENGLAND 38-43 (l765) [hereinafter BLACKSTONE].

expounded in a celebrated case the inherent limitations on general legislative authority under any republican form of government:

> The nature and ends of legislative power will limit the exercise of it. This fundamental principle flows from the very nature of our free Republican governments, that no man should be compelled to do what the laws do not require; nor to refrain from acts which the laws permit. There are acts which the Federal, or State, Legislatures cannot do, without exceeding their authority. There are certain vital principles in our free Republican governments, which will determine and over-rule an apparent and flagrant abuse of legislative power; as to authorize manifest injustice by positive law; or to take away that security for personal liberty, or private property, for the protection whereof the government was established.[28]

There can be no serious dispute as to the nature of the original idea. In view of the transformations accomplished by the American Revolution, general legislative authority was understood to be the power of enacting necessary and proper laws to provide for the common defense and general welfare, in conformity with natural law and legal tradition. And this idea, fully justiciable, was imposed before the Fourteenth Amendment was ever thought of, by the so-called Guarantee Clause in of the United States Constitution, which demands that in and for every State of the Union there shall be a "Republican Form of Government."[29]

The term "police power" later appeared as a term of jurisprudence in antebellum litigation which arose under the Guarantee Clause, used to describe the legislative powers of the several States to enact regulations of domestic life.[30] The Guarantee Clause largely disappeared as a restraint upon the several States as a consequence of misunderstanding the interesting old case of *Luther v. Borden*.[31] Many generations of judges and lawyers have been deeply confused about it.

In 1842, there was a civil war between two state governments in Rhode Island, each claiming to be lawful.[32] Both the majority and the dissent agreed that the court could not resolve this question[33], which was said to be nonjusticiable, because of the enormous

---

28. Calder v. Bull, 3 U.S. (3 Dal.) 386, 388 (l798).
29. U.S. CONST. art IV, § 4.
30. *See* Thurlow v. Massachusetts, 46 U.S. (5 How.) 504, 582-83 (1847).
31. 48 U.S. (7 How.) 1 (l849).
32. *See id.* 34-38, 48-57.
33. *See id.* at 39-47, 51-58.

practical difficulties involved. Thus began the doctrine of political questions which says that a question is nonjusticiable and so cannot be judicially decided if, in the circumstances, a practical remedy cannot be given by the courts, or if there are no objective legal standards upon which a judicial decision can be made, or if the question is plainly referred by fundamental law to the political organs of government or society.[34] Nothing could ever be so likely to injure the dignity or reputation of the bench than failure of judges to honor these inherent limits to their power.

But there was another important question in the case which most students have overlooked. This question was whether the charter government of Rhode Island, assumed legitimate, could impose martial law during the unrest which appears in retrospect to have been remarkably trivial. This question was decided on the merits.[35] The majority held that the charter government could impose martial law, but there was a strong dissent, mainly based on the Petition of Right.[36]

In any event, there has never been any reason for saying, as has sometimes been held,[37] that any constitutional question arising under the Guarantee Clause is per se nonjusticiable. And a number of courts have occasionally recognized the Guarantee Clause as an appropriate basis of judicial decision,[38] as clearly suggested by Justice Samuel Chase when John Adams was President. During the twentieth century, the Guarantee Clause has been a sleeping giant of the United States Constitution, yet there is no reason why, if the need becomes urgent in future years, the giant cannot be awakened and put to good use.

The Fourteenth Amendment followed the American Civil War and has since been the main basis in the United States Constitution for judicial decisions restraining the exercise of police power by the several States. There are some well-kept secrets about the Fourteenth Amendment, which are highly pertinent to the question of police power, and these may conceivably become more widely understood or even become legal orthodoxy in the twenty-first century.

---

34. *See* Baker v. Carr, 369 U.S. 186, 208-37(1962).

35. *See* Luther v. Borden, 48 U.S. (7 How.) at 46, 58-88.

36. 3 Car. I, ch. 1 (1628).

37. *See, e.g.,* Taylor v. Beckham, 178 U.S. 548, 578-79 (1900); Pacific States Tel. & Tel. Co. v. Oregon, 223 U.S. 118, 142-53 (1912).

38. *See, e.g.,* Harrington v. Plainview, 6 N.W. 777 (Minn. 1880).

In the *Slaughter House Cases*,[39] the majority spoke the dark language of police power and upheld a Louisiana statute which required all slaughtering of animals as food for consumption in and around New Orleans to be done in facilities maintained under the auspices of a certain corporation.[40] The holding rests mainly on a notoriously unconvincing rationalization to accommodate an unwillingness to face the full impact of the Fourteenth Amendment.

The first well-kept secret about the Fourteenth Amendment is found in the four dissenting votes to the *Slaughter House Cases*, which rest mainly on the very capable and powerful opinions of Justice Stephen Field[41] and Justice Joseph Bradley.[42] Section 1 of the Fourteenth Amendment restrains the several States from abridging the privileges and immunities of citizens of the United States. Most certainly these dissenters were right in maintaining that this clause serves to incorporate all guarantees of civil liberty found in the United States Constitution as further restraints on the several States, including the First through Ninth Amendments.[43] And in light of legal tradition, they were right in maintaining that the Fourteenth Amendment, by incorporating the Ninth Amendment, imposes the old Statute of Monopolies[44] upon the several States.

Another well-kept secret about the Fourteenth Amendment, which may be unpleasant to some people yet ever so true, is that the article was never lawfully adopted,[45] mainly because it was proposed by a Congress which unlawfully excluded representatives and senators from ten States for having had the temerity of holding views not to the liking of an impassioned and factious majority.[46] Moreover, adoption was unlawful because ratification by those ten States, essential to adoption, was coerced by keeping them under

---

39. 83 U.S. (16 Wall.) 36 (1873).

40. *See id.* at 58-82.

41. *See id.* at 83-111

42. *See id*. at 111-24.

43. It is impossible to attribute any other cogent meaning to this clause in light of *Corfield v. Coryell*, 6 F. Cas. 546 (C.C.E.D. Pa. 1823) (No. 3230), and *Barron v. Baltimore*, 32 U.S. (7 Pet.) 243 (1833).

44. *See* 21 Jac., ch. 3 (1623). The Statute of Monopolies expressly ordained that monopolies granted by the Crown were "contrary to the ancient and fundamental laws of the realm, and are utterly void." *Id.* at § 1. The statute created an express proviso allowing patents of invention for terms of fourteen years. *See id.* at § 6. Royal grants of monopoly had previously been declared unlawful in the *Case of Monopolies*, 11 Coke 84a (K.B. 1603).

45. This unhappy truth has been subject to protest from the most respectable quarters. *See, e.g.,* Dyett v. Turner, 439 P.2d 266 (Utah 1968).

46. Such exclusion was unconstitutional for reasons then clearly understood and long since judicially settled. *See, e.g.*, Powell v. McCormick, 395 U.S. 486 (1969).

martial law until they ratified,[47] contrary to principles already known and adjudicated to be unconstitutional.[48] Because time is a wonderful solvent of truth, we may anticipate that in the twenty-first century the Fourteenth Amendment may well be stricken from the United States Constitution.

The final well-kept secret about the Fourteenth Amendment is this: if and when it is finally acknowledged that the Fourteenth Amendment was never lawfully adopted, we shall not be deprived of means, under the fundamental law of the Union, to restrain the several States from acts of invidious discrimination or other forms of injustice. The reason is that everything worthwhile so far done in the name of the Fourteenth Amendment, and much more besides, can also be done upon a more enlightened view of the American Revolution, in the name of the Guarantee Clause.[49] *E pluribus unum. Annuit coeptis novus ordo seclorum.*

III. NATURAL LAW JURISPRUDENCE

Between now and the hopeful future of clearer vision, we can use principles common both to the Guarantee Clause or the Fourteenth Amendment as a constitutional restraint on the "police power" of the several States, and we may be guided by judicial decisions rendered under either provision. And for this purpose, especially as it relates to artificial fluoridation of public water supplies, it is important to understand what has been done right, what has been done wrong, and why there has consequently been both progress and deterioration in American jurisprudence.

We first need to understand what has been done wrong and learn from it. With this objective in mind, we need to pay attention to Justice Hugo Black. During his tenure on the United States Supreme Court, Justice Black managed to sow more confusion, yet with important kernels of truth and distinguished erudition, than almost

---

47. The Reconstruction Act was passed over a veto based on constitutional grounds. *See* 14 Stat. 428 (1867). The unanswerable veto message of President Andrew Johnson is reprinted in, 1 DOCUMENTS OF AMERICAN HISTORY 481-85 (Henry Steele Commager ed., 9th ed. 1973).

48. Although the Reconstruction Act imposed martial law under circumstances disallowed in *Ex Parte Milligan*, 71 U.S. (4 Wall.) 2 (1866), the constitutional infraction was allowed by systematic evasion of the question by the judiciary. *See generally* Texas v. White, 74 U.S. (7 Wall.) 700 (1869); Georgia v. Stanton, 73 U.S. (6 Wall.) 50 (1868); *Ex Parte* McCardle, 73 U.S. (6 Wall.) 318 (1868); *Ex Parte* Yerger, 75 U.S. (8 Wall.) 85 (1868); Mississippi v. Johnson, 71 U.S. (4 Wall.) 475 (1867).

49. The possibilities for this development have already been considered in two articles by Arthur E. Bonfield, Baker v. Carr: *New Light on the Constitutional Guarantee of Republican Government*, 50 CAL. L. REV. 245 (1962) and *The Guarantee Clause of Article IV, Section 4: A Study in Constitutional Desuetude*, 46 MINN. L. REV. 513 (1962).

any judicial figure in the world during the twentieth century. His mistakes have pronounced characteristics which are particularly instructive when viewed in retrospect.

His trademark position, stated in his famous dissent in *Adamson v. California*,[50] was that the Fourteenth Amendment incorporates the Federal Bill of Rights, including the First through Eighth Amendments.[51] But, if the Fourteenth Amendment incorporates the Federal Bill of Rights, it necessarily also incorporates the Ninth Amendment which says that the enumeration of certain rights "shall not be construed to deny or disparage others retained by the people."[52] Why no mention of the Ninth Amendment?

Throughout his dissent, Justice Black fairly radiated hostility against the ancient and venerable idea of natural law,[53] which he plainly did not understand either as a force shaping legal tradition or as a category of jurisprudence.[54] He acted as if the Ninth Amendment did not exist, because this article of fundamental law, construed in light of constitutional history, cannot possibly exclude those "certain unalienable Rights" with which all human beings are "endowed by their Creator" under the "Laws of Nature and Nature's God."[55]

Justice Black carried his hostility to natural law even further in his majority opinion in *Ferguson v. Skrupa*.[56] At issue in that case was a Kansas statute prohibiting any person from engaging in the business of debt adjusting, except as incident to the authorized practice of law.[57] At the time, there was a venerable precedent which held that, under the l4th Amendment, no State has constitutional

---

50. 332 U.S. 46, 68-123 (1947).

51. The historical evidence supporting this thesis is found in the appendix to Justice Black's opinion. *See id.* at 92-123.

52. This provision was intended to meet the objection of Alexander Hamilton in THE FEDERALIST NO. 84, at 513-14 (Clinton Rossiter ed., 1961), that an enumeration of rights was dangerous, because it might be used as a false pretext to claim power for seizing rights not mentioned. See the observations of James Madison in the United States House of Representatives on June 8, 1789, recorded in 1 ANNALS OF CONGRESS 439-40 (Gales & Seaton 1834).

53. *See* Adamson v. California, 332 U.S. at 79-80, 91.

54. Justice Black was plainly not aware of such distinguished works on natural law as HEINRICH A. ROMMEN, *DIE EWIGE WIEDERKEHR DES NATÜRRECHTS* (1936), translated as THE NATURAL LAW (Thomas R. Hanley trans., 1955). Hanley's introduction movingly relates how Rommen as a lawyer in Nazi Germany discovered the reality of natural law and was led to reject legal positivism in resisting Hitler's violations of human rights. *See id.* at xi-xxxviii.

55. THE DECLARATION OF INDEPENDENCE para. 1, 2 (U.S. 1776). This language obviously corresponds to those "certain inherent rights" which are mentioned in the first article of the Virginia Bill of Rights of 1776, reprinted in 9 Hening's Statutes at Large, at 109.

56. 372 U.S. 726 (1963).

57. *See id.* at 727.

authority to prohibit a useful business which is not inherently immoral or dangerous to public welfare.[58] Black flippantly overruled this old case with the remark, "Whether the legislature takes for its textbook Adam Smith, Herbert Spencer, Lord Keynes, or some other is no concern of ours."[59]

Black's attitude was founded upon one of the most unfortunate falsehoods ever to pollute American jurisprudence. He assumed, out of ignorance, that cases like *Lochner v. New York*,[60] were founded on political prejudice, not legal standards. In *Lochner*, the court held that a law limiting the right of bakers to contract for their hours of work was unconstitutional.[61] No reason was even suggested on the record why bakers should not enjoy such discretion, or why they needed the protection of the law, as might have been true if, say, it had been shown that the bakers are typically in an uneven bargaining position in dealing with their employers. If such a showing had been at least attempted, as might well have been easily done, the statute would certainly have been upheld.[62]

It is true that the freedom to contract, cited as the justification for holding the statute unconstitutional, came from natural law jurisprudence. But the theory was not woven out of thin air. It came from venerable and historic roots, ultimately the decision of Lord Mansfield in *Sommersett's Case*[63] which held that, because slavery runs against natural law, it could be sustained only by acts of Parliament,

---

58. *See* Adams v. Tanner, 244 U.S. 590 (1917). As with many other cases like it, this case turned on the clause of the Fourteenth Amendment which forbids any state from denying life, liberty, or property without due process of law. The clause is ultimately traceable to the 39th Article of the Magna Carta of King John. It was probably added to the Fourteenth Amendment to cure the unfortunate holding of the majority in *Satterlee v. Matthewson*, 27 U.S. (2 Pet.) 380 (1829), and drew inspiration from cases such as *University of North Carolina v. Fox*, 5 N.C. (1 Mur.) 83 (1805).

59. 372 U.S. at 732. This case echoed of the thoughtless satyrism of Oliver Wendell Holmes in *Lochner v. New York*, 198 U.S. 45, 75 (1905) ("The Fourteenth Amendment does not enact Mr. Herbert Spencer's Social Statics"). Under this theory, we should be equally indifferent as to whether the legislature of a State were to take guidance from Maxmillien de Robespierre, Vladimir Lenin, Adolf Hitler, Joseph Stalin, Mao Tse Tung, or Pol Pot.

60. 198 U.S. 45 (1905).

61. *See id.* at 64-65.

62. Pope Leo XIII issued the encyclical *Rerum Novarum* (1891), which was one of the greatest statements on natural law in history. He expounded rights of labor and the duty of governments to enact legislation protecting labor from unjust exploitation. It was on this basis that legislation protecting labor from unjust exploitation was repeatedly approved as constitutional in natural law jurisprudence, whenever a plausible justification of legislative judgment was made to appear on the record. *See, e.g.,* Bunting v. Oregon, 243 U.S. 426 (1917); Muller v. Oregon, 208 U.S. 412 (1908); Holden v. Hardy, 169 U.S. 366 (1898).

63. 20 How. St. Tr. l, 82 (K.B. 1771).

and all statutes allowing it had to be strictly construed so as to make a slave free the moment he set foot on the free soil of England.[64]

This idea was, of course, adopted and expanded by the Thirteenth Amendment. It follows, by legal inference, that nobody in the United States may be denied a liberal right to earn a livelihood or to engage in business as he or she sees fit. Thus, it has been held under the Fourteenth Amendment that, unless a statute limiting the right of a citizen to contract freely can be plausibly justified, it is unconstitutional.[65] The idea does not embrace irresponsible freedom and it does not outlaw legislation to prevent unjust exploitation of labor or activity harmful to the public good. The right is confirmed by natural law and legal tradition and is suited to the circumstances of a free people. There has always been just cause to apply this notion with judicious caution,[66] but there never has been any reason to reject or overrule it altogether.[67]

Black took his extremism to the *ne plus ultra* in his bitter dissent in *Griswold v. Connecticut*.[68] Complaining that natural law is mysterious and uncertain and that the Ninth Amendment has only nominal but no substantive meaning, Black insisted that even a statute intruding into the sexual intimacy of husband and wife, disallowing them to be instructed by their physician on artificial methods of birth control, could not be struck down as unconstitutional.[69] Fortunately, his fellow justices had no trouble in understanding privacy as a

---

64. This principle originated in the policy of the common law which favored liberty, and thus nudged villeinage into extinction. *See, e.g.*, Pigg v. Caley, Noy 27 (K.B. 1618). Strict construction of laws allowing slavery was adopted by judges of the old South, and many slaves were freed because of it. *See, e.g.*, Murray v. M'Carty, 16 Va. (2 Mun.) 393 (1811). It was also applied by the circuit court of Missouri in granting Dred Scott and his family their freedom, and was the main basis of the dissent of Justice Benjamin Curtis in *Dred Scott v. Sandford*, 60 U.S. (19 How.) 391, 602-603 (1857).

65. *See* Allgeyer v. Louisiana, 165 U.S. 578 (1897).

66. So as to avoid unfortunate decisions like *Coppage v. Kansas*, 236 U.S. 1 (1915), which was simply a mistake. No apology can be offered for it in any school of thought.

67. *Nebbia v. New York*, 291 U.S. 502 (1934), is sometimes cited as the beginning of the end of natural law jurisprudence in the field of economic regulation, but the case is better understood as a just extension of *Munn v. Illinois*, 94 U.S. 113 (1877), in light of pressing economic circumstances not existing at the time of *Fairmont Creamery Co. v. Minnesota,* 274 U.S. 1 (1926). Likewise, *West Coast Hotel Co. v. Parrish*, 300 U.S. 379 (1937), is often cited as the definitive end of natural law jurisprudence in the field of economic regulation. Yet in *Parrish*, the majority disregarded the intended meaning of the Nineteenth Amendment as expounded in *Adkins v. Children's Hospital of the District of Columbia*, 261 U.S. 525, 552-53 (1923), and later revived in *Frontiero v. Richardson*, 411 U.S. 677, 686-88 (1977). *Parrish* allowed a kind of sex discrimination which would never be allowed today and may be considered virtually overruled.

68. 38l U.S. 479, 507-27 (1965).

69. *See id.* at 523-25.

liberty protected by fundamental law, and they declared the statute unconstitutional.[70]

If Hugo Black condemned natural law because he did not understand it, the founding fathers of the United States did understand it, and they built a new constitutional order upon it. They knew that natural law is a timeless moral and physical order which enforces itself and can be discovered by natural reason.[71] They knew that it constrains governments no less than markets. They knew that, if its lofty commands were disobeyed, there would be misfortunes in public affairs, requiring the accommodations of temporal law. They knew, therefore, that natural law was elaborated and given objective form by legal tradition.

The dissenters in the *Slaughter House Cases* rested their erudite opinions on the facts of history. They did not make things up to suit their political fancies but relied instead on legal custom acknowledged by the King's Bench and an organic statute of the English Parliament. In light of long experience, it became clear in the past, as it is impossible to deny today, that, by the wonderful operation of unseen but undeniable forces of nature, the practice of monopoly creates painful economic congestions. So it was that legal tradition accommodated and expressed the reality of natural law.

Likewise, if the statute in *Griswold* had not been left to fade in desuetude, but had been actively enforced, Connecticut would have faced political upheaval or revolution. Hence, the reality of natural law, which, fortunately, did not produce unhappy consequences, but only because prosecutors had the good sense not to file accusations, and the statute was eventually found unconstitutional. In this way temporal law honored privacy as an unenumerated constitutional immunity which had always existed by natural law. After transitions

---

70. *See id*. at 484-86 (penumbras of the Bill of Rights), 498-99 (the Ninth Amendment), 500-04 (due process of law under the Fourteenth Amendment). By acknowledging a constitutional right of privacy on the basis of natural law jurisprudence, the Court in no way committed itself to *Roe v. Wade*, 410 U.S. 113 (1973), which did not rest on natural law jurisprudence but rather overthrew the traditional protection of the unborn by both the common law and the civil law. *See e.g.*,Thulluson v. Woodford, 4 Ves. Jr. 227, 321-22 (Ch. 1799); Montreal Tramways v. Leveille, [1933] 4 D. L. R. 337, 340-41 (Can.). Nor did the Court contradict the moral teaching of Pope Paul VI against artificial birth control in the encyclical HUMANE VITAE (1968). Natural law jurisprudence actually restrains temporal law from attempting to prohibit some activities, especially those of a private nature, which, right or wrong, are not proper subjects for public regulation. *See, e.g.,* THOMAS AQUINAS, SUMMA THEOLOGICA, Ia IIae, q. 93, art. 3, ad 3, *translated in*, BASIC WRITINGS OF SAINT THOMAS AQUINAS, 766 (Anton Pegis ed. 1945).

71. See the abundant references to natural law in the opening passages of THE DECLARATION OF INDEPENDENCE (1776) and the corresponding language of Sir William Blackstone, *supra* note 27, at 38-43.

and adjustments, legal tradition will mature into a sturdier and sounder landmark which can be used with greater wisdom and confidence in future years.

IV. HEALTH FREEDOM

One of the most distinguished civil liberties decisions of the twentieth century, never overruled and often cited,[72] rests on the opinion of Justice James McReynolds in *Meyer v. Nebraska*.[73] Citing the duty of government to promote education, founded on the Northwest Ordinance, McReynolds struck down as unconstitutional under the Fourteenth Amendment a law prohibiting the teaching of German to children in the primary grades of public schools in Nebraska. His general formula is particularly worthy of notice:

> While this court has not attempted to define with exactness the liberty thus guaranteed, the term has received much consideration, and some of the included things have been definitively stated. Without doubt, it denotes not merely freedom from bodily restraint, but also the right of the individual to contract, to engage in any of the common occupations in life, to acquire useful knowledge, to marry, to establish a home and bring up children, to worship God according to the dictates of conscience, and, generally, to enjoy privileges long recognized at common law as essential to the orderly pursuit of happiness by free men.[74]

It is noteworthy that Sir William Blackstone mentioned the "preservation of man's health from such practices as may prejudice or annoy it" not as a legislative power, but as among "absolute rights of individuals,"[75] -- in other words, as among "those privileges long recognized at common law as essential to the orderly pursuit of happiness by free men."[76]

Therefore, it is clear enough that there are natural rights protected by fundamental law, even if not constitutionally enumerated. As there are such natural rights to marry and have children, to seek knowledge, to enjoy personal privacy, and to earn a livelihood by honest work of choice, subject only to such regulation as may be reasonably needed to protect the rights of others and the common good, so too there is a domain of personal freedom, which limits the

---

72. *See, e.g.*, Griswold v. Connecticut, 38l U.S. at 481-82, 495, 502.
73. 261 U.S. 390 (1923).
74. *See id.* at 399-400.
75. BLACKSTONE, *supra* note 27, at 134.
76. 261 U.S. at 400.

"police power" of a State in regulating health. It is an area given some but not full judicial development in the twentieth century.

Two classic cases stand out like beacons, the first being *Jacobson v. Massachusetts*,[77] in which a citizen challenged a statute compelling small pox vaccinations to counteract a pending epidemic of deadly disease. The act of the legislature was upheld under the Fourteenth Amendment. The holding is understandable, because the statute addressed a public danger, and failure to comply might have tangibly increased the chances that an offender might become a carrier of disease which thereby could infect others. Public emergency has always justified intrusions, even upon incomplete knowledge, which normal situations will not.

Of much interest in this case is the discussion of the fact that, while the general belief of the legislature on the need for smallpox vaccinations was supported by respectable medical authority, there was nevertheless responsible dissent within the medical profession over the efficacy and in some degree even of the safety of this particular measure. In *Jacobson,* the court reasoned, "The possibility that the belief [favoring smallpox vaccinations] may be wrong, and that science may yet show it to be wrong is not conclusive; for the legislature has the right to pass laws which, according to [reasonable belief] are adapted to prevent the spread of contagious diseases."[78]

No less of interest is an exception to the general principle of the judgment. The court plainly said that the statute could never be interpreted to compel a vaccination where it could be shown "with reasonable certainty" that application of the statute to an objecting citizen "would seriously impair his health or probably cause his death."[79] This observation was added as an essential feature of the *ratio decidendi* to avoid misinterpretation.

The court did not define what exactly it meant in saying that a statutory regulation of public health may not be extended to situations in which serious impairment of personal health is shown with "reasonable certainty." But this characteristic phrase has long been a term of art in the law of damages. It has long been used to

---

77. 197 U.S. 11 (1905).

78. *Id.* at 35. Language has been substituted in brackets for the phrase "the common belief of the people" in the opinion, because the obvious intent of the court was that the belief of the legislature acting on behalf of the people must at least be reasonable in view of available knowledge and evidence. The court said, "if a statute purporting to have been enacted to protect the public health, the public morals, or the public safety, has no real or substantial relation to those objects," then it is the duty of the judiciary to intervene and declare such statute unconstitutional. *Id.* at 31.

79. *Id.* at 39.

describe the legal standard of proving an injury in civil proceedings: while damages may not be based on speculation or guess, it will be enough to show the approximate degree of harm by fair preponderance of the evidence adduced in a judicial hearing.[80] And, in such case, injury may be proved by the opinions of experts who can demonstrate that they are well informed on the subject investigated.[81]

The other outstanding case on generic principles of health freedom is *Toronto v. Forest Hill*,[82] in which the majority opinion was written by Justice Ivan Rand, who was probably the most eminent jurist on the Supreme Court of Canada, in any event one of the finest natural law judges in the world, during the twentieth century.[83] This case arose under the British North America Act of 1867, before it was possible, except on a very limited basis,[84] for the judiciary of Canada to strike down acts of the dominion Parliament or of the provincial Legislatures as unconstitutional and thus null and void.[85] The judiciary of Canada was then obliged to protect civil liberties by strict construction of statutes, as far as possible, so as to avoid collision with natural law and legal tradition.[86] It was by

---

80. *See, e.g.*, Bigelow v. RKO Radio Pictures Inc., 327 U.S. 25l (1946); Story Parchment Co. v. Paterson Parchment Paper Co., 282 U.S. 555 (1930); Eastman Kodak Co. v. Southern Photo Material Co., 273 U.S. 359 (l927).

81. *See, e.g.*, Julian Petroleum Corp. v. Courtney Petroleum Co., 22 F.2d 360, 362 (9th Cir. 1927).

82. [1957] 9 D.L.R. 2d 113 (Can.).

83. *See, e.g.*, Michael Schneiderman, *The Positivism of Hugo Black v. The Natural Law of Ivan Rand: A Study in Contrasting Judicial Philosophies*, 33 SASKATCHEWAN LAW REV. 267 (1968). Another great natural law jurist in Canada during the twentieth century was Chief Judge Jules Deschenes of the Superior Court of Quebec. *See, e.g.*, Nissan Auto. Co. v. Pelletier, 77 D.L.R. 3d 646 (Que. 1976).

84. Mainly where statutes were enacted contrary to the organic provisions of the British North America Act of l867, as held by the British Privy Council in *In re Initiative and Referendum Act* [1919] App.Cas. 935, and the Supreme Court of Canada in *Saumer v. Quebec*, [1953] 4 D.L.R. 641 (Can.).

85. The situation has since changed beginning with the Canadian Bill of Rights of 1960, an organic statute of the dominion Parliament, which unlike the English Bill of Rights of 1689, was more than a venerable guide for the interpretation of statutes. In *Queen v. Drybones* [1970] 9 D.L.R. 3d 473 (Can.), the Canadian Bill of Rights of 1960 was held to be a statutory directive to restrain federal laws from operation. Later came the Canadian Charter of Rights and Freedoms consisting of sections 1 through 35 of the Constitution Act of 1982, which restrains the federal and provincial governments, and cannot be repealed by legislative act. Even so, section 33 of the Constitution Act of 1982 concedes to legislative power the prerogative of making statutes operable for five-year intervals, notwithstanding important provisions of the Canadian Charter. The Constitution Act of 1982 is part of the Canada Act of 1982, an organic statute of the British Parliament which renounced the last vestiges of imperial control over Canada.

86. Lord Coke held in *Dr. Bonham's Case,* 8 Coke 114a (C.P. 1610), that the courts of common law could declare acts of Parliament null and void. This doctrine was overthrown on the weight of the principle that the Commons, Lords, and King in Parliament are omnipotent and sovereign, and that, therefore, the judiciary cannot declare an act of Parliament null and void. Even so, the judges can and must construe acts in keeping with the principle that the

using such conservative yet effective principles that Justice Rand became distinguished as a civil libertarian on the bench.

In *Forest Hill*, a provincial law allowed municipal corporations to treat public water supplies so as to make the vended water "pure and wholesome."[87] Justice Rand construed this statute strictly, so as to disallow fluoridation. He protested,

> 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.[88]

Similar language appears in the concurring opinion of Justice Cartwright, regarding the municipal by-law to initiate fluoridation then in question:

> 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.[89]

Jacobson and *Forest Hill* expound complementary principles of natural law jurisprudence, and thereby supply a cogent idea of health freedom which is inherent in the respected constitutional formulation expressed in *Meyer v. Nebraska*.[90]

Under the Guarantee Clause, the Ninth Amendment, and the Fourteenth Amendment, understood in light of natural law and legal tradition, "police power" to regulate public health includes discretion to compel submission of citizens to medical intervention, but only if three necessary conditions are met. First, legislative judgment underlying the statute may discount responsible professional dissent,

---

King can do no wrong, and thus that all acts of Parliament must be construed, if possible, in keeping with natural law and legal tradition. The judges should do so, even if they must read statutes *quoad hoc* or contrary to their literal meaning in unusual situations. *See, e.g.*, BLACKSTONE, *supra* note 27, at 91, 160, 246.

87. *Forest Hill*, 9 D.L.R. 2d at 114-15.

88. *Id.* at 118. The same distinction appears in the Safe Drinking Water Act, 42 U.S.C. § 300g-1(b)(11), which states, "No national primary drinking water regulation may require the addition of any substance for preventative health care purposes unrelated to contamination of drinking water." This provision was intended by Congress to prohibit the use of the Safe Drinking Water Act as a means of imposing artificial fluoridation of public water supplies throughout the United States.

89. *Id.* at 124.

90. 261 U.S. 390 (1923).

yet must at least rest upon reasonable medical or scientific evidence. Second, it must be fairly justified by grave cause or public emergency, such as the need to prevent the spread of a contagious disease. Third, the intervention prescribed cannot be imposed upon protesting citizens who are able to prove, by a fair preponderance of the evidence, a tangible danger of serious injury to their health. But the legislative power cannot otherwise impose compulsory medication on protesting citizens. This much is the ideal of natural law jurisprudence which is inseparable from the intended meaning of the United States Constitution.

V. THE KEY DECISIONS SUSTAINING FLUORIDATION

It is not our purpose to provide a general review of all judicial decisions that have touched upon the constitutionality of imposing fluoridation on the general public.[91] Suffice it to say that the great majority of cases sustain it, we think wrongly, but there can be no doubt about the clear trend of American jurisprudence.

Our objective here is to note highly important developments in the last twenty-five years, which strenuous efforts have been made to camouflage behind smiling propaganda orchestrated by the ADA and the USPHS to promote fluoridation, as if all were well. In fact an end to this episode of public health malpractice is foreseeable. If we consider scientific and legal revolutions of the past, say from the discovery of the true cause of puerperal fever by Dr. Ignaz Semmelweiss until his eventual posthumous vindication, or in the development of freedom of the press from the founding of the Star Chamber to the adoption of the First Amendment, we should not be astonished to see the passing of considerable time in the rise and fall of fluoridation, and not a little confusion along the way.

Among all others, the most distinguished judgment sustaining the constitutionality of mandatory fluoridation of public water supplies has always been, and still is *Paduano v. City of New York*,[92] which arose upon a suit brought in 1965 to enjoin the practice in New York City.[93] At that time the clear weight of available medical and scientific evidence, then respectable but long since shown to be

---

91. A recent article reviewing many such cases is by Douglas Balog, *Fluoridation of Public Water Systems: Valid Exercise of State Police Power or Constitutional Violation?*, 14 PACE ENVTL. L. REV. 645 (1997).

92. 257 N.Y.S. 2d 531 (S.Ct. N.Y. County l965), *aff'd* 24 App. Div. 2d 437, 260 N.Y. S. 2d 831 (1965), *aff'd* 17 N. Y. 2d 875, 271 N. Y. S. 2d 305 (1966), *cert. denied* 385 U.S. 1026 (1967).

93. *See id.* at 533.

unfounded,[94] suggested that fluoridation was effective in reducing tooth decay in children.[95] Evidence of potential danger then existed,[96] but it was little known, in an undeveloped state, and effectively concealed by ADA-USPHS disinformation.[97] Most physicians and dentists then believed that fluoridation was beneficial and safe. It is fair to say that most available evidence -- at least what could be easily orchestrated into a courtroom appearance of the most available evidence -- then suggested that fluoridation was beneficial and safe.

True enough, then available evidence suggested the need for caution among the wise. But there were not many in those days who had good credentials, independent means, leisure time for deep study, the persuasiveness to expose the slick sales pitches of ADA-USPHS spokesmen, the capacity to survive assaults on their careers and reputations mounted by fluoridation promoters,[98] -- and wisdom besides.

It is wrong to justify fluoridation by reference to *Jacobson*, because fluoridation, unlike small pox vaccinations, does not address a contagious disease, but it is at least understandable that the Supreme Court of New York should have cited it as persuasive legal authority.[99] The court said:

> The question of the desirability of fluoridation is immaterial. In the face of the overwhelming precedents previously cited, and in accordance with general principles of stare decisis, this court sitting at Special Term, feels constrained to deny plaintiffs' application for a temporary injunction and to grant defendants' motion for a dismissal of the complaint. *Until the scientific evidence as to the deleterious effects of fluoridation reaches beyond the purely speculative state now existing*, decisional law mandates the holding that the controversy should remain within the realm of the legislative and executive branches of government. While the courts do not have a right to impose fluoridation upon anyone, judicial restraint requires us to adhere to the uniform decisions holding that the executive and legislative branches of government do -- *at least*

---

94. *See* Kalsbeek & Verrips, *supra* note 8; Ziegelbecker, *supra* note 10; Kumer, *supra* note 8; Imai, *supra* note 9; Colquhoun, *supra* note 11; Yiamouyiannis, *supra* note 12, and accompanying text.

95. *See, e.g.*, Hilliboe et al., *supra* note 4, at 314-24.

96. *See* Taylor, *supra* note 16, and accompanying text.

97. *See, e.g.*, Hilleboe et al., *supra* note 4; HARRIS, *supra* note 18, and accompanying text.

98. Literally volumes could be written on the notorious and ruthless tactics of fluoridation promoters seeking to silence all credible opposition. A sober and factual introduction to this subject of political intrigue can be found in WALDBOTT, ET AL., *supra* note l, at 258-352.

99. Paduano v. New York, 257 N.Y.S. 2d 531, 539 (S. Ct. N.Y. County 1965).

> *until some proof is adduced that fluoridation has harmful side effects* and therefore is not in the interests of the community.[100]

The court obviously had in mind the qualifying dictum in *Jacobson* that a public health regulation, obliging a citizen to accept a medical remedy, cannot be extended to a situation in which it is shown with reasonable certainty, or by a fair preponderance of the evidence exceeding speculation or guess, that the remedy will impose a danger of serious injury to the personal health of protesting citizens. Note clearly what the court did not say, should not have said, and, in light of its reliance on *Jacobson*, cannot be interpreted to have said: -- that such danger or injury must be proven by evidence so powerful as to eliminate all reasonable controversy on the subject. Such a burden of proof is legally impossible on any question of public health, nor does it comport with public justice or safety, nor does it have any legitimate basis in legal authority.

Another key judgment sustaining imposed fluoridation merits passing notice because it concerns legal ideals of the type suggested by the natural law jurisprudence of Ivan Rand. In *State Board of Health v. Brainerd,*[101] a mandatory fluoridation law was applied to a community which protested as a whole body politic in a special referendum[102] by a vote of 9 to 1 against implementing the law, and by a vote of 5 to 1 authorizing the city fathers to sit as a convention which met and declared the statute unconstitutional.

The state board of health sued the municipal government which pleaded the express and formal protest of the residents and voters of the city, the want of a public emergency occasioned by a pending epidemic of contagious disease, the existence of a responsible medical and scientific controversy over the effectiveness and safety of fluoridation, the availability of fluoride to persons desiring it by less intrusive means, and, therefore, the invasion of a natural right of the people, protected by fundamental law under these circumstances, to enjoy freedom of choice in maintaining personal health.[103] The Minnesota Supreme Court upheld the constitutionality of the mandatory fluoridation law, and sustained the writ of mandamus

---

100. *Id.* at 542 (emphasis added).

101. 241 N.W.2d 624, 626 (Minn. 1976), *appeal dismissed* 429 U.S. 803 (1976).

102. *See* State Board of Health v. City of Brainerd, No. 38183, Respondents' Answer, part VII, plea in avoidance, filed Oct. 31, 1974 (Crow Wing County District Court, Minn.). Judge John Alexander Jameson expressed his warm approbation of such citizen assemblies in his classic TREATISE ON CONSTITUTIONAL CONVENTIONS 4-5 (4th ed. 1887, reprint 1972).

103. *See* City of Brainerd, Respondent's Answer, part VIII, plea in avoidance and demurrer, filed Oct. 31, 1974.

ordering city officers to implement the statute.[104] But there was a compelling dissent that speaks to the future.[105]

If it can be established "with reasonable certainty" that fluoridation is dangerous to human health, and has caused massive injury to the health of the American people, two very important legal consequences should ultimately follow: (1) the standard of unconstitutionality set forth in *Jacobson* and *Paduano* will have been met, and fluoridation will be unlawful throughout the United States; and (2) the wisdom of a broader constitutional principle of health freedom, envisioned by the majority in *Forest Hill* and the dissent in *Brainerd*, will then be evident, and its eventual judicial recognition as a blessing of liberty may be anticipated for our children, grandchildren, and great grandchildren.

VI. THE EPIDEMIOLOGICAL EVIDENCE

The question now to be addressed is whether, in keeping with *Jacobson* and *Paduano*, it can be proved with "reasonable certainty" in judicial proceedings that fluoridation is dangerous to public health by causing cancer and other ailments in man. In assessing trends in human cancer, we have two main sources of information which can be used as evidence.

Laboratory studies enable us to view a disease at the molecular and cellular levels, and to consider reactions in living plants, insects and animals. The advantage of laboratory studies is that precise experimental conditions can be designed and implemented to control for known and unknown variables, which is critical in the identification of causal operations in the empirical sciences.[106] Whatever legitimate doubt may once have been voiced on the subject, it is now abundantly clear that a significant body of laboratory research reveals carcinogenic potential in fluoride artificially introduced in water at 1.0 ppm.[107]

The disadvantage of laboratory studies is that some caution is required in extrapolating results to human beings, and here is where

---

104. *See* Brainerd, 241 N.W.2d at 629-34.

105. *See id.* at 634-35.

106. Sir Francis Bacon expounded this demand of inductive logic in the third, fourteenth, nineteenth, twenty-second, eighty-second, and ninety-ninth aphorisms in Book I of *Novum Organum*. The meaning of these aphorisms is discussed in 3 COPELSTON, A HISTORY OF PHILOSOPHY, pt. II, 112-22 (1963) [hereinafter COPLESTON].

107. *See, e.g.*, Taylor, *supra* note 16; Taylor & Taylor, *supra* note 20; sources cited *supra* note 21.

epidemiology comes into the picture. Epidemiology is the branch of medicine which studies the diseases of man in his actual environment. If the controls in epidemiological surveys are not as precise, the results are more pertinent to human experience. Therefore, both laboratory studies and epidemiological surveys can profitably be considered together, and, when parallels between them become striking, causal relationships between agents in the environment and human disease can be more readily identified and explained.

Hence the question: Has the carcinogenic potential of fluoride observed in laboratory studies been reflected in human experience? The answer, based on very extensive epidemiological data, is certainly in the affirmative.[108] This fact removes the speculative character of objections previously expressed by physicians and other learned persons when the world first hailed fluoride as a wonder of modern science.

The leader in gathering pertinent epidemiological data and organizing it in a usable form was Dr. Dean Burk, who retired in 1974 as the head of the cytochemistry section of the National Cancer Institute (NCI) of the United States.[109] In his time, he was one of the most famous cancer research scientists in the world. He was well read, highly cultured, disarmingly humble, and had a delicious sense of humor. But standing out above every other trait was his ability to view a problem of empirical observation with clear insight and to give reality, as he put in conversation with those who knew him, "the simplest rational expression."[110]

---

108. The most important versions of the epidemiological data here in question, including reference to related laboratory studies, and conventional adjustments for age, race, and sex, are the following: Dean Burk & John Yiamouyiannis, *Fluoridation and Cancer: Age Dependence of Cancer Mortality Related to Artificial Fluoridation*, 10 FLUORIDE 123 (1977) [hereinafter Burk & Yiamouyiannis]; Dean Burk and J. R. Graham, *Lord Jauncey and Justice Flaherty: Opposing Views of the Fluoridation-Cancer Link*, 17 FLUORIDE 63 (1984) [hereinafter Burk & Graham]; Pierre Morin et al., *Les fluorures versus le cancer et les maladies congentales: l'image globale*, GOURVERNEMENT DU QUEBEC, MINISTERE DES AFFAIRES SOCIALES (1984); Pierre Morin et al., *Fluorides, Water Fluoridation, Cancer, and Genetic Diseases*, 12 SCI. & PUB. POL'Y 36 (1985); Rudolf Ziegelbecker, *Zur Frage eines Zusammenhanges zwischen Trinkwasserfluordierung, Krebs, und Leberzirrhose*, 218 GWF WASSER/ABWASSER 111 (1987); Dean Burk et al., *A Current Restatement and Continuing Reappraisal Concerning Demographic Variables in American Time-Trend Studies on Water Fluoridation and Human Cancer*, 61 PROC. PA. ACAD. OF SCI. 138 (1988) [hereinafter Burk, Graham, & Morin].

109. *See* WHO'S WHO IN THE WORLD 1974-1975 161 (2d ed., Marquis Who's Who, Inc., 1975); *National Cancer Program (Part 2), Hearings Before a Subcomm. of the Comm. on Government Operations*, 95th Cong. 471 (1977) [hereinafter *National Cancer Program*].

110. Dr. Burk's capacity to view and characterize phenomenal reality is illustrated in his trademark paper, Dean Burk & Hans Lineweaver, *The Determination of Enzyme Dissociation Constants*, 56 J. AM. CHEM. SOC'Y 658 (1934), which has been one of the most often cited and discussed papers in biochemstry during the twentieth century.

The epidemiological work here in question was done under the direction of Dr. Burk from his retirement until his death in 1988. As with so much of his work before his retirement, he was years ahead of his time.

On December 16, 1975, Congressman James Delaney of New York inserted into the *Congressional Record* data gathered and organized under the direction of Dr. Burk, showing a striking association between fluoridation and cancer.[111] It is important to appreciate the basic data, because it was the principal and decisive focus of the judicial hearings that followed.[112]

The year-by-year average observed cancer death rates of ten large central cities of the United States, which served as the control group and remained unfluoridated from 1940 through 1968, were compared for the years 1940 through 1968 with the year-by-year average observed cancer death rates of ten large central cities of the United States which served as the experimental group and remained unfluoridated from 1940 through 1951, but fluoridated between 1952 and 1956, and remained fluoridated through 1968 and thereafter.[113] The experiment came to an end in 1968 because fluoridation was introduced in the control cities step-by-step from and after 1969. The necessary data are available for all years except for 1951 and 1952.

The central cities in question are all very large, comparable in size, and spread out across the whole country. In the control group were: Los Angeles; Boston; New Orleans; Seattle; Cincinnati; Atlanta; Kansas City (Missouri); Columbus (Ohio); Newark; and Portland.[114] In the experimental group were: Chicago; Philadelphia; Baltimore; Cleveland; Washington D.C.; Milwaukee; St. Louis; San Francisco; Pittsburgh; and Buffalo.[115]

Roughly speaking, the comparison is between about seven million people in the ten control cities and about eleven million people in the ten experimental cities over about thirty years.[116]

---

111. *See* 121 CONG. REC. 40773-75 (1975).

112. The technical particulars of the selection, derivation, and arrangement of the basic data are precisely described in the method section of Burk & Yiamouyiannis, *supra* note 108, at 103-05, and Burk, Graham, & Morin, *supra* note 108, at 138-39.

113. *See* Burk & Yiamouyiannis, *supra* note 108, at 104; Burk, Graham, & Morin, *supra* note 108, at 138.

114. *See* Burk & Yiamouyiannis, *supra* note 108, at 104; Burk, Graham, & Morin, *supra* note 108, at 138.

115. *See* Burk & Yiamouyiannis, *supra* note 108, at 104; Burk, Graham, & Morin, *supra* note 108, at 138.

116. *See* Burk, Graham, & Morin, *supra* note 108, at 139.

There has hardly ever been a published epidemiological study using so much data, arranged in such powerful experimental design.

The basic data can be expressed as unweighted averages (giving each city equal weight, regardless of size) and as weighted averages (giving each city weight according to size). All cancer death rates here discussed are expressed as so many cancer deaths per 100,000 persons.

The basic data are given in detail in the appendix of this article.[117] For the sake of convenience an observed or crude cancer death rate for all sites in an entire population will be designated as CDRo. It does not matter in this case whether unweighted or weighted averages are used. The pattern is numerically and visibly the same, and the differences emerging from mathematical analysis of the figures for the two types of averages are trivial. Either way the possibility of chance occurrence is far less that 1 in 1000. The weighted averages will be used here because weighted averages have been used by all critics of Dr. Burk's work, and Dr. Burk frequently used weighted averages himself.

The data are arranged in standard experimental design, comparing like with like along a base line from 1940-50 in which cancer death rates grew equally, then continuing the comparison after fluoridation was introduced in the experimental cities. It was after fluoridation began that there was a pronounced acceleration in cancer mortality in the experimental group (+F) as compared with the control group (-F). The resulting association between fluoridation and cancer can be conveniently quantified by linear regression[118] analysis for the data for 1940-50, also for 1953-68 then extending the resulting lines to achieve values for 1950 and 1970:[119]

---

117. The figures and tables set forth in the appendix are taken from Burk, Graham, & Morin, *supra* note 108, at 139-40. The basic data can be recapitulated by any informed and impartial investigator drawing from census figures and vital statistics published by the government of the United States.

118. Linear regression is a standard technique in statistics for characterization of a field of points on a two-dimensional graph as a straight line. This line is so drawn that the sum of the squares of the distances of the several points to the line is the lowest possible number. Such line is assumed in the product moment formula for the linear correlation coefficient, designated "r" to express the degree of association between the two axes. By use of related operations, a statistical confidence level, represented by the coefficient "P" can be derived. P determines the extent to which an observed association may or may not have occurred by chance. The subject is discussed in standard textbooks. *See, e.g.*, SIR AUSTIN BRADFORD-HILL, A SHORT TEXTBOOK OF MEDICAL STATISTICS 161-67, 173-80 (10th ed. 1977); MURRAY SPIEGEL, THEORY AND PROBLEMS OF STATISTICS 218-20, 226-28, 244-45, 253-54 (1961).

119. *See* Burk & Graham, *supra* note 108, at 65; Burk, Graham, & Morin, *supra* note 108, at 142-43.

	1940	1950	1950	1970
CDRo(+F)	154.2	181.8	186.3	222.6
CDRo(- F)	153.5	181.3	l83.6	188.8

The size of the association between fluoridation and cancer can be expressed as follows: [(222.6-188.8) – (186.3-183.6)] + [(154.2-153.5) – (181.8-181.3)] or 31.3 excess cancer deaths per 100,000 persons exposed within fifteen to twenty years after fluoridation began in the experimental group of cities. If this figure is multiplied against 130 million Americans who have been drinking fluoridated water over the past fifteen to twenty years or more, an excess of over 40,000 cancer deaths in the United States every year is attributable to fluoridation.

Not long after the foregoing figures were first called to the public's attention, Dr. Burk was called to testify before Congress on April 6, 1976. And testify he did:

> Oliver Wendell Holmes Sr., M.D., of Civil War medical fame, and professor of anatomy at Harvard University, in 1843 and 1855 described then prevailing treatment of puerperal fever in lying-in hospitals as criminal manslaughter. It was only manslaughter, however, not murder because the physicians of that day did not have, and could not have had a sufficiently knowledgeable idea of the bacteriological basis of the doctor-nurse-patient transmission of the disease until the work of Pastuer and Lister decades later.
>
> The scientific and medical status of artificial fluoridation or public water supplies has now advanced to the stage of the possibility of socially imposed mass murder on an unexpectedly large scale involving tens of thousands of cancer deaths of Americans annually.[120]

The shock resulting from this firm statement by a world-renowned cancer research scientist evoked an emergency response from the USPHS. Needles to say, the USPHS did not admit that they had exposed the American people to an environmental hazard which produced "tens of thousands of cancer deaths of Americans annually." As night follows day, they claimed that Dr. Burk had failed to take elementary precautions.[121]

---

120. *Departments of Labor and Health, Education, and Welfare Appropriations for 1977 (Part 7), Hearings Before a Subcomm. of the Comm. on Appropriations*, 94th Cong. 1063-64 (1976) (statement of Dr. Burk).

121. This protest first appeared in a letter of February 6, 1976, from Dr. Donald Frederickson, Director of the National Institutes of Health, to Congressman James Delaney of New York. This letter has not been officially published, but the particulars are set forth in the

Their pretext was that he and his associates had not adjusted the basic data for age, race and sex, and that, when such adjustments were done, there was no association between fluoridation and cancer.[122] Their claim essentially was that, among 18 million people in twenty large cities over thirty years, it so happened that the experimental cities grew older faster just as they were fluoridated, and that this aging occurred precisely to the extent necessary to create the shocking appearance of an association between fluoridation and cancer.[123] This association, they held, was merely an illusion deceiving the ignorant. It sounds far-fetched. It was worse than far-fetched.

It is obligatory to note that Dr. Burk and those working with him adjusted for demographic variables on numerous occasions.[124] Beyond his published scholarship, he repeatedly gave detailed testimony on these questions in public hearings[125] and courts of justice.[126] But his view was that the basic data are best not adjusted in this particular case, because the base line established by the data for 1940 through 1950 already controls for all known and unknown variables.[127]

Cancer incidence and mortality are influenced by countless demographic, environmental, dietary, socio-economic, and other factors, some tending to increase, others tending the decrease the extent of the disease. It is known, for example, that older people tend to experience more cancer than younger people, yet good diet and environment can significantly offset the effects of age. Adjustments

---

prepared statement of Dr. Arthur Upton, Director of the NCI, to Congress on October 12, 1977. *See National Cancer Program, supra* note 109 at 104-20.

122. *See id.* at 98-103 (statement of Dr. Guy Newell, Deputy Director of NCI).

123. *See id.* at 80-83 (statement of Dr. Robert Hoover, NCI).

124. Dr. Burk's interest in such adjustments first surfaced at the meeting of the American Society of Biological Chemists in San Fransisco on June 6-10, 1976, where he joined Dr. John Yiamouyiannis in a paper setting forth partial adjustments of the basic data for age and race by the direct method. *See* Dean Burk & John Yiamouyiannis, *Fluoridation of Public Water Supplies and Cancer Death Rates*, 35 FED. PROC. AM. SOC. BIOL. CHEM. 1707, (1976). Dr. Burk's more advanced adjustments of the basic data for demographic variables absorbed twelve years of his life's work and included, among others, articles published by the International Society of Fluoride Research and the Pennsylvania Academy of Science. *See* Burk & Yiamouyiannis, *supra* note 108; Burk & Graham, *supra* note 108; Burk, Graham, & Morin, *supra* note 108. He was the major inspiration of these several articles. His matured views are best expressed in the last, published in 1988 not long before his death.

125. For example, see his formal statement to a hearing panel of the EPA on June 17, 1985, including nineteen tables outlining multiple adjustments by the indirect method for age, race and sex, *reprinted in* NATIONAL FLUORIDATION NEWS, Vol. XXXI, no. 4 (1985).

126. *See* Safe Water Found. of Tex. v. City of Houston, No. 80-52271, Trial Transcript, Jan. 13-14, 1982, at 48-105 (151st Jud. Dist., Tex.)

127. *See id.* at 46-48, 105-07.

for age in particular, and perhaps also for race and sex, may be important in comparing two populations at one point in time, because such adjustments may serve as a control for such demographic variables.[128] Yet a very different situation emerges when, as in the case of the basic data here in question, there is a comparison of trends over time, including a long base line.[129]

There are established principles of inductive logic which are associated historically with William of Ockham[130] and Sir Isaac Newton.[131] They are used in the empirical sciences for the discovery or identification of causes in nature. Given a strong trend or association observed in nature, take the simplest and most fitting explanation as the cause, unless and until the contrary be shown. Likewise, attribute like causes to like effects, unless and until the contrary be shown. Finally, where cause and effect in certain circumstances are fairly ascertained by proper experiment, such cause and effect may be generalized throughout the universe, unless and until the contrary be shown.

Given these principles of natural reason, and given what is known about fluoride, including especially its demonstrated carcinogenic potential,[132] the simplest and most fitting explanation of the basic data is that all cancer-influencing factors counterbalanced each other during the long base line period before 1950; that all these factors continued to counterbalance each other after 1950 except for the one factor known to be new, viz., fluoridation; and that, therefore, the entire observed association between fluoridation and cancer in the basic data, i.e., 31.3 excess CDs/100,000 after 15-20 years of exposure, is attributable to fluoridation as the cause.[133] We can then generalize by saying that artificial fluoridation of public water supplies causes an immense amount of cancer in the United

---

128. *See, e.g.*, Burk & Graham, *supra* note 108, at 65; Burk, Graham, & Morin, *supra* note 108, at 139-40.

129. *See, e.g.*, Burk & Graham, *supra* note 108, at 65; Burk, Graham, & Morin, *supra* note 108, at 140.

130. Ockham's emphasis on the simplest explanation as the best explanation, often called "Ockham's razor," grew out of his philosophical treatment of universals, relations, causation, and motion. *See* COPLESTON, *supra* note 106, pt. I, at 69-71, 80-81, 83-88.

131. At the beginning of the third book of his PHILOSOPHIAE NATURALIS PRINCIPIA MATHEMATICA, Sir Isaac Newton laid down his "rules of reasoning in natural philosophy"for the identification of causes in phenomenal reality, including the simplicity principle, sometimes called "Ockham's Razor." *See* 5 COPLESTON, A HISTORY OF PHILOSOPHY, pt. I, 162-64 (1964).

132. *See generally* Taylor, *supra* note 16; Taylor & Taylor, *supra* note 20; sources cited *supra* note 21.

133. *See* Burk & Graham, *supra* note 108, at 65; Burk, Graham, & Morin, *supra* note 108, at 139-40.

States, "involving tens of thousands of cancer deaths of Americans annually."

Adjustments for age, race, and sex are here meant to account for demographic factors which have already been addressed by the base line. Such adjustments will therefore tend to control more than once for the same factors and so, in this context, will tend to understate reality. Changes in the demographic composition of the control and experimental cities have in some degree been counteracted by other factors, and the adjusted figures will not reflect this counteracting effect. So again, adjustments will tend to understate reality.

Dr. Burk respected conventional opinion, but he did not adore it. And since conventional opinion demands adjustments for age, race, and sex, not because he thought they clarified the meaning of the basic data, he cheerfully went along. It is ironic that the scientist who thought these adjustments least useful did more than all others to assure that they were properly done. His guiding principle in dealing with the subject was that, if adjustments were to be executed, they should rest upon standard methods, and be carried out as comprehensively and thoroughly as possible, otherwise not at all.

It is no less ironic that the attack against his epidemiological work was spearheaded by the National Cancer Institute which he had served with such distinction before his retirement. The confrontation initially developed in hearings on September 21 and October 12, 1977, in Congress.[134]

In these hearings, the National Cancer Institute came forth with its objections in a definitive, 17-page document.[135] It was presented under the signature of the director Dr. Arthur Upton, and introduced in committee by the deputy director Dr. Guy Newell. This "Upton Statement" was then and still is the official position of the government of the United States. It is reputed to be the irrefutable answer to the thesis of Dr. Burk and his colleagues. The scientific debate since then has turned upon the Upton Statement, which lays down a characteristic adjustment of the basic data for age, race, and sex by the indirect method, an orthodox procedure for this purpose.[136]

In this procedure, we ordinarily compare two populations at a certain point in time in terms of the ratio of the observed cancer death rate (which we have called CDRo) to the "index" or

---

134. The key contributions of historic significance on both sides are reprinted in *National Cancer Program*, *supra* note 109, at 3-60, 75-83, 98-140, 181-212, 219-30, 305-18 (1977).

135. *See id.* at 104-20.

136. *See* BRADFORD-HILL, *supra* note 118, at 190-96.

"expected" cancer death rate (which we shall call CDRe) of each population.

In deriving an "expected" CDR, we ascertain from census figures the number of persons in each demographic category of the observed populations. In addressing Dr. Burk's basic data, the staff at NCI used forty such categories, viz., age groups 0-4, 5-14, 15-24, 25-34, 35-44, 45-54, 55-64, 65-74, 75-84, and 85+, each divided into white male, white female, nonwhite male, and nonwhite female.

We must then select a "standard population," drawn from census figures and vital statistics for a certain territory and year: this standard population really consists of a set of known cancer death rates for each category in the population. The choice of this standard population requires some judgment. The staff at NCI selected the United States in 1950,[137] which is not, in our view, an unreasonable choice, because it represents a fair estimate of what cancer experience should be, category by category, in the absence of anything tending to make cancer deaths higher or lower than usual.

For each population compared, the number of persons in each category is multiplied by the corresponding rate in the standard population. Expected cancer deaths so determined are added up, then divided by the total population, and reduced to a common denominator of 100,000. The resulting "expected" CDR will be what may be anticipated for the population in view of its demographic composition.

The fraction CDRo/CDRe is called a standardized mortality ratio or SMR. If based on good judgment, it will indicate the extent to which the observed cancer death rate of a given population is higher or lower than what should be expected under normal circumstances in view of its demographic structure.

The Upton Statement sets forth an adjustment of the basic data expressed in weighted averages. The SMRs are as follows:[138]

	1950	1970	Change
CDRo/CDRe (+F)	1.23	1.24	+.0l
CDRo/CDRe (-F)	1.15	1.l7	+.02

Using these figures, the NCI asked Congress to believe that, relative to what may be expected in light of the age structure of the two

137. *See National Cancer Program, supra* note 109, at 112, 224.
138. *See National Cancer Program*, *supra* note 109, at 118.

groups of cities observed, cancer mortality actually grew 1% faster in the unfluoridated cities than in the fluoridated cities.[139]

Dr. Burk and his colleagues had a remarkable answer:[140] The available and pertinent data for the years after 1950 were 1953-1968. Without the trends in these years, nobody would suspect that there is a causal relationship between fluoridation and cancer. In its adjustment, the NCI considered l950 before fluoridation began in the experimental cities, and 1970 after fluoridation had already been initiated in the control cities, and did not consider the years 1953-1968 which were the whole basis of concern. In other words, the NCI simply derived their CDRo values from data reported for 1950 and 1970, and ignored all else, as if 1953-1968 were unimportant.

Having omitted all available and pertinent data in their adjustment, it is not surprising that the NCI came up with the wrong answer. In the same hearings before Congress, it was demonstrated by a colleague of Dr. Burk that, if the adjustment proposed by the NCI is undertaken using all available and pertinent data after 1950, there emerges an impressive association between fluoridation and age-race-sex adjusted cancer mortality.[141]

---

139. *See id.* at 81, 112.

140. *See id.* at 64-65. *See also* Burk & Graham, *supra* note 108, at 67-68; Burk, Graham, & Morin, *supra* note 108, at 142-43.

141. Dr. John Yiamouyiannis executed an adjustment of the basic data, using weighted averages and US-1950 as the standard population, exactly as stipulated in the Upton Statement. He adjusted only for the years after 1950, deriving CDRo values for 1950 and 1970, by linear regression analysis of the CDRo data for 1950 and 1953-1969, and showed an association in terms of CDRo/CDRe = +.042, and in terms of CDRo-CDRe = 12.4 cancer deaths per 100,00 persons exposed within after fifteen to twenty years after the introduction of fluoridation in the experimental cities. *See National Cancer Program*, *supra* note 109, at 64-65. The main objection to this technique came from Dr. David Newell of the Royal Statistical Society in defense of the Upton Statement. He claimed that, because populations between census years and thus denominators in intercensal CDRs must be estimated by linear interpolation, they are not reliable data, and therefore not suitable for linear regression analysis. *See* Aitkenhead v. Borough of West View, No. GD-4585, Trial Transcript, May 8, 1978, at 72, 72A, 73-76 (Allegheny Court of Common Pleas, Pa). This criticism was exploded by none other than Dr. Guy Newell, Deputy Director of the NCI, who supervised preparation of the Upton Statement and introduced it before Congress. Later speaking as a professor of epidemiology at the University of Texas, he stated emphatically that use of linear interpolation to derive denominators in intercensal CDRs is "accepted procedure" in modern applied epidemiology, and, therefore, perfectly reliable. *See* Safe Water Found. of Texas v. City of Houston, No. 80-52271, Trial Transcript, Jan. 26, 1982, at 1648-54 (151st Jud. Dist., Tex.). The correctness of undertaking a linear regression analysis of intercensal CDRs in which the denominators were estimated by linear interpolation was further confirmed by Dr. Hubert Arnold, professor of statistics at the University of California, Davis. *See National Cancer Program, supra* note 109, at 580. The propriety and necessity of such use of interpolated data, based on fundamental principles of inductive logic, is discussed in Burk & Graham, *supra* note 108, at 68-69, and Burk, Graham, & Morin, *supra* note 108, at 143-44.

Dr. Burk developed even more comprehensive adjustments. In doing so, he considered the years before and after 1950, because the observed CDRs portray a change in trends after 1950 and a change from trends before 1950.[142] The data representing 1953-1968 were important, but they were especially important in view of what happened in 1940-1950. The need to consider the years before and after 1950 became clearer from the fact that there were demographic fluctuations before and after 1950: it appeared that these fluctuations both before and after 1950 could materially influence the size the association adjusted for age, race, and sex.

Dr. Burk derived CDRo values for 1940 and 1950 by linear regression analysis of the data for 1940-1950, and for 1950 and 1970 by linear regression analysis of the data for 1953-1968.[143] He derived CDRe values, using US-1950 as the standard population, exactly as stipulated in the Upton statement.[144] He used the SMR or CDRo/CDRe, and also the difference between observed and expected CDRs, i.e., CDRo-CDRe, which is also used by conventional epidemiologists.[145] His results can be summarized as follows:[146]

Cities	1940	1950	1950	1970
CDRo (+F)	154.2	181.8	186.3	222.6
CDRe (+F)	128.1	146.9	146.9	174.7
CDRo/CDRe (+F)	1.204	1.238	1.268	1.274
CDRo-CDRe (+F)	26.1	34.9	39.4	47.9
CDRo (-F)	153.5	181.3	183.6	188.8
CDRe (-F)	140.3	155.5	155.5	166.0
CDRo/CDRe (-F)	1.094	1.166	1.181	1.137
CDRo-CDRe (-F)	13.2	25.8	28.1	22.8

142. On the importance of adjusting both for the period before fluoridation was begun in the experimental cities and the period after, then reaching a combined result, see Burk & Graham, *supra* note 108, at 67, and Burk, Graham, & Morin, *supra* note 108, at 142-43.

143. *See* Burk & Graham, *supra* note 108, at 67; Burk, Graham, & Morin, *supra* note 108, at 142.

144. The particulars of the NCI adjustments are laid out more clearly in the paper of the Royal Statistical Society defending the Upton Statement. *See National Cancer Program*, *supra* note 109, at 224-29.

145. *See id.* at 227-28 (Royal Statistical Society).

146. *See* Burk & Graham, *supra* note 108, at 67-68. Dr. Burk preferred another similar adjustment based on the indirect method, using weighted averages, and US-1940 as the standard population, then combining the impact of changes both before and after 1950 in "time independent" terms. This adjustment yields the conclusion that 69.2% of the observed association between fluoridation and cancer, as reflected in the basic data, cannot be explained by demographic differences. *See* Burk, Graham, & Morin, *supra* note 108, at 142-43.

These figures can be transformed into coefficients which reflect an association between fluoridation and CDRs adjusted for age, race, and sex, as it developed from 1940 to 1970:

The change in CDRo/CDRe = [(1.274-1.137) – (1.268-1.181)] + [(1.204-1.094) – (1.238-1.166)] = +.088. This coefficient means that, relative to what might be expected in light of the demographic structure of the two populations here in question, adjusted cancer mortality grew about 9% faster in the fluoridated cities.

In terms of CDRo-CDRe, fluoridation is associated with [(47.9-22.8) – (39.4-28.1)] + [(26.1-13.2) – (34.9-25.8)] = 17.6 excess cancer deaths per 100,000 persons exposed after 15-20 years. This adjusted figure, multiplied against 130 million Americans now drinking fluoridated water 15-20 years, works out to something on the order of 23,000 excess cancer deaths every year in the United States.

Whether adjusted or unadjusted figures are preferred, the size of the human casualty is so large and tragic that it is almost indecent to quibble over the numbers. Over twenty years have passed, and the casualty has mounted, since the NCI represented to Congress, on the basis of demographic adjustments which left out all available and pertinent data, that there is no association between fluoridation and cancer.

VII. THE JUDICIAL FINDINGS CONDEMNING FLUORIDATION

In the wake of the hearings in Congress just discussed, litigation seeking to resist or restrain further implementation of fluoridation began in several places in the United States. In Ohio it had recently been held that fluoridation was a constitutional exercise of police power.[147]

But in light of the recent publication of the basic data gathered under the direction of Dean Burk, opportunities for a new judicial hearing vastly improved. When such a hearing was sought, the Ohio Supreme Court commented:

> A more difficult question is raised by the claim that fluoride is a carcinogen based on statistics that the cancer death rate has increased in certain cities with fluoridated water, while remaining the same in certain other cities which do not fluoridate. The evidence for this claim has not been tested by litigation and is disputed by other authorities. This evidence has also been submitted to federal agencies and to the Congress. If scientifically proved,

147. *See* City of Canton v. Whitman, 337 N.E.2d 766 (Ohio 1975); City of Cincinnati v. Whitman, 337 N.E. 2d 773 (Ohio 1975).

> these claims could raise legitimate questions as to the constitutionality of fluoridation as a public health measure, and, since these claims are based upon very recent studies, the purposes underlying the principle of res judicata would probably not be served by barring litigation to determine the validity of these claims.[148]

Reading this statement side by side with *Jacobson v. Massachusetts*,[149] and *Paduano v. City of New York*[150], a suit before the judiciary attacking the constitutionality of mandatory fluoridation should succeed if it could be established by a fair preponderance of the evidence that the measure causes or contributes to the cause of cancer in man. But the court held that the judiciary had no original jurisdiction to consider the question, ostensibly because, in Ohio, the power to find the facts was vested by statute in an administrative agency.[151] The holding seems to have been created post hoc to avoid a touchy question.

It would have been easy for the court to rely on respectable authority to the effect that, where a constitutional question is fairly raised, and the outcome depends on facts, especially where personal rights are involved, exhaustion of administrative remedies is not necessary, and the judiciary can take jurisdiction to hear the evidence and decide the controversy on the merits.[152] No further headway was made in Ohio because the plaintiffs too well understood that impartial consideration by the administrative agency, where fluoridation was institutional policy, was as hopeless as an unbiased attitude by the NCI and other institutes in the USPHS.

A. The Pittsburgh Case

However, it was not necessary to wait very long for the opportunity to be fairly heard on the new evidence in Pittsburgh in the case of *Aitkendead v. Borough of West View*.[153] The case was assigned to Judge John Flaherty who has since become the Chief Justice of Pennsylvania. The suit rested on a theory of nuisance, and

---

148. City of Cincinnati *ex rel.* Crotty v. City of Cincinnati, 36l N.E.2d 1340, 1341-42 (Ohio 1977).

149. *See* 197 U.S. 11, 39 (1905).

150. 257 N.Y.S.2d 531, 542 (N.Y. Sup. Ct. 1965)

151. *See* 361 N.E.2d at 1342.

152. *See, e.g.*, United States v. Sisson, 297 F. Supp. 902, 906 (D. Mass. 1969) *appeal dismissed*, 399 U.S. 267 (1970); Bare v. Gorton, 526 P.2d 379, 383-84 (Wash. 1974). This exception to the rule on exhaustion of administrative remedies is ultimately rooted in the "constitutional fact" doctrine in *Ng Fung Ho v. White*, 259 U.S. 276, 282-83 (1922) and *Ohio Valley Water Co. v. Ben Avon Borough*, 253 U.S. 287, 289 (1920).

153. No. GD-4585-78 (Allegheny County Court of Common Pleas, Pa.).

went to hearing on a motion for a preliminary injunction. Expert witnesses from the National Cancer Institute, the National Academy of Sciences, the Royal Statistical Society, and the Royal College of Physicians appeared to oppose the testimony of Dr. Burk and his colleagues, as had occurred in Congress.[154] After many sessions, followed by extensive summations on both sides, Judge Flaherty made his findings on November 16, 1978. He first described the main evidence by stating:

> Over the course of five months, the court held periodic hearings which consisted of extensive expert testimony from as far away as England. At issue was the most recent time trend study of Dr. Burk and Dr. Yiamouyiannis, which compared the cancer mortality of 10 cities which fluoridated their water systems with 10 cities which did not fluoridate over a period of 28 years from 1940 to 1968. The study concluded that there was a significant increase in cancer mortality in the fluoridated cities.[155]

He defined the sole issue of fact as "whether fluoride may be a carcinogen."[156] He then found that "[p]oint by point, every criticism made of the Burk-Yiamouyiannis study was met and explained by the plaintiffs. Often, the point was turned around against defendants. In short, this court was compellingly convinced of the evidence in favor of plaintiffs."[157]

Judge Flaherty entered a preliminary injunction. Since the facts of the case had been fully tried, a motion was prepared for an amended complaint to attack the constitutionality of imposed fluoridation, and for a permanent injunction, based on danger to public health. The motion was about to be filed when raw power showed itself with lightning speed and impressive clout to limit the political

---

154. The most critical dispute in the trial was whether the basic data (set forth in the appendix of this article) should be adjusted for age, race, and sex by the methods proposed by Dr. Dean Burk or Dr. John Yiamouyiannis in *National Cancer Program*, *supra* note 109, at 18-40, 61-72, or by the method proposed in the Upton Statement, *id*. at 104-20, 220-30. The defense of the Upton Statement collapsed when Dr. David Newell of the RSS conceded that he used data only for 1950 and 1970, and considered nothing in between "for the main and simple reason" that he was sent his data from the NCI. *See* Aitkenhead v. Borough of West View, No. GD-4585-78, Trial Transcript, May 9, 1978, at 72-72A, 75-6 (Allegheny County Court of Common Pleas, Pa.). Dr. Marvin Schneiderman of NCI admitted that such intermediate data should be used, but could give no specific alternative to linear regression analysis of intercensal CDRs between 1950 and 1970. *See id.* Trial Transcript, May 9, 1978, at 47-56.

155. *See* No. GD-4585-78, Opinion, Nov. 16, 1978, at 6.

156. *Id.* at 6.

157. *Id.* at 9.

damage.[158] The Chief Judge of the Commonwealth Court of Pennsylvania quickly stayed the preliminary injunction, ignoring the facts judicially found, as if public safety were not an issue.[159]

An administrative agency, which favored fluoridation as institutional policy, quickly and summarily entered "findings" which parroted USPHS propaganda.[160] Another administrative agency, which had a similar institutional policy, then entered an "order" which purported to deny the Borough of West View "permission" to obey Judge Flaherty's injunction.[161] Events thus took bizarre turns to save a sacred cow.

Jurisdiction to enter the findings supporting the preliminary decree of November 16, 1978, was sustained on appeal shortly before Judge Flaherty was elevated to the Supreme Court of Pennsylvania.[162] The Commonwealth Court then held that the cause could go no further before the judiciary under the pretext that exclusive jurisdiction belonged to the administrative agency.[163] That was the end of the case, for all understood the notorious bias of the administrative agency which was not about to admit that it had promoted the dumping of carcinogenic agents into the environment. The appellate decisions left the findings of Judge Flaherty untouched, but departed widely from the traditional rule that, once a court of equity takes jurisdiction over the subject matter of a suit, such jurisdiction continues until the final decree, even though a basis for legal or administrative jurisdiction might later appear.[164]

As the USPHS tried to press-release its way out of the crisis in the United States, the findings of Judge Flaherty became highly influential abroad. In the British House of Lords, the Earl of Yarborough accurately summed up the meaning of the case:

---

158. The odd appellate history of the cause is summarized in *Aitkenhead v. West View*, 442 A.2d 364 (Pa. Commw. Ct. 1982), and *Aitkenhead v. West View*, 397 A.2d 878, 878-79 (Pa. Commw. Ct. 1979)

159. *See* 397 A.2d at 879-80.

160. *See* Aitkenhead v. Borough of West View, No. GD-4585-78, Exhibit C (Pa. Dept. of Health, Dec. 21, 1978), Plaintiffs' Motion to Dismiss Preliminary Objections, Feb. 21, 1979 (Allegheny County Court of Common Pleas, Pa.).

161. *See id.* Exhibit A (Pa. Dept. of Env. Res., Jan. 8, 1979), Plaintiffs' Motion to Dismiss Preliminary Objections, Feb. 21, 1979. *See also id.* Order Dismissing Preliminary Objections, May 25, 1979.

162. *See* Aitkenhead, 397 A.2d at 880.

163. *See* Aitkenhead, 442 A.2d at 366.

164. The rule can be traced to Lord Eldon in *Eyre v. Everett*, 2 Russ. 381 (Ch. 1826), and *Adley v. Whitstable*, 17 Ves. Jr. 316 (Ch. 1810). *See also* Gulbenkian v. Gulbenkian, 147 F.2d 173, 176 (2d Cir. 1945); Rosen v. Mayer, 113 N.E. 217 (Mass. 1916).

> Already this evening examples have been quoted of what occurred in America. What I read was rather different from the picture painted this evening. It was my understanding—if the case quoted was the case in Allegheny [County] in Pennsylvania—that it was found proven that fluoride was a danger to health. I know that there was some legal wrangle about jurisdiction but I thought, on the facts presented by a number of experts, that that was the finding and that the facts had not been challenged but merely the jurisdiction of the court.[165]

So important was the meaning of this case that it also attracted the attention of an investigative commission of the Environment Ministry of Quebec, chaired by Dr. Benoît Bundock who had been the principal medical officer for special projects in the Canadian Ministry of Health. The commission had been diligently studying world literature on fluoridation for over a year when Judge Flaherty returned his findings. They obtained the entire record of the proceedings in Pittsburgh.

Dr. Bundock and his colleagues returned a comprehensive report on November 30, 1979, acknowledging the laboratory studies of Dr. Taylor and the basic data of Dr. Burk, specifically concurred with the findings of Judge Flaherty, and recommended executive suspension of all efforts to enforce the mandatory fluoridation law of Quebec.[166] This recommendation was accepted, and the moratorium has now continued almost twenty years through no less than six governments both pequist and liberal. So well regarded is this report that a standard ecology textbook, widely used in the secondary schools of Quebec, forthrightly acknowledges that fluoride in drinking water, as introduced through artificial fluoridation of public water supplies, is an environmental pollutant which causes cancer in man.[167]

B. The Alton Case

One important early case sustaining the constitutionality of imposed fluoridation on sweeping notions of police power came out

---

165. 402 PARL. DEB. H.L. (5th ser.) 1446-50 (1979). Another important contribution on the same occasion, including learned discussion on the epidemiological work of Dr. Dean Burk, came from the Deputy Speaker, Lord Douglas of Barloch. *See id.* at 1461-68. See also the recent and informed speeches by the Earl Baldwin of Bewdley in 593 PARL. DEB. H. L. (5th ser.) 1394-99, 1427-29 (1998).

166. *See* Jean-Benoît Bundock et al., *Les fluorures, la fluoruration, et la qualité de l'environnement*, MINISTERE DE L'ENVIRONNEMENT, GOUVERNEMENT DU QUEBEC, at 1-2, 103-04, 107-08, 116-17, 197-200 (1979).

167. *See* JACQUES VIEL ET PAUL DARVEAU, POUR UNE PENSEE ECOLOGIQUE 35 (1984).

of the Illinois Supreme Court.[168] Some years later a suit was brought to enjoin fluoridation on allegations of new evidence not previously considered. The complaint was dismissed on demurrer, but the Appellate Court of Illinois held that, taking the facts alleged as true, res judicata did not bar the suit, because res judicata cannot bar reconsideration of an issue on the basis of evidence which did not exist when the judgment was initially entered.[169] The remand occurred in 1972, and the case floundered in legal horseplay in the circuit court until a trial was forced eight years later in Alton, where Lincoln and Douglas had debated the Dred Scott case before the Civil War.

Illinois Pure Water Committee v. Director of Public Health[170] was tried from April through June 1980 before Judge Ronald Niemann. It was a case of uncommon ferocity with endless dilatory motions and preposterous contentions by the State, causing the trial to move at a snail's pace.

Judge Niemann endured the experience with almost inhuman patience. He had a highly skeptical attitude about the testimony offered on behalf of the plaintiffs and he reacted to the large numbers generated by the basic data with astonishment and disbelief. He discounted much of what he heard, but at length was satisfied that the plaintiffs had at least made a prima facie case of danger to public safety.[171]

Judge Niemann turned to the State and asked it to account for the association between fluoridation and cancer reflected by the basic data.[172] It should be kept in mind that Chicago is the home of the ADA which has at its command every expert in the world to support fluoridation as a public health measure. Even so, no world class scientists appeared to defend fluoridation as in the hearings before Congress and the trial in Pittsburgh.[173]

---

168. *See* Schuringa v. City of Chicago, 198 N.E.2d 326 (Ill. 1964).

169. *See* Illionois Pure Water Comm. v. Yoder, 286 N.E.2d 155, 157-58 (Ill. App. Ct. 1972).

170. *See* No. 68-E-128 (Madison County Circuit Court, Ill.). The full record of the proceedings is not available to us, but the final decree entered by Judge Nieman on February 24, 1982, is fairly detailed in describing the procedural history and the scientific evidence presented on both sides. Moreover, the summations of the evidence and the legal arguments on both sides, only slightly abridged, have been conveniently and accurately published by the National Health Action Committee in 2 HEALTH ACTION, NO. 11-12 (1981) [hereinafter HEALTH ACTION].

171. *See* Illinois Pure Water Comm'n v. Dir. of Pub. Health, No. 68-E-128, Final Decree, Feb. 24, 1982, at 9-10, 20-1, 29 (Madison County Circuit Court, Ill.).

172. *See id.* at 10, 29, 33.

173. *See id.* at 10.

A state-hired epidemiologist went so far as to claim that Dr. Burk's work was invalid because the basic data linking fluoridation with cancer had been selected and organized to meet the requirements of experimental design. In other words, he condemned the comparison of like with like before introducing fluoridation in the experimental cities, then observing the subsequent difference in cancer mortality between the two groups invalidated the data. Instead, he said, it was statistically necessary to select fluoridated and unfluoridated cities of the country at random,[174] which, of course, would have assured no control for known and unknown variables.

The same epidemiologist spoke of the need for adjustments for age, race, and sex, yet the plaintiffs' case in chief was full of detailed demographic adjustments of the basic data by the direct and indirect methods.[175] A large box of original data, rows of government publications, and a thick bundle of sheets of calculations were brought into the courtroom for inspection. The same epidemiologist made generalized claims that his adjustments wiped away any association between fluoridation and cancer, yet he conspicuously offered no specific figures or documented calculations in support of his projections.[176]

"What causes cancer?" asked the attorney general of Illinois in his summation, "Apparently, nobody knows."[177] Judge Niemann pondered the case for almost two years. On February 24, 1982, he entered judgment. He thus stated the law:

> The presumption of the validity of legislation is overcome when the plaintiff makes a prima facie case. The traditional concept of burden of proof resting on the plaintiff, once met, shifts to the government to justify its intrusion into the life and health of the individual. When the State is involved, the traditional view is that the 'King can do no wrong.' Although the King must constantly act for his subjects, certainly he has been wrong a time or two.[178]

Judge Niemann specifically found, "[This legislation] exposes the public to the risk, uncertain in its scope, of unhealthy side effects of artificial fluoridation of public water supplies, is unreasonable, and

---

174. *See* HEALTH ACTION, *supra* note 170, 16-19 (Plaintiffs' Summation), and 53-54 (Defendant's Summation).

175. *See id.* at 20-26 (Plaintiffs' Summation).

176. *See id.* at 56-58 (Defendant's Summation).

177. *Id.* at 62 (Defendant's conclusion in final argument).

178. Illinois Pure Water Comm. v. Director of Pub. Health, No. 68-E-128, Final Decree, Feb. 24, 1982, at 29 (Madison County Circuit Court, Ill.).

[is] a violation of the due process clause of the Illinois Constitution of 1970."[179] He added with disappointment, "This record is barren of any credible and reputable scientific epidemiological studies and/or analysis of statistical data which would support the Illinois Legislature's determination that fluoridation of public water supplies is both a safe and effective means of promoting public health."[180] Accordingly, Judge Niemann entered a permanent injunction enjoining the State and its subdivisions from further implementation of fluoridation in Illinois.[181]

A direct appeal was immediately taken to the Illinois Supreme Court. Like lightning, the injunction was stayed without any consideration of the evidence, as if power, and not public health, were the name of the game.[182] As night follows day, the Illinois Supreme Court reversed the judgment of the circuit court citing broad notions of police power.[183] Particularly offensive about the opinion were numerous petty and vindictive comments made against the plaintiffs' witnesses,[184] harmful to the dignity of the bench.

There was also dissimulation regarding the record, as may be illustrated. Judge Niemann had specifically found that the statute was "unreasonable," and therefore unconstitutional, because a prima facie case had been made that fluoridation exposes the population to a tangible risk, albeit uncertain in extent, of unhealthy side effects, and that no "credible and reputable" evidence had been given to justify the intrusion.[185] Yet the Illinois Supreme Court attempted to characterize Judge Niemann's position to be "not that the risk was so great that fluoridation was unreasonable, but that the question was shown to be debatable. Under these circumstances the plaintiffs have failed to show an unreasonable exercise of the police power."[186]

C. The Houston Case

A third case arose in the Lone Star State, entitled *Safe Water Foundation of Texas v. City of Houston*.[187] The case brought to trial in January 1982, before Judge Anthony Farris. The petition prayed for a

---

179. *Id.* at 32.
180. *Id.* at 33.
181. *See id.* at 44.
182. *See* Illinois Pure Water Comm. v. Director of Pub. Health, 470 N.E.2d 988-89 (Ill. 1984).
183. *See id.* at 991-92.
184. *See id.* at 989-90
185. *See id.* No. 68-E-128, Final Decree, Feb. 24, 1982, at 29, 32, 33.
186. 470 N.E.2d at 992.
187. No. 80-52271 (151st Jud. Dist., Tex.).

declaratory judgment that a recently enacted city ordinance imposing fluoridation in Houston was unconstitutional, and it sought an injunction prohibiting implementation of the ordinance within the municipality.[188]

The trial before Judge Farris moved at an energetic pace, not atypical of judicial proceedings in Texas. It was distinguished by polished testimony on both sides. The best available witnesses from several universities defended fluoridation. Cross-examination was crisp and businesslike. The rules of evidence were somewhat relaxed[189] so as to permit practical inclusion of more information in less time. The bench firmly managed the proceedings. The trial was efficient, ample, rigorous, and thorough.

Whereas in Pittsburgh and Alton the issue was reduced to whether or not fluoridation induces cancer in man, in Houston a larger range of evidence was considered. These issues included, aside from cancer, whether fluoridation induces genetic damage,[190] intolerant reactions,[191] and chronic toxicity,[192] not to mention other disputed points

Counsel and witnesses for the plaintiffs conceded that a rational controversy exists over the effectiveness and safety of fluoridation.[193] It was so stipulated, because a good measure of knowledge is awareness of both sides of the question. There were a few fanatical pro-fluoridation witnesses who made fabulous claims of Newburgh-Kingston orthodoxy, but they did not do well. Pro-fluoridation

---

188. *See id.* in Second Amended Petition, Dec. 3, 1980, at 6-8.

189. *See id.* Trial Transcript, Jan. 14, 1982, at 280-287. Relying on *Urquhart v. Barnes*, 335 S.W.2d 666, 669 (Tex. Civ. App. 1960), Judge Farris held that learned treatises could be marked, introduced and received to prove their existence and the basis of the opinion offered. This ruling was made during the testimony of Doctor Albert Burgstahler, one of the foremost scholars in the world on fluoride and fluoridation. The impact of Judge Farris' ruling was to promote an excellent record for this kind of case, as illustrated by Dr. Burgstahler's testimony on direct examination. *See* No. 80-52271, Trial Transcript, Jan. 14-15, 1982, at 276-429.

190. *See, e.g.*, No. 80-52271, Trial Transcript, Jan. 18, 1992, at 539-59 (testimony of Dr. Pierre Morin). Dr. Morin testified on the laboratory studies of fluoride and mutagenesis noted by Dyson Rose and John Maurier in *Environmental Fluoride*, NAT'L RES. COUNCIL OF CANADA PUBL. NO. 16081 69-70 (1977), as confirmed by epidemiological data linking fluoride in drinking water and mongoloid births. *See* Ionel Rapaport, *Les opacifications du cristallin mongolisme et cataracte sénile*, 2 REV. ANTHROP. (Paris) 133 (1954); Ionel Rapaport *Contribution a l'étude du mongolisme. Rôle pathologénique du fluor*, 140 BULL. ACAD. NAT'L. MED. (Paris) 529 (1956).

191. *See, e.g.*, No. 80-52271, Trial Transcript, Jan. 19, 1982, at 579-96 (testimony of John Lee, M.D., on the work of Dr. George L. Waldbott in *Fluoridation: A Clinician's Experience*, 73 SO. MED. J. 301 (1980), and his own clinical experience.).

192. *See* No. 80-52271, Trial Transcript, Jan. 19, 1992, at 609-14 (testimony of Dr. Lee on the strong association between the fluoride content of public water supplies and dental fluorosis, described by Rudolf Ziegelbecker, *Natürlicher Fluoridgehalt des Trinkwassers und Karies*, 122 GWF WASSER/ABWASSER 495 (1981)).

193. *See* No. 80-52271, Plaintiffs' Summation, Feb. 4, 1982, at 4.

witnesses who displayed broader understanding were more appreciated.

At the conclusion of the trial, plaintiffs argued that they proved serious injury to the public health by a fair preponderance of the evidence, and that for this reason they were entitled to an injunction.[194] On the other side, counsel argued that there was a reasonable debate, and that for this reason the City was entitled to a judgment of dismissal.[195]

On February 22, 1982, Judge Farris denied the plaintiff's motion for permanent injunction, holding that the plaintiffs "had the burden to introduce overwhelming evidence in this case. Plaintiffs had to prove that no rational relationship exists between fluoridation of city surface water and the public health. Plaintiffs had to prove that no controversial facts exist."[196]

The plaintiffs immediately made a motion for new trial or amended order.[197] The argument on the motion, heard on April 19, 1982, centered on the burden of proof necessary to prevail. Judge Farris stated from the bench that the plaintiffs had proven harm by a fair preponderance of the evidence.[198] "If this were your run-of-the-mill litigation asking for injunctive relief," he said, "plaintiffs would have prevailed, but this is not the run-of-the-mill case."[199]

The question was one of burden of proof, a pure question of law. It was agreed by the court and counsel that "[t]hat is why we have appellate courts."[200] Counsel for the plaintiffs then asked for findings based on a fair preponderance of the evidence to prepare the record for appeal.[201] The court acceded to the suggestion, asking for proposals from both sides.[202] On May 24, 1982, Judge Farris entered his findings which were about as comprehensive and

---

194. *See id.* Plaintiffs' Summation, Feb. 4, 1982, at 4, 25.

195. *See id.* Defendant's Summation, Feb. 4, 1982, at 12-13.

196. *See id.* Opinion, Feb. 22, 1982, at 8. Judge Farris relied on *City of Houston v. Johnny Frank's Auto Parts Co.*, 480 S.W.2d 774 (Tex. Civ. App. 1972), which rests squarely of *Ferguson v. Skrupa*, 372 U.S. 726 (1963).

197. *See* No. 80-52271, Plaintiffs' Amended Motion for New Trial, Etc., April 14, 1982, at 1 (stating that, while the evidence at trial "did not eliminate the existence of a rational controversy, and was not intended or claimed to do so, the preponderance of the said evidence tended to show" that fluoridation causes or contributes to the cause of "cancer, genetic damage, intolerant reactions, and chronic toxicity, including dental mottling in man.").

198. *See id.* Hearing Transcript, Apr. 19, 1982, at 11.

199. *See id.* at 10.

200. *See id.* at 12.

201. *See id.* at 12-13.

202. *See id.* at 13-14.

desirable as any judicial findings have been in environmental law.[203] The court found:

> [That] the artificial fluoridation of public water supplies, such as is contemplated by [Houston] City Ordinance No. 80-2530 may cause or contribute to the cause of cancer, genetic damage, intolerant reactions, and chronic toxicity, including dental mottling, in man; that the said artificial fluoridation may aggravate malnutrition and existing illnesses in man; and that the value of said artificial fluoridation is in some doubt as to the reduction of tooth decay in man.[204]

This assessment of the facts, based on a fair preponderance of the evidence, was a reasonable and impartial picture of scientific reality as it was then understood.

If the municipal government of Houston had acted rationally in the face of these findings of fact, effectively a declaratory judgment on the weight of the evidence, the city council would have noted the danger, repealed the ordinance in the public interest, and perhaps established an investigative commission as had occurred in Quebec. But a city councilwoman, smiling broadly as cameras flashed, started the machinery which injected into public drinking water a substance judicially found, after an intensive and disciplined trial of the facts, to be carcinogenic and mutagenic.[205]

An appeal was taken, based mainly on a venerable old case decided by the Texas Supreme Court which held that, where exercise of police power rests on assumed facts, those facts may be judicially examined and, if upon such inquiry it fairly appears that the means chosen are disproportionate to the end desired, the ordinance should be declared unconstitutional.[206] This principle is typical of the best natural law jurisprudence which prevailed earlier in the twentieth century. Given the findings of Judge Farris, fluoridation was unconstitutional under this principle, because endangering the public with cancer and other ailments cannot be justified by a dubious possibility of reducing tooth decay. The Texas Court of Appeals

---

203. The findings of Judge Farris, based on a fair preponderance of the evidence, are similar to the findings of Judge Miles Lord in *United States v. Reserve Mining Co.*, 380 F. Supp 11, 15-17 (D. Minn. 1974), and *United States v. Reserve Mining Co.*, 417 F. Supp 789 (D. Minn. 1976), affirmed 543 F. 2d 1210 (8th Cir. 1976). The dumping of taconite tailings was terminated on the principle that, where substantial evidence shows harm to human health, a question of public health should be judicially determined by resolving doubt against the introduction of foreign material into environment.

204. *See* No. 80-52271, Findings of Fact, May 24, 1982, at 1-2.

205. *See id.* at 1-2.

206. *See* Houston & T. C. Ry. v. City of Dallas, 84 S.W. 648, 653-54 (Tex. 1905).

expressly found that a fair preponderance of the evidence showed "the injection of fluoride into the City's water system would be harmful,"[207] but, with the full support of higher tribunals, held that such proof of harm was not enough to arrest an exercise of police power.[208]

Therefore, it is evident that, at least for the time being, we are saddled with Hugo Black's positivist and anti-libertarian doctrines, and some years must pass before our judiciary sees the need for a change of course. Years must pass as surely as years had to pass from the death of Sir John Elliot following his arrest in 1630 for a speech in Parliament, and the grand day in 1667 when the House of Lords reversed the judgment of the King's Bench which denied Sir John release on a writ of habeas corpus.[209] Meanwhile, the findings of Judge Flaherty, Judge Niemann, and Judge Farris have since been quoted to legislative bodies from Montreal to Honolulu and from London to Canberra. Not always, but occasionally legislators have listened.

There has been other interesting political fallout from these judicial findings. On August 9-10, 1983, a strategic conference of pro-fluoridation activists, most of them deeply involved in ADA and USPHS politics, took place at the University of Michigan.[210]

The proceedings began with a presentation by a special counsel of the American Dental Association.[211] The gentleman was introduced as a member of the rules committee of the Illinois Supreme Court, so it is clear that he was a powerful insider.[212] He told the audience that it was he who had secured the stay of the injunction from the Illinois Supreme Court issued by Judge Niemann.[213]

Counsel did not clearly inform his listeners that, from 1978 through 1982, three American judges in courts of superior jurisdiction had fully heard evidence on both sides: the first of these judges, by then a supreme court justice of eminent standing, entered findings undisturbed on appeal, saying he was compellingly convinced

---

207. Safe Water Found. of Tex. v. City of Houston, 661 S.W.2d 190, 192 (Tex. App. 1983), *writ ref'd n.r.e.* (Tex. 1984), *appeal dismissed* 469 U.S. 801 (1984).

208. *See id.* at 192-93.

209. *See, e.g.*, HENRY HALLAM, CONSTITUTIONAL HISTORY OF ENGLAND 299-300 (Garland Pub. 1978) (1846).

210. The proceedings were recorded verbatim in FLUORIDATION: LITIGATION & CHANGING PUBLIC POLICY, (Michael W. Easley et al. eds. 1983) [hereinafter CHANGING PUBLIC POLICY].

211. *See id.* at 3-11.

212. *See id.* at 3.

213. *See id.* at 5-6; *see also* Illinois Pure Water Comm., Inc. v. Director of Pub. Health, 470 N.E.2d. 988, 989 (Ill. 1984).

of the danger of cancer; the second entered findings of no credible or reputable evidence to redeem fluoridation; and the third had entered comprehensive findings based on a preponderance of the evidence, expressly sustained on appeal, condemning fluoridation as posing a tangible danger of cancer and a good many other human diseases, while expressing doubt even of its capacity to reduce tooth decay.

Another speaker at the University of Michigan announced a significant change of litigation policy to perpetuate and expand fluoridation in future years. Whereas in earlier years it had been standard practice to invite trials, as had occurred in a number of earlier fluoridation cases, a new policy, following the trials in Pittsburgh, Alton, and Houston, was announced: "By avoiding a trial on the merits of fluoridation, we prevent the subjection of what we feel is a purely scientific issue to scrutiny by a judge who is likely not to have proper scientific training with which to make an objective ruling."[214] To recapitulate this interesting phase of legal and scientific history, in the trials in Pittsburgh, Alton, and Houston, one trial judge after another heard the evidence and found that fluoridation appears to be injurious to human health. Therefore, the new ADA-USPHS policy is to avoid, by all means, a trial on the merits.

This policy has been remarkably successful for over fifteen years. No case has ever gotten to trial. No pro-fluoridation witness has been cross-examined in court. Sales pitches continue before legislative bodies with a fair degree of success in the sense that mandatory or imposed fluoridation has considerably expanded. In legislative committees, witnesses usually cannot be effectively held to account for what they say.

We understand that the judicial process is far from perfect. But, now, the "purely scientific issue" mentioned at the University of Michigan -- and fluoridation is a purely scientific issue until legally imposed -- is tried in legislative proceedings by frantic political lobbying, maneuvers, ambushes, speechifying, applause, horse-trading, buttonholing, demagoguery, infighting, and posturing.

VIII. THE COMING END OF FLUORIDATION

One of the results of the hearings in Congress on September 21 and October 12, 1977, was a suggestion that the National Toxicology Program (NTP) should investigate fluoride.[215] Over twelve years,

---

214. CHANGING PUBLIC POLICY, *supra* note 210, at 84.

215. *See National Cancer Program, supra* note 109, at 319.

the NTP sputtered. At last some news was leaked to the press. On December 28, 1989, the *Medical Tribune* reported on the front page:

> Fluoride appears to have caused bone cancer in rodents in a recently completed National Toxicology Program study, and the chemical is now at risk of being classified as a carcinogen, according to internal documents and statements obtained by the Medical Tribune from the Environmental Protection Agency.[216]

Press fanfare erupted, and the main feature of this media blitz was the impression that there had been a discovery of something entirely new and previously unknown, as if the work of Alfred Taylor, Dean Burk and many others had never been done. Soon, however, the public was assured that all is well.[217]

The "official" evaluation, while leaving much to be desired, gives a very different impression. The authors conceded that, although the numbers were small, the data gathered by the NTP study reveal a statistically significant dose-response trend of osteosarcomas of bone in male rats.[218] Additionally, the authors cited no less than eleven studies published in good journals, showing that fluoride is capable of inducing genetic mutation in mammalian cells and fruit flies, aggravating chromosomal aberrations in animal systems, and causing morphological transformations in Syrian hamster ovary cells.[219]

The article concludes with the sedate comment that "it would appear prudent to re-examine previous animal studies and human epidemiological studies, and perform further studies as needed to evaluate more fully any possible association between exposure to fluorides and the occurrence of osteocarcomas of bone."[220] We join this recommendation, adding that meanwhile artificial fluoridation of public water supplies ought to be halted across the country pending such review of the evidence, as was recommended by Dr. Bundock and his colleagues in Quebec, and that nobody having any direct or indirect interest in the conclusions ought to participate.

The recommendation for reevaluation has not been fulfilled. There are interesting reasons why.

---

216. Joel Griffiths, *Fluoride Linked to Bone Cancer in Fed Study*, 30 MED TRIB., DEC. 28, 1989, 1, 6.

217. *See e.g., Additive approved, Federal study says fluoride no threat*, PITTSBURGH POST-GAZETTE, Feb. 20, 1991, at 1-2.

218. *See* John Bucher et al., *Results and Conclusions of the National Toxicology Program's Rodent Carcinogenicity Studies with Sodium Fluoride*, 48 INT. JOUR. CANCER 733, 734-35 (1991).

219. *See id.* at 736.

220. *Id.*

On May 1, 1990, the acting Director of the Criteria and Standards Division, Office of Drinking Water in the United States Environmental Protection Agency, received a memorandum from Dr. William Marcus, Senior Scientific Advisor in the Criteria and Standards Division.[221] Dr. Marcus reviewed the NTP study and pointed to results suggesting carcinogenic potential of fluoride.[222] He also cited the most recent published version of the epidemiological data gathered and adjusted under the direction of Dr. Burk.[223] Dr. Marcus urgently recommended an independent review by the EPA.[224]

To put it mildly, Dr. Marcus' memorandum did not inspire a warm and friendly response from the management of the EPA. In due course, Dr. Marcus sent his document to the Administrator of the EPA and to his union representative who in turn released it to the press. The public reaction was rather agitated, causing a bureaucrat from the "health effects branch" within the agency to approach Dr. Marcus' supervisor with the suggestion that he memorandum sent "the wrong message to the public."[225] Shortly thereafter, Dr. Marcus was accused of "violent and aberrant behavior" and discharged.[226]

On December 3, 1992, following extended hearings, an administrative law judge found that Dr. Marcus had been fired on false pretexts because of his warnings against artificial fluoridation of public water supplies.[227] The ALJ ordered Dr. Marcus reinstated with back salary, money damages, and attorney's fees,[228] and, on February 7, 1994, the Secretary of Labor affirmed the reinstatement as ordered.

The simple and blunt meaning of this episode is impossible to misunderstand. The scientists, lawyers, and engineers at the national headquarters of the EPA have since used their union for protection against their administrators who, as the case of Dr. Marcus demonstrates, have a political agenda not necessarily in the public interest, and certainly not in the interest of the professionals at EPA

---

221. Dr. Marcus' historic memorandum of May 1, 1990, is a matter of public record. *See* Marcus v. Environmental Protection Agency, No. 92-TSC-5, Complainant's Exhibit 56, mentioned in the Recommended Decision and Order, Dec. 3, 1992, at 5 (U.S. Dep't Labor).

222. *See id.* at 1-3.

223. *See id.* at 3.

224. *See id.* at 4.

225. *Id.* , Recommended Decision and Order, Dec. 3, l992, at 5.

226. *See id.* at 6-9.

227. *See id.* at 25-28.

228. *See id.* at 30-31.

who desire the independence required to act honestly for the general welfare.

Under the protection of their union they have made plain that their administrators may set policy, but that they as professionals refuse to conceal the errors of policy set. The subject of fluoridation has come to their attention. On July 2, 1997, the union members, at a duly called meeting,[229] voted unanimously in support of a resolution that read:

> Our members review of evidence over the last eleven years, including animal and human epidemiology studies, indicate a causal link between fluoride/fluoridation and cancer, genetic damage, neurological impairment, and bone pathology. Of particular concern are recent epidemiology studies linking fluoride exposures to lower I.Q. in children. As professionals who are charged with assessing the safety of drinking water, we conclude that the health and welfare of the public are not served by the addition of this substance to the public water supply.[230]

If artificial fluoridation of public water supplies causes cancer in man, as the published laboratory studies and epidemiological surveys indicate, and as judicial findings confirm, then nobody should be surprised to see that it produces a host of other human ailments. Who should be surprised to learn that dumping a

---

229. At the time of this resolution, scientists, lawyers, and engineers at the national headquarters of EPA were organized in the National Federation of Federal Employees, Local 2050. These professional people are now organized as the National Treasury Employees Union, Chapter 280.

230. This resolution has been released to the press by the professional union at the national headquarters of EPA, but, not surprisingly, the government of the United States has not seen fit to publish the document. We are indebted to Dr. J. William Hirzy at EPA for our copy. Aside form the material cited in this article, the evidence considered in support of this resolution included, on the question of cancer, PERRY COHN, NEW JERSEY DEPARTMENT OF HEALTH, A BRIEF REPORT ON THE ASSOCIATION OF DRINKING WATER FLUORIDATION AND THE INCIDENCE OF OSTEOSARCOMA AMONG WHITE MALES (1992). This epidemiological survey is particularly important because its finding with respect to human males parallels the NTP study which suggests that sodium fluoride induces osteosarcomas in male rats. To the same effect, is John Yiamouyiannis, *Fluoridation and Cancer: The Biology and Epidemiology of Bone and Oral Cancer Related to Fluoridation*, 26 FLUORIDE 83 (1993). Also considered in support of the resolution of July 2, 1997, on the question of bone pathology was Lawrence Riggs et al., *Effect of Fluoride Treatment on the Fracture Rate in Postmenopausal Women with Osteoporosis*, 322 NEW ENG. J. MED. 802 (1990). Taken into account on the question of neurological impairment was Phyllis J. Mullenix et al., *Neurotoxicity of Sodium Fluoride in Rats*, l7 NEUROT. & TERAT. 169 (1995). Since published to the same effect is Julie Varner et al., *Chronic Administration of Aluminum Fluoride or Sodium Fluoride to Rats in Drinking Water: Alterations in Neuronal and Cerebrovascular Integrity*, BRAIN RES. 784 (1998) 284-98. The epidemiological studies on fluoride exposure and the I.Q.'s of children were done in China. They are abstracted in English as X. S. Li et. al., *Effect of Fluoride Exposure on Intelligence in Children*, 28 FLUORIDE 189 (1995), and L.B. Zhao et. al., *Effect of a High Fluoride Water Supply on Children's Intelligence*, 29 FLUORIDE 190 (1996).

carcinogen and mutagen in public drinking water has not only been accompanied by devastating increases in cancer mortality, but may also reduce human intelligence?

The end of fluoridation will take time, but not because time is necessary to develop essential scientific information. We already know enough to appreciate the enormity of the risk. We knew enough many years ago.

But the end will finally arrive, because, as Aristotle said at the beginning of the *Metaphysics*, all men by nature desire to know.[231] Ignorance cannot be perpetuated forever. The necessary legal and scientific reforms will come in the twenty-first century. Our descendants will look back on us, and they will be amazed.

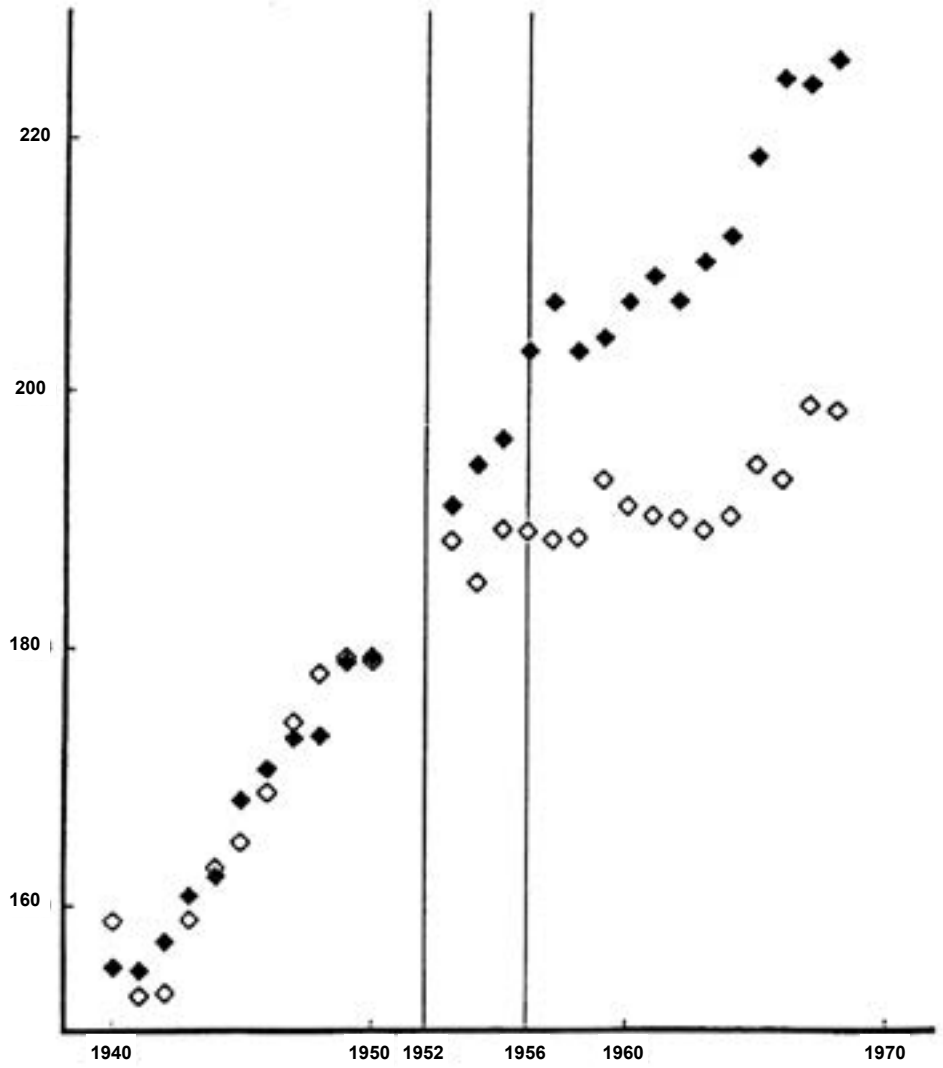
231. *See* BASIC WORKS OF ARISTOTLE 689 (W.D. Ross trans., Richard McKeon ed. 1941).

APPENDIX

TABLE 1. The Basic Data in Unweighted Averages for 1940-1950 and 1953-1968.

Year	CDRo Control Cities (-F)	CDRo Experimental Cities (+F)
1940	158.4	155.5
1941	152.4	155.2
1942	153.9	157.2
1943	159.2	161.6
1944	162.5	162.3
1945	165.6	168.4
1946	168.5	171.6
1947	174.5	172.6
1948	178.0	173.2
1949	179.5	179.4
1950	178.9	179.6
1953	188.2	191.3
1954	185.6	194.1
1955	189.5	196.3
1956	189.1	203.6
1957	188.4	207.1
1958	188.6	203.5
1959	193.0	204.7
1960	191.1	207.0
1961	190.4	209.3
1962	190.2	207.2
1963	189.4	210.9
1964	190.3	212.6
1965	194.3	218.6
1966	193.4	224.8
1967	198.8	224.4
1968	199.4	226.4

FIGURE 1. The Basic Data in Unweighted Averages for 1940-1950 and 1953-1968.[a]

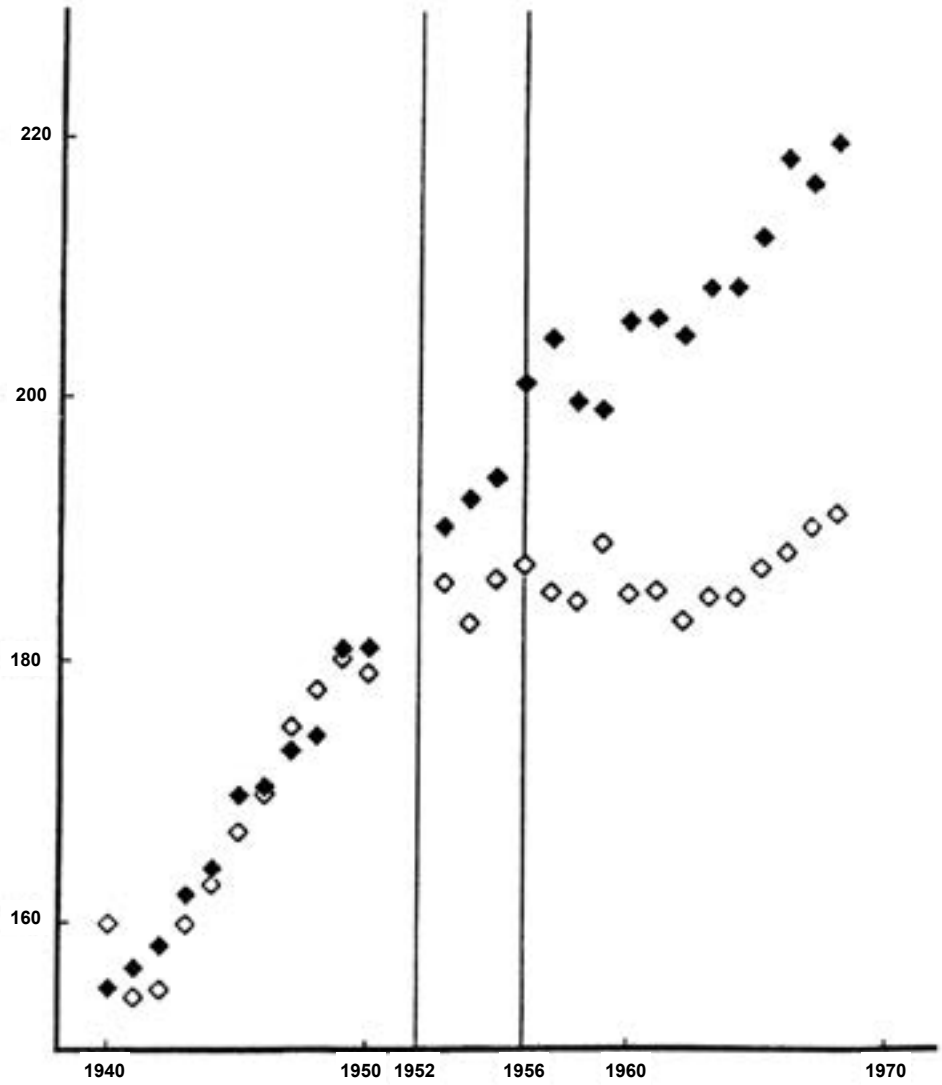


a The vertical axis represents observed cancer death rates per 100,000 (CDRo). The horizontal axis represents years. The white diamonds represent the control (-F) cities. The black diamonds represent the experimental (+F) cities. The vertical lines touching the horizontal axis at 1952 and 1956 represent the period during which fluoridation was started in the experimental cities.

TABLE 2. The Basic Data in Weighted Averages for 1940-1950 and 1953-1968.

Year	CDRo Control Cities (-F)	CDRo Experimental Cities (+F)
1940	159.9	155.6
1941	154.5	156.3
1942	154.7	158.3
1943	159.8	162.4
1944	163.2	164.2
1945	167.0	168.9
1946	169.9	171.8
1947	175.0	173.9
1948	177.8	174.3
1949	180.4	181.1
1950	179.0	180.8
1953	185.9	190.2
1954	182.6	192.3
1955	186.1	193.9
1956	187.6	201.6
1957	185.2	204.5
1958	184.3	199.7
1959	188.8	201.0
1960	185.0	205.8
1961	185.7	206.0
1962	183.8	204.6
1963	184.8	208.6
1964	184.8	208.7
1965	187.0	212.5
1966	188.2	218.5
1967	190.1	218.4
1968	191.1	219.7

FIGURE 2. The Basic Data in Weighted Averages for 1940-1950 and 1953-1968.[b]



b The vertical axis represents observed cancer death rates per 100,000 (CDRo). The horizontal axis represents years. The white diamonds represent the control (-F) cities. The black diamonds represent the experimental (+F) cities. The vertical lines touching the horizontal axis at 1952 and 1956 represent the period during which fluoridation was started in the experimental cities.

NTEU
The National Treasury Employees Union

CHAPTER 280
BEN FRANKLIN STATION
P.O. BOX 7672
WASHINGTON, DC 20044
202-566-2785(V)
202-566-1460(F)
Website www.nteu280.org

STATEMENT OF Dr. J. WILLIAM HIRZY
NATIONAL TREASURY EMPLOYEES UNION CHAPTER 280
BEFORE THE
SUBCOMMITTEE ON WILDLIFE, FISHERIES AND DRINKING WATER
UNITED STATES SENATE
JUNE 29, 2000

Good morning Mr. Chairman and Members of the Subcommittee. I appreciate the opportunity to appear before this Subcommittee to present the views of the union, of which I am a Vice-President, on the subject of fluoridation of public water supplies.

Our union is comprised of and represents the professional employees at the headquarters location of the U. S. Environmental Protection Agency in Washington D.C. Our members include toxicologists, biologists, chemists, engineers, lawyers and others defined by law as "professionals." The work we do includes evaluation of toxicity, exposure and economic information for management's use in formulating public health and environmental protection policy. I am not here as a representative of EPA, but rather as a representative of EPA headquarters professional employees, through their duly elected labor union. The union first got involved in this issue in 1985 as a matter of professional ethics. In 1997 we most recently voted to oppose fluoridation. Our opposition has strengthened since then.

Summary of Recommendations

1) We ask that you order an independent review of a cancer bioassay previously mandated by Congressional committee and subsequently performed by Battelle Memorial Institute with appropriate blinding and instructions that all reviewer's independent determinations be reported to this Committee.

2) We ask that you order that the two waste products of the fertilizer industry that are now used in 90% of fluoridation programs, for which EPA states they are not able to identify any chronic studies, be used in any future toxicity studies, rather than a substitute chemical. Further, since federal agencies are actively advocating that each man woman and child drink, eat and bathe in these chemicals, silicofluorides should be placed at the head of the list for establishing a MCL that complies with the Safe Drinking Water Act. This means that the MCL be protective of the most sensitive of our population, including infants, with an appropriate margin of safety for ingestion over an entire lifetime.

3) We ask that you order an epidemiology study comparing children with dental fluorosis to those not displaying overdose during growth and development years for behavioral and other disorders.

4) We ask that you convene a joint Congressional Committee to give the only substance that is being mandated for ingestion throughout this country the full hearing that it deserves.

National Review of Fluoridation The Subcommittee's hearing today can only begin to get at the issues surrounding the policy of water fluoridation in the United States, a massive experiment that has been run on the American public, without informed consent, for over fifty years. The last Congressional hearings on this subject

were held in 1977. Much knowledge has been gained in the intervening years. It is high time for a national review of this policy by a Joint Select Committee of Congress. New hearings should explore, at minimum, these points:

1) excessive and un-controlled fluoride exposures;
2) altered findings of a cancer bioassay;
3) the results and implications of recent brain effects research;
4) the "protected pollutant" status of fluoride within EPA;
5) the altered recommendations to EPA of a 1983 Surgeon General's Panel on fluoride;
6) the results of a fifty-year experiment on fluoridation in two New York communities;
7) the findings of fact in three landmark lawsuits since 1978;
8) the findings and implications of recent research linking the predominant fluoridation chemical with elevated blood-lead levels in children and anti-social behavior; and
9) changing views among dental researchers on the efficacy of water fluoridation

Fluoride Exposures Are Excessive and Un-controlled According to a study by the National Institute of Dental Research, 66 percent of America's children in fluoridated communities show the visible sign of over-exposure and fluoride toxicity, dental fluorosis (1). That result is from a survey done in the mid-1980's and the figure today is undoubtedly much higher.

Centers for Disease Control and EPA claim that dental fluorosis is only a "cosmetic" effect. God did not create humans with fluorosed teeth. That effect occurs when children ingest more fluoride than their bodies can handle with the metabolic processes we were born with, and their teeth are damaged as a result. And not only their teeth. Children's bones and other tissues, as well as their developing teeth are accumulating too much fluoride. We can see the effect on teeth. Few researchers, if any, are looking for the effects of excessive fluoride exposure on bone and other tissues in American children. What has been reported so far in this connection is disturbing. One example is epidemiological evidence (2a, 2b) showing elevated bone cancer in young men related to consumption of fluoridated drinking water.

Without trying to ascribe a cause and effect relationship beforehand, we do know that American children in large numbers are afflicted with hyperactivity-attention deficit disorder, that autism seems to be on the rise, that bone fractures in young athletes and military personnel are on the rise, that earlier onset of puberty in young women is occurring. There are biologically plausible mechanisms described in peer-reviewed research on fluoride that can link some of these effects to fluoride exposures (e.g. 3,4,5,6). Considering the economic and human costs of these conditions, we believe that Congress should order epidemiology studies that use dental fluorosis as an index of exposure to determine if there are links between such effects and fluoride over-exposure.

In the interim, while this epidemiology is conducted, we believe that a national moratorium on water fluoridation should be instituted. There will be a hue and cry from some quarters, predicting increased dental caries, but Europe has about the same rate of dental caries as the U.S. (7) and most European countries do not fluoridate (8). I am submitting letters from European and Asian authorities on this point. There are studies in the U.S. of localities that have interrupted fluoridation with no discernable increase in dental caries rates (e.g., 9). And people who want the freedom of choice to continue to ingest fluoride can do so by other means.

Cancer Bioassay Findings In 1990, the results of the National Toxicology Program cancer bioassay on sodium fluoride were published (10), the initial findings of which would have ended fluoridation. But a special commission was hastily convened to review the findings, resulting in the salvation of fluoridation through systematic down-grading of the evidence of carcinogenicity. The final, published version of the NTP report says that there is, "equivocal evidence of carcinogenicity in male rats," changed from "clear evidence of carcinogenicity in male rats."

The change prompted Dr. William Marcus, who was then Senior Science Adviser and Toxicologist in the Office of Drinking Water, to blow the whistle about the issue (22), which led to his firing by EPA. Dr. Marcus sued EPA, won his case and was reinstated with back pay, benefits and compensatory damages. I am submitting material from Dr. Marcus to the Subcommittee dealing with the cancer and neurotoxicity risks posed by fluoridation.

We believe the Subcommittee should call for an independent review of the tumor slides from the bioassay, as was called for by Dr. Marcus (22), with the results to be presented in a hearing before a Select Committee of the Congress. The scientists who conducted the original study, the original reviewers of the study, and the "review commission" members should be called, and an explanation given for the changed findings.

Brain Effects Research Since 1994 there have been six publications that link fluoride exposure to direct adverse effects on the brain. Two epidemiology studies from China indicate depression of I.Q. in children (11,12). Another paper (3) shows a link between prenatal exposure of animals to fluoride and subsequent birth of off-spring which are hyperactive throughout life. A 1998 paper shows brain and kidney damage in animals given the "optimal" dosage of fluoride, viz. one part per million (13). And another (14) shows decreased levels of a key substance in the brain that may explain the results in the other paper from that journal. Another publication (5) links fluoride dosing to adverse effects on the brain's pineal gland and pre-mature onset of sexual maturity in animals. Earlier onset of menstruation of girls in fluoridated Newburg, New York has also been reported (6).

Given the national concern over incidence of attention deficit-hyperactivity disorder and autism in our children, we believe that the authors of these studies should be called before a Select Committee, along with those who have critiqued their studies, so the American public and the Congress can understand the implications of this work.

Fluoride as a Protected Pollutant The classic example of EPA's protective treatment of this substance, recognized the world over and in the U.S. before the linguistic de-toxification campaign of the 1940's and 1950's as a major environmental pollutant, is the 1983 statement by EPA's then Deputy Assistant Administrator for Water, Rebecca Hanmer (15), that EPA views the use of hydrofluosilicic acid recovered from the waste stream of phosphate fertilizer manufacture as,

"...an ideal solution to a long standing problem. By recovering by-product fluosilicic acid (sic) from fertilizer manufacturing, water and air pollution are minimized, and water authorities have a low-cost source of fluoride..."

In other words, the solution to pollution is dilution, as long as the pollutant is dumped straight into drinking water systems and not into rivers or the atmosphere. I am submitting a copy of her letter.

Other Federal entities are also protective of fluoride. Congressman Calvert of the House Science Committee has sent letters of inquiry to EPA and other Federal entities on the matter of fluoride, answers to which have not yet been received.

We believe that EPA and other Federal officials should be called to testify on the manner in which fluoride has been protected. The union will be happy to assist the Congress in identifying targets for an inquiry. For instance, hydrofluosilicic acid does not appear on the Toxic Release Inventory list of chemicals, and there is a remarkable discrepancy among the Maximum Contaminant Levels for fluoride, arsenic and lead, given the relative toxicities of these substances.

Surgeon General's Panel on Fluoride We believe that EPA staff and managers should be called to testify, along with members of the 1983 Surgeon General's panel and officials of the Department of Human Services, to explain how the original recommendations of the Surgeon General's panel (16) were altered to allow EPA to set otherwise unjustifiable drinking water standards for fluoride.

Kingston and Newburg, New York Results In 1998, the results of a fifty-year fluoridation experiment involving Kingston, New York (un-fluoridated) and Newburg, New York (fluoridated) were published (17). In summary, there is no overall significant difference in rates of dental decay in children in the two cities, but children in the fluoridated city show significantly higher rates of dental fluorosis than children in the un-fluoridated city.

We believe that the authors of this study and representatives of the Centers For Disease Control and EPA should be called before a Select Committee to explain the increase in dental fluorosis among American children and

the implications of that increase for skeletal and other effects as the children mature, including bone cancer, stress fractures and arthritis.

Findings of Fact by Judges In three landmark cases adjudicated since 1978 in Pennsylvania, Illinois and Texas (18), judges with no interest except finding fact and administering justice heard prolonged testimony from proponents and opponents of fluoridation and made dispassionate findings of fact. I cite one such instance here.

In November, 1978, Judge John Flaherty, now Chief Justice of the Supreme Court of Pennsylvania, issued findings in the case, Aitkenhead v. Borough of West View, tried before him in the Allegheny Court of Common Pleas. Testimony in the case filled 2800 transcript pages and fully elucidated the benefits and risks of water fluoridation as understood in 1978. Judge Flaherty issued an injunction against fluoridation in the case, but the suit was discontinued on jurisdictional grounds. His findings of fact were not disturbed by appellate action. Judge Flaherty, in a July, 1979 letter to the Mayor of Aukland New Zealand wrote the following about the case:

"In my view, the evidence is quite convincing that the addition of sodium fluoride to the public water supply at one part per million is extremely deleterious to the human body, and, a review of the evidence will disclose that there was no convincing evidence to the contrary...

"Prior to hearing this case, I gave the matter of fluoridation little, if any, thought, but I received quite an education, and noted that the proponents of fluoridation do nothing more than try to impugn the objectivity of those who oppose fluoridation."

In the Illinois decision, Judge Ronald Niemann concludes: "This record is barren of any credible and reputable scientific epidemiological studies and or analysis of statistical data which would support the Illinois Legislature's determination that fluoridation of the water supplies is both a safe and effective means of promoting public health."

Judge Anthony Farris in Texas found: "[That] the artificial fluoridation of public water supplies, such as contemplated by [Houston] City ordinance No. 80-2530 may cause or contribute to the cause of cancer, genetic damage, intolerant reactions, and chronic toxicity, including dental mottling, in man; that the said artificial fluoridation may aggravate malnutrition and existing illness in man; and that the value of said artificial fluoridation is in some doubt as to reduction of tooth decay in man."

The significance of Judge Flaherty's statement and his and the other two judges' findings of fact is this: proponents of fluoridation are fond of reciting endorsement statements by authorities, such as those by CDC and the American Dental Association, both of which have long-standing commitments that are hard if not impossible to recant, on the safety and efficacy of fluoridation. Now come three truly independent servants of justice, the judges in these three cases, and they find that fluoridation of water supplies is not justified.

Proponents of fluoridation are absolutely right about one thing: there is no real controversy about fluoridation when the facts are heard by an open mind.

I am submitting a copy of the excerpted letter from Judge Flaherty and another letter referenced in it that was sent to Judge Flaherty by Dr. Peter Sammartino, then Chancellor of Fairleigh Dickenson University. I am also submitting a reprint copy of an article in the Spring 1999 issue of the Florida State University Journal of Land Use and Environmental Law by John Remington Graham and Pierre Morin, entitled "Highlights in North American Litigation During the Twentieth Century on Artificial Fluoridation of Public Water. Mr. Graham was chief litigator in the case before Judge Flaherty and in the other two cases (in Illinois and Texas).

We believe that Mr. Graham should be called before a Select Committee along with, if appropriate, the judges in these three cases who could relate their experience as trial judges in these cases.

Hydrofluosilicic Acid There are no chronic toxicity data on the predominant chemical, hydrofluosilicic acid and its sodium salt, used to fluoridate American communities. Newly published studies (19) indicate a link between use of

these chemicals and elevated level of lead in children's blood and anti-social behavior. Material from the authors of these studies has been submitted by them independently.

We believe the authors of these papers and their critics should be called before a Select Committee to explain to you and the American people what these papers mean for continuation of the policy of fluoridation.

Changing Views on Efficacy and Risk In recent years, two prominent dental researchers who were leaders of the pro-fluoridation movement announced reversals of their former positions because they concluded that water fluoridation is not an effective means of reducing dental caries and that it poses serious risks to human health. The late Dr. John Colquhoun was Principal Dental Officer of Aukland, New Zealand, and he published his reasons for changing sides in 1997 (20). In 1999, Dr. Hardy Limeback, Head of Preventive Dentistry, University of Toronto, announced his change of views, then published a statement (21) dated April 2000. I am submitting a copy of Dr. Limeback's publications.

We believe that Dr. Limeback, along with fluoridation proponents who have not changed their minds, such as Drs. Ernest Newbrun and Herschel Horowitz, should be called before a Select Committee to testify on the reasons for their respective positions.

Thank you for you consideration, and I will be happy to take questions.

CITATIONS

1.Dental caries and dental fluorosis at varying water fluoride concentrations. Heller, K.E, Eklund, S.A. and Burt, B.A. J. Pub. Health Dent. 57 136-43 (1997).

2a. A brief report on the association of drinking water fluoridation and the incidence of osteosarcoma among young males. Cohn, P.D. New Jersey Department of Health (1992).

2b. Time trends for bone and joint cancers and osteosarcomas in the Surveillance, Epidemiology and End Results (SEER) Program. National Cancer Institute. In: Review of fluoride: benefits and risks. Department of Health and Human Services.1991: F1-F7.

3.Neurotoxicity of sodium fluoride in rats. Mullenix, P.J., Denbesten, P.K., Schunior, A. and Kernan, W.J. Neurotoxicol. Teratol. 17 169-177 (1995)

4a. Fluoride and bone - quantity versus quality [editorial] N. Engl. J. Med. 322 845-6 (1990)

4b. Summary of workshop on drinking water fluoride influence on hip fracture and bone health. Gordon, S.L. and Corbin, S.B. Natl. Inst. Health. April 10, 1991.

5. Effect of fluoride on the physiology of the pineal gland. Luke, J.A. Caries Research 28 204 (1994).

6. Newburgh-Kingston caries-fluorine study XIII. Pediatric findings after ten years. Schlesinger, E.R., Overton, D.E., Chase, H.C., and Cantwell, K.T. JADA 52 296-306 (1956).

7. WHO oral health country/area profile programme. Department of Non-Communicable Diseases Surveillance/Oral Health. WHO Collaborating Centre, Malm" University, Sweden. URL:
www.whocollab.odont.lu.se/countriesalphab.html

8. Letters from government authorities in response to inquiries on fluoridation status by E. Albright. Eugene Albright: contact through J. W. Hirzy, P.O. Box 76082, Washington, D.C. 20013.

9. The effects of a break in water fluoridation on the development of dental caries and fluorosis. Burt B.A., Keels ., Heller KE. J. Dent. Res. 2000 Feb;79(2):761-9.

10. Toxicology and carcinogenesis studies of sodium fluoride in F344/N rats and B6C3F1 mice. NTP Report No. 393 (1991).

11. Effect of high fluoride water supply on children's intelligence. Zhao, L.B., Liang, G.H., Zhang, D.N., and Wu, X.R. Fluoride 29 190-192 (1996)

12. Effect of fluoride exposure on intelligence in children. Li, X.S., Zhi, J.L., and Gao, R.O. Fluoride 28 (1995).

13. Chronic administration of aluminum- fluoride or sodium-fluoride to rats in drinking water: alterations in neuronal and cerebrovascular integrity. Varner, J.A., Jensen, K.F., Horvath, W. And Isaacson, R.L. Brain Research 784 284-298 (1998).

14. Influence of chronic fluorosis on membrane lipids in rat brain. Z.Z. Guan, Y.N. Wang, K.Q. Xiao, D.Y. Dai, Y.H. Chen, J.L. Liu, P. Sindelar and G. Dallner, Neurotoxicology and Teratology 20 537-542 (1998).

15. Letter from Rebecca Hanmer, Deputy Assistant Administrator for Water, to Leslie Russell re: EPA view on use of by-product fluosilicic (sic) acid as low cost source of fluoride to water authorities. March 30, 1983.

16.Transcript of proceedings - Surgeon General's (Koop) ad hoc committee on non-dental effects of fluoride. April 18-19, 1983. National Institutes of Health. Bethesda, MD.

17. Recommendations for fluoride use in children. Kumar, J.V. and Green, E.L. New York State Dent. J. (1998) 40-47.

18. Highlights in North American litigation during the twentieth century on artificial fluoridation of public water supplies. Graham, J.R. and Morin, P. Journal of Land Use and Environmental Law 14 195-248 (Spring 1999) Florida State University College of Law.

19. Water treatment with silicofluorides and lead toxicity. Masters, R.D. and Coplan, M.J. Intern. J. Environ. Studies 56 435-49 (1999).

20. Why I changed my mind about water fluoridation. Colquhoun, J. Perspectives in Biol. And Medicine 41 1-16 (1997).

21. Letter. Limeback, H. April 2000. Faculty of Dentistry, University of Toronto.

22.. Memorandum: Subject: Fluoride Conference to Review the NTP Draft Fluoride Report; From: Wm. L. Marcus, Senior Science Advisor ODW; To: Alan B. Hais, Acting Director Criteria & Standards Division Office of Drinking Water. May 1, 1990.

DOMINION OF CANADA

PROVINCE OF QUÉBEC

John Remington Graham, being first duly sworn, deposes and says:

Yesterday morning, I was arranging my air travel to Toronto in anticipation of appearing personally before the community water fluoridation committee of the Peel Region in Ontario to speak on judicial findings on water fluoridation, when I encountered the after-effects of a minor stroke which I suffered last summer. My physician, Dr. Louis Grenier, has recommended that I undertake no further travel, and today my wife observed that my physical condition was not good enough for the trip. Sylvie is a former Crown prosecutor in Quebec, and served twelve years as mayor of our municipality. I am sorry that I cannot appear personally as planned.

Materials already submitted include copies of (1) my letter of January 14, 2015, to Dr. David Kennedy, including (2) a résumé of highlights in my career; (3) a law review article authored by Dr. Pierre Morin, an eminent Canadian medical research scientist, and myself, the same entitled *Highlights on North American Litigation during the Twentieth Century on Artificial Fluoridation of Public Water Supplies*, 14 Journal of Land Use and Environmental Law 195-248 (Florida State University, 1999); and (4) the report of the union of scientists at the United States Environmental Protection Agency on June 29, 2000, submitted by their executive vice president, Dr. J. W. Hirzy, to subcommittee of the United States Senate. I affirm of my own knowledge that those materials correctly recite the facts, save for minor errors, including in particular that, in the year 2000, 161 million (not 130 million) Americans drank water fluoridated at one part per million. It may now be conservatively estimated from data discussed in the foregoing materials that a million or more persons in the United States have died of cancer induced or promoted by water fluoridation since the United States Public Health Services

endorsed such measure in 1951, and Congress has since spent millions of dollars every year to promote it. I might here mention that the National Institute of Environmental Health Sciences has in 2012 and again 2017 published large and impressive studies which suggest that fluoride in public drinking water may cause neurological injury to man, including lower IQ in children. This recent work on neurological injury is of high quality, but is not yet as well developed as the work on cancer already found lethal to man in judicial findings which I secured before veteran trial judges, after historic trials in Pennsylvania, Illinois, and Texas, as reported in the law review article already provided. I should say that the evidence we presented before judicial tribunals in three States was somewhat understated at the time presented in court, but the casualty in cancer mortality is now known to be substantially greater than we originally thought. If the community water fluoridation committee wishes to inquire on details, I invite questions which I shall address by affidavit from evidence in my files, including detailed adjustments of epidemiological surveys done by Dr. Dean Burk, one of the most decorated and famous cancer research scientists in the world during the 20th Century.

I summarize salient points: I have practiced law, as a member of the Minnesota Bar (#3664X) over fifty years, including appearances before courts of record in sixteen jurisdictions of the United States, and service as a public defender, a law professor, and a chief public prosecutor in Minnesota, not to mention consultation in major litigation in Canada. I have studied Canadian constitutional law and history at Laval University under Professor Henri Brun, who was at the time the leading French-speaking constitutional lawyer in Canada.. I can say from my experience in presenting forensic evidence on water fluoridation in Pennsylvania, Illinois, and Texas that **it is now possible to prove by fair preponderance of the evidence in judicial proceedings before courts of superior jurisdiction in the United States or Canada**

water fluoridation causes large-scale cancer and other ailments in man. I can predict the outcomes in future judicial proceedings, first, because the United States Public Health Service, supported by the American Dental Association, covered up large laboratory studies proving that fluoride in drinking water at 1.0 part per million, introduced as sodium fluoride so as to resemble fluoride treatment of public water supplies, is a carcinogen, capable of producing significant cancer-related reactions in mice. Secondly, the United States National Cancer Institute has attempted to adjust massive epidemiological surveys of twenty large central cities for age, race, and sex, but did so by leaving out all or nearly all available and pertinent data, which, when included by standard statistical methods, shows a huge association of human cancer mortality with water fluoridation, -- something on the order of 200 excess cancer deaths per million persons exposed after 15-20 years of exposure. The actual casualty, established by the unadjusted data, already controlled for known and known variables by a long base line, is probably half again as great.

I have studied Canadian decisions on health freedom, and the most telling are *Toronto v. Forest Hill,* [1957] S. C. R. 569, and *Chaoulli v. Québec*, [2005] 1 S. C. R. 791. In light of these Canadian decisions and *Jacobson v. Massachusetts*, 197 U. S. 11 at 39 (1905), it appears that the Supreme Court and superior courts of Canada would hold that water fluoridation cannot be imposed on citizens who can establish on the face of the pleadings or can prove by fair preponderance of the evidence that water fluoridation causes harm to human health, as veteran trial judges have already found in Pennsylvania, Illinois, and Texas. As revealed on pages 237 and 238 of the law review article already provided, Judge Anthony Farris of the District Court of Texas found that the **"artificial fluoridation of public water supplies may cause or contribute to the cause of cancer, genetic damage, intolerant reactions, and**

chronic toxicity, including dental mottling in man; may aggravate malnutrition and existing illnesses in man; and is in some doubt as to the reduction of tooth decay in man.[9] The Texas Court of Appeals upheld these findings based on a fair preponderance of the evidence. The report of Dr. Hirzy in behalf of the union of scientists at the USEPA confirms on page 4 that these judicial findings are scientifically correct. Similar findings were entered after long trials by Judge John Flaherty, later Chief Justice of the Pennsylvania Supreme Court, and Judge Ronald Niemann of the Circuit Court of Illinois. The public officers of the Peel Region who must decide whether to impose water fluoridation over the protest of their fellow citizens are presumed know and understand the dangers which the foregoing materials portray, and will sooner or later be answerable one way or another for their decisions. They will have no excuse for harm done if they rely on advice of bureaucrats who have not studied the forensic evidence, or misrepresent their qualifications.

John Remington Graham

Sworn and subscribed before me on this 12th day of September, 2018

Sylvie Forin, Member of the Bar (retired), and
Commissioner for the Taking of Oaths,
Dominion of Canada, Province of Québec

Region of Peel
working with you

REPORT
Meeting Date: 2018-09-27
Community Water Fluoridation Committee

For Information

DATE: September 19, 2018

REPORT TITLE: **COMMUNITY WATER FLUORIDATION - USING EVIDENCE TO INFORM PUBLIC HEALTH PRACTICE**

FROM: Nancy Polsinelli, Commissioner of Health Services
Jessica Hopkins, MD MHSc CCFP FRCPC, Medical Officer of Health

OBJECTIVE

This report is a supplement to the report on Community Water Fluoridation – Staff Response to Committee Selected Studies, prepared for the September 27, 2018 Community Water Fluoridation Committee (CWFC) meeting. The purpose of the report is to provide information on how Public Health uses evidence to make and inform decisions regarding community water fluoridation (CWF).

REPORT HIGHLIGHTS

- Protecting the health and safety of Peel residents is central to Peel Public Health's commitment and mandate to report on the best available research evidence to inform public health decision-making.
- Public Health uses a systematic and objective process to assess all evidence and identify the best quality studies that are most relevant for how CWF is practiced in Peel.
- Where possible, systematic reviews, rather than single studies, should be used for public health decisions. Systematic reviews compile the results from high quality single studies to come to a conclusion about a topic.
- To assess quality, research evidence is critically appraised to determine if methods controlled for different types of bias. Bias is defined as systematic errors in the way the study is designed, conducted or interpreted that could affect the study results.
- Peel Public Health continues to systematically and objectively monitor and appraise evidence on community water fluoridation and will advise Council, in its capacity as the Board of Health, of any significant changes to the evidence base.

DISCUSSION

1. Background

This report contains detailed information about the types of evidence used for public health decision-making about the practice of CWF.

2. Evidence-Informed Decision Making

Public health professionals rely on the best available evidence to inform public health decision-making. According to the Ontario Public Health Standards, Regional Council, in its capacity as the Board of Health, "…shall ensure all programs and services are informed by evidence." Evidence-informed decision-making (EIDM) acknowledges that different types of evidence are appropriate and useful to support decision-making. EIDM in public health balances the evidence with other factors that influence decision-making, such as community health priorities, local context, political mandates and actions, and public health resources.

3. Types of Evidence

The hierarchy of quantitative evidence (Figure 1, Appendix I) shows how some study designs are considered stronger than others; while the overall quality of any study depends on how well the study was conducted (see Quality of Evidence below). The strongest study designs are found at the top of the hierarchy, while weaker study designs are found at the bottom. Appendix 1: Hierarchy of Quantitative Evidence provides a detailed breakdown of the types of study designs included within the hierarchy of evidence.

The hierarchy of evidence indicates that where possible, systematic reviews, rather than single studies, should be used for public health decision-making. Systematic reviews, or studies of studies, provide a summary of the quality and findings of available evidence related to a defined question. These reviews are developed through a process that is rigorous, transparent and reproducible, with measures to reduce sources of bias throughout the review process. The initial steps of the review process are performed independently by a minimum of two reviewers to verify the findings.

Randomized controlled trials (RCTs) are single studies that randomly assign individuals to intervention and non-intervention groups and follow each group over a sufficient time based on what the study is trying to determine. Studies with human participants should be reviewed by an ethics committee, comprised of individuals with scientific and medical expertise, to ensure appropriate ethical standards are being followed. The research ethics committee seeks to answer the fundamental question of whether it is ethical to provide a potentially beneficial intervention to one group of participants but not to others. It would be unethical to conduct an RCT to determine if seatbelts save lives, as the non-intervention group would be exposed to potential harm by not using seatbelts. Similarly, it is unethical to randomize participants to start smoking in a smoking intervention group to determine if smoking is associated with lung cancer.

RCTs that study CWF are not feasible due to the inability to assign individuals from the same population to exclusively fluoridated and non-fluoridated water supplies. Specifically, conducting an RCT to study CWF would require the recruitment of a group of people who have never been exposed to fluoride. Additionally, all water consumed would need to be provided by the research team, a long study observation period would be cost prohibitive, and the research ethics committee may have ethical concerns approving such a study given the current documented effectiveness of community water fluoridation.

COMMUNITY WATER FLUORIDATION - USING EVIDENCE TO INFORM PUBLIC HEALTH PRACTICE

4. Quality of Evidence

It has been estimated that less than 20 per cent of published literature is scientifically sound. To determine which studies are valid sources of information, the methods of each study need to be critically appraised to determine if appropriate methods were used to control for different types of bias.

a) Bias

When bias is used as a scientific term, it refers to systematic errors in the way the study is designed, conducted or interpreted that could affect study results. Studies with a higher likelihood of bias are considered lower quality and less reliable. In the context of CWF, potential biases that may exist in some studies include:

- **Selection bias** - occurs when study participants are not representative of the population or when the intervention and non-intervention groups have differences that could explain the results;

- **Observer bias** - occurs when the researcher considers the outcome subjectively. This can be avoided by ensuring the observer is not aware of whether the participant they are observing is a member of the intervention or non-intervention group;

- **Confounding bias** - refers to factors (e.g., socioeconomic status, nutrition, etc.) that may not have been accounted for which can influence or explain the outcome of the study;

- **Aggregation bias** - occurs when assumptions about individuals are drawn from population-level data. It is incorrect to assume that a relationship present at the population-level of analysis will exist at the same strength at the individual level; and

- **Publication bias** - refers to the selective publication of studies. It can include the tendency to publish only studies with significant results and not those without significant findings (e.g., studies that do not demonstrate statistically significant results or do not differ from previously published data).

5. Relevance of Evidence

A significant amount of published scientific evidence is available on water fluoridation. However, not all of these are relevant to how CWF is practiced in Peel. Peel Public Health has criteria set to determine the relevance of evidence about the safety and efficacy of CWF.

Inclusion criteria:
- studies published in English;
- systematic reviews, experimental or observational studies;
- study assesses the effect of CWF at the optimal range (0.7 to 1.0 parts per million) on any health outcome; and
- study has humans as the subject.

Exclusion criteria:

- study assesses the effect of consuming water that contains fluoride outside the optimal range (0.7 to 1.0 parts per million);
- study is based on in vitro or in animal studies;
- study is a non-systematic (literature) review, opinion note or editorial; or
- study does not describe study methodology.

6. Assessing Quality

The critical appraisal process is used to assess the quality of study methods to determine if findings are trustworthy, significant and relevant to community water fluoridation as it is practiced in Peel. All sources of evidence that contribute to the decision-making process should be critically appraised to identify potential biases and determine the overall quality of the evidence.

The report "Updated Review of Evidence on the Effectiveness and Safety of Community Water Fluoridation," presented to CWFC on November 24, 2016, provided an overview of the review process used by Peel Public Health. Peel Public Health utilizes a systematic and objective process to review evidence on all matters of public health significance, including the effectiveness and safety of CWF. This process involves a series of predetermined, replicable, and transparent steps. In summary, these steps include:

- comprehensive searches of electronic databases by a trained librarian, to ensure any and all relevant published evidence is identified;
- application of a set of criteria to determine the relevance of research regarding CWF;
- critical appraisal of relevant studies using validated tools; and
- two independent reviewers conducting all the review procedures.

a) Critical Appraisal Tools

Research evidence is critically appraised to determine how well the review is conducted. Selection of an appropriate appraisal tool is dependent on study design. For example, Peel Public Health uses the Health Evidence Quality Assessment Tool developed by Health Evidence, part of the National Collaborating Centre for Methods and Tools based out of McMaster University. The criteria within the tool consider the following factors:

- clarity of the review question;
- thoroughness of the search;
- size and precision of the outcome; and
- applicability of the intervention to local populations.

COMMUNITY WATER FLUORIDATION - USING EVIDENCE TO INFORM PUBLIC HEALTH PRACTICE

CONCLUSION

Peel Public Health is committed to using rigorous, tested scientific methods to monitor and assess evidence. These methods are designed to obtain the highest quality evidence available and reduce bias as much as possible. These methods are applied to all health issues that are being addressed by Peel Public Health, including CWF.

Nancy Polsinelli, Commissioner of Health Services

Jessica Hopkins, MD MHSc CCFP FRCPC
Medical Officer of Health

Approved for Submission:

D. Szwarc, Chief Administrative Officer

APPENDICES

Appendix I: The Hierarchy of Quantitative Evidence

For further information regarding this report, please contact Paul Sharma, Director, Chronic Disease and Injury Prevention, Ext. 2013.

Authored By: Fatime Grigorescu, Analyst, Research & Policy, Chronic Disease and Injury Prevention

APPENDIX I
COMMUNITY WATER FLUORIDATION - USING EVIDENCE TO INFORM PUBLIC HEALTH PRACTICE

The Hierarchy of Quantitative Evidence

What is the best available evidence?

The hierarchy of evidence attempts to address this question. It uses a top-down approach to locate the best evidence by searching for systematic reviews or meta-analyses. If these are not available the researches move down to the next level that is appropriate to answer the research question.

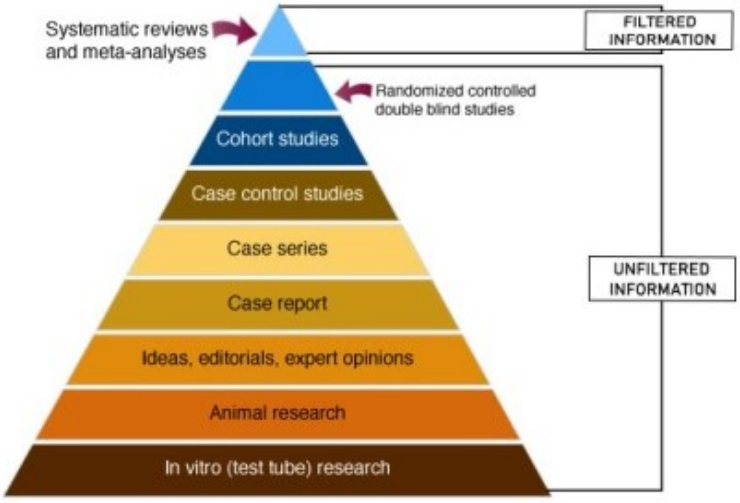


FIGURE 1: The hierarchy of quantitative evidence

The hierarchy ranks study types based on the rigour (strength and accuracy) of their research methods. The higher up the study design is positioned, the more rigorous the methodology and more likely that the study design is able to minimize bias on the study results.

Systematic Reviews and Meta-Analyses (Filtered Information)

Filtered information assesses the quality of a study and provides recommendations for practice. The critical appraisal of individual studies included within systematic reviews has already been done. Filtered information will often provide a more definite answer to the research question compared with single studies.

Systematic Review	• Considered to provide the best quality evidence for all question types. • Authors have comprehensively searched for, appraised, and summarized all evidence for a specific topic. • Through the search, poor quality studies are eliminated in an attempt to make recommendations based on well-done studies. • The systematic review may also include a meta-analysis, where quantitative data is combined to summarize the findings.
Meta-Analysis	• Quantitative summary of study results which may be included in a systematic review.

APPENDIX I
COMMUNITY WATER FLUORIDATION - USING EVIDENCE TO INFORM PUBLIC HEALTH PRACTICE

Single Studies (Unfiltered Information)

Unfiltered information consists of single, original research studies that have not yet been assessed or combined. Therefore, alone, they are difficult to interpret and apply to practice. When current, well-designed systematic reviews are not available, single studies are used to answer a particular question.

Study Type	Definition
Randomized Controlled Trial (RCT)	• Experiment in which participants are randomly assigned to two or more groups (intervention or non-intervention groups) and compared over time. Participants in the intervention group receive the intervention while participants in the non-intervention group do not. • As with many public health interventions, an RCT design is not possible because its community-wide nature does not allow randomization of individuals to intervention and non-intervention groups. **Uses:** Therapy & Prevention • Determines the effect of interventions on people.
Cohort Study	• A defined group of people (the cohort) are followed over time. They are compared with another group of people who do not receive the intervention. **Uses:** • Provides insight into effects over time related to a variety of different types of changes (e.g. social, cultural, political, economic, etc.). • Determines the effects of potentially harmful agents. Harm/Etiology • Determines the effects of potentially harmful agents.
Case Control Study	• Compares people who have experienced an event with a group of people who have not experienced the same event. • Researchers interview the two groups or check their medical files to find associations between the outcome and prior exposure to risk factors. **Uses:** • Determines the cause of rare events, such as rare cancers.
Case Series & Case Report	• Analyzing a series of people with the disease. • These studies do not have a comparison group (non-intervention group). • Able to provide outcomes for only one subgroup of the population (those with the intervention). • Lots of potential for bias: incomplete data collection or follow-up which may happen with studies looking in the past for information. • Usually based on single surgeon's or center's experience, unlikely to be generalizable to the whole population. • Study design useful for developing hypothesis, providing information on rare diseases or complications that may be associated with certain procedures.
Ideas, Editorials, Expert Opinions	Published by experts in the field.

APPENDIX I
COMMUNITY WATER FLUORIDATION - USING EVIDENCE TO INFORM PUBLIC HEALTH PRACTICE

Animal Research	Studies conducted using animal subjects.
In Vitro (test tube) Research	Test tube experiments conducted in a laboratory setting.

Region of Peel
working with you

Community Water Fluoridation

HOW PUBLIC HEALTH USES EVIDENCE TO INFORM ITS PRACTICE: RESPONSE TO SELECTED STUDIES REQUESTED BY THE COMMITTEE

Community Water Fluoridation Committee
Peel Regional Council | September 27, 2018

Jessica Hopkins, MD MHSc CCFP FRCPC
Medical Officer of Health, Region of Peel

Introduction

- At the July 5, 2018 meeting, the Community Water Fluoridation Committee (the "Committee") requested staff report on three studies
- This presentation will:
  - Explain how Public Health assesses scientific evidence
  - Review the findings of the three studies as requested by the Committee
    - Cochrane systematic review
    - Australian systematic review
    - Mexico study

The Big Picture: Assessing Evidence

Public Health uses the following approach to use evidence to inform its practice:

1. Identify and review the body of evidence
2. Critically appraise relevant evidence
3. Interpret the findings
4. Apply the findings

1. Identify and Review the Body of Evidence

Public Health uses set criteria set to determine the **relevance** of evidence to the practice of CWF in Peel:

- studies published in English;
- systematic reviews, experimental or observational studies;
- study assesses the effect of CWF at the optimal range (0.7 to 1.0 parts per million) on any health outcome;
- and study has humans as the subject

1. Identify and Review the Body of Evidence

- The hierarchy of evidence shows that some study designs are considered stronger than others
- Generally, the higher in the pyramid, the more robust it is assumed to be

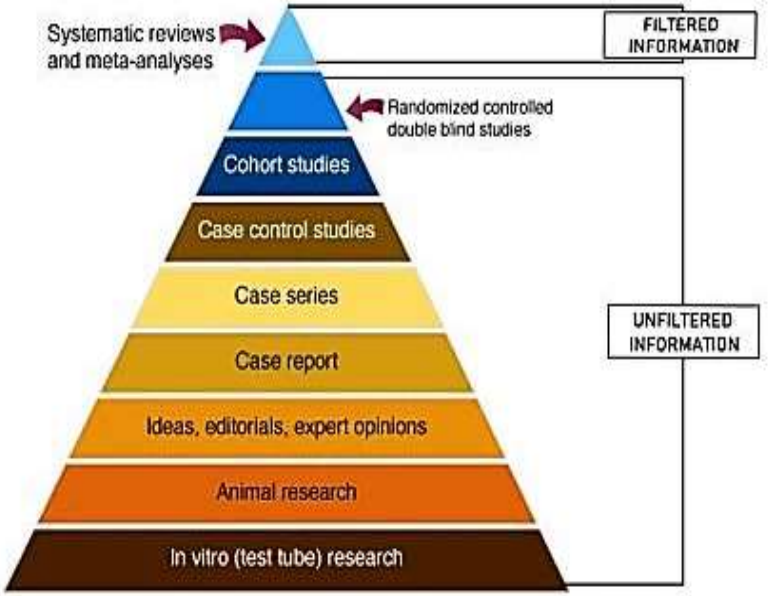


FIGURE 1: The hierarchy of quantitative evidence

1. Identify and Review the Body of Evidence

- A **systematic review** is a research approach to accessing, acquiring, quality-assessing, and synthesizing a body of research on a particular topic

- All phases of the systematic review development should be well described, such that the process is transparent and replicable by others

2. Critically Appraise Relevant Evidence

Critical appraisal is the process of assessing the quality of study methods in order to determine if findings are trustworthy, meaningful and relevant to your situation. Critical appraisal helps you answer the question:

"Were the methods used in this study good enough that I can be confident in the findings?"

Elements of critical appraisals include:

- Appropriate inclusion criteria
- Comprehensive search strategy
- Adequate timeframe
- Appropriate level of evidence included
- Assessment of the methods (research design, study sample, participation rates, sources of bias, data Collection, follow-up/attrition rates, data analysis)
- Transparency of review results
- Appropriateness of combining results across studies included and combined in appropriate ways

Note: Different tools are used to appraise different types of research (i.e. review, guideline or single study)

2. Critically Appraise Relevant Evidence

- We often think about **bias** in terms of unfair perceptions (either too positively or negatively). “One-sided”, “lacking a neutral point of view” or “not having an open mind” are other ways we sometimes talk about bias in our day-to-day lives

- When bias is used as a scientific term, it refers to unintentional or intentional **systematic errors** in the way the study is designed, conducted or interpreted that could affect study results

- Studies with a higher likelihood of bias are considered lower quality and less reliable

3. Interpret the Findings

- Are the results valid? Is the study design relevant? What biases are the study design prone to?
- What are the results? How precise are the results? How much uncertainty surrounds the results?
- Are the results relevant to the local context? Were all important outcomes considered? Do the benefits outweigh any harms and costs?

4. Apply the Findings

- Evidence-informed public health practice is about identifying and effectively addressing public health issues that will result in health, wellness and health protection of the residents of Peel.

Review of Requested Studies

- The following slides summarize the three studies identified by the Committee at the July 5th, 2018 CWFC meeting
  - Cochrane systematic review
  - Australian systematic review
  - Mexico study

Cochrane Systematic Review: Overview

Type of study	**Systematic review and meta-analyses**		
Looked at	Effects of fluoride in water (added or naturally occurring) on the prevention of tooth decay and markings on teeth (dental fluorosis)		
Search strategy	Searched the following databases from database inception to February 19, 2015: • The Cochrane Oral Health Group's Trials Register (to February 19, 2015) • The Cochrane Central Register of Controlled Trials (February 19, 2015) • MEDLINE via OVID (1946 and up) • EMBASE via OVID (1980 and up) • Proquest (to February 19, 2015) • Web of Science Conference Proceedings (1990 and up) • ZETOC Conference Proceedings (1993 and up) For ongoing trials: • US National Institutes of Health Trials Registry • World Health Organization's WHO International Clinical Trials Registry Platform		
Relevant studies	<u>Tooth decay:</u> Studies that compared at least two populations with outcomes evaluated at least two points in time	<u>Fluorosis:</u> Study designs that compared populations exposed to different fluoride concentrations (up to 5 ppm)	<u>Participants:</u> Populations of all ages receiving fluoridated water (naturally or artificially) and those receiving non-fluoridated water (less than 0.4 ppm) from many different countries

Cochrane Systematic Review: Findings

Author's conclusion	The review concluded that CWF is effective in preventing tooth decay in children

Effectiveness in Children:

- 35% less cavities in children's baby teeth
- 26% less cavities in children's permanent teeth
- 15% increase in children with no cavities

Effectiveness in Adults:

- Unable to draw conclusions
- Cochrane's strict criteria excluded many available and relevant studies on adults

Dental Fluorosis:

- 12% of people had fluorosis that may be of aesthetic concern

Cochrane Systematic Review:

Study Strengths

- Clear inclusion/exclusion criteria
- Stringent review process to assess quality of single studies
- Assessed the risk of bias of included studies
- Systematic review with meta-analyses (most reliable evidence to inform the practice of CWF)

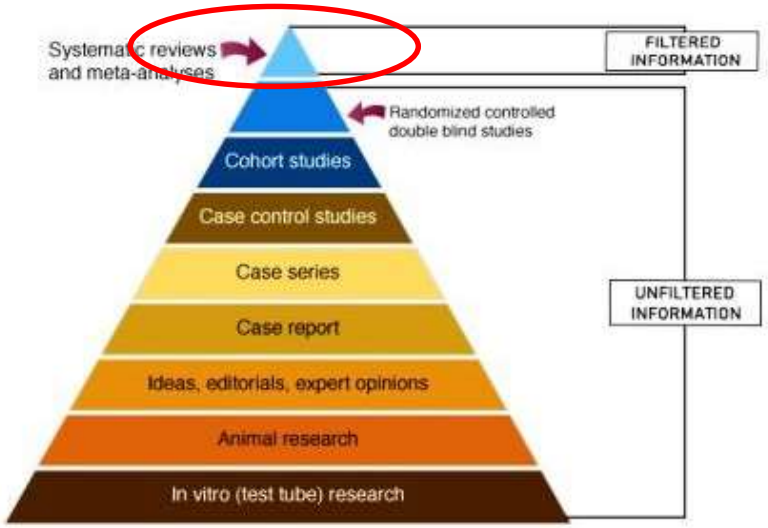


FIGURE 1: The hierarchy of quantitative evidence

Cochrane Systematic Review:

Study Limitations

- Unable to draw conclusions for adults
  - No studies regarding the effectiveness of water fluoridation in adults met Cochrane's strict criteria for inclusion
- Cochrane typically includes studies evaluated at two points in time in the same sample of adults
  - This type of long-term evaluation can be difficult and unfeasible when assessing public health interventions such as CWF
- Most of the studies were conducted prior to 1975; before the widespread use of fluoridated products such as fluoridated toothpaste

Cochrane Systematic Review:

Applicability to Peel

- The review looks at tooth decay in communities that practice community water fluoridation at levels similar to Peel and compares them to communities where the water is not fluoridated and has a naturally low fluoride concentration.

- Research published in peer-reviewed literature found CWF to be effective in preventing tooth decay in adults.

Australian Systematic Review: Overview 4.1-25

Type of study	**Systematic review**
Looked at	1. Dental effects of water fluoridation 2. Other health effects of water fluoridation This is an update to the Australian National Health and Medical Research Council's (NHMRC) 2007 review

Search strategy	<u>Dental effects (systematic review)</u>
	• Identified and evaluated existing systematic reviews published between October 1, 2006 and November 12, 2015
	  ○ Searched five major databases which include additional databases
	• Identified recent single studies published between October 1, 2006 and November 12, 2015
	  ○ Searched five major databases which include additional databases
	• Critically appraised evidence on dental fluorosis included in Cochrane review (Iheozor-Ejiofor et al. 2015)
	
	<u>Other health effects (systematic review)</u>
	• Identified single studies published between October 1, 2006 and October 14, 2014
	  ○ Searched five major databases which include additional databases)

Relevant studies	<u>Dental effects</u> Studies included compared non-fluoridated drinking water (less than 0.4 ppm) with water fluoridated within Australian levels (0.4 ppm-1.5 ppm) <u>Other health effects</u> Studies included reported on a health effect (other than tooth decay or dental fluorosis) in humans

Australian Systematic Review: Findings

Author's conclusion	The review concluded that CWF is safe and effective in preventing tooth decay in both children and adults Findings consistent with initial review conducted in 2007 and previous systematic reviews

Tooth decay:

- 26-44% less tooth decay in people living in fluoridated areas (0.4-1.5 ppm) compared to those living in low/non-fluoridated areas (less than 0.4 ppm)

Health outcomes:

- CWF is not associated with changes in intelligence
- CWF is not associated with cancer, hip fracture and Down syndrome

Australian Systematic Review:

Study Strengths

- The methods of the systematic review were of strong quality
- Clear inclusion/exclusion criteria
- Studies assessed for quality by two independent reviewers using validated tools
- Appropriate methods used for comparing results

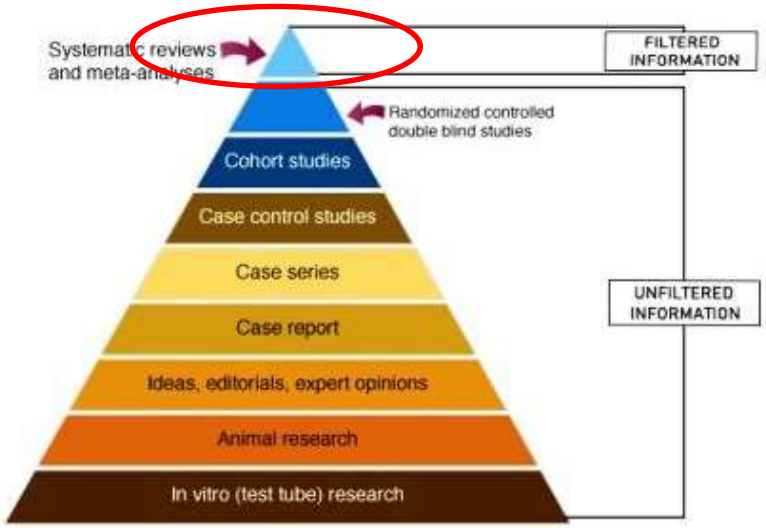


FIGURE 1: The hierarchy of quantitative evidence

Australian Systematic Review:

Study Limitations

- The single studies included were of poor quality
- The one review showing an association between fluoride at 0.7 ppm and fluorosis was graded low quality for high risk of bias, lack of recent evidence and inconsistency
  - It included cases where dental fluorosis can only be detected under clinical conditions (such as by a dentist)

Australian Systematic Review:

Applicability to Peel

- Study findings related to tooth decay are directly comparable to how CWF is practiced in Peel
- Findings include participants from a wide range of age groups and settings and provide evidence that CWF reduces caries in children and adults

Mexico Study: Overview

Type of study	**Single study (cohort)**
Looked at	Association of prenatal exposure to fluoride with offspring cognitive development

Methods	Study description
	• Study conducted in Mexico City using stored samples from cohorts that were part of previous research studies
	• Mexico does not fluoridate its drinking water
	  ○ Study participants were exposed to fluoridated salt at 250 ppm
	  ○ Study participants exposed to varying levels of naturally occurring fluoride in drinking water (ranging from 0.15 to 1.38 mg/L)
	
	Study participants
	• Total of 512 participants (mothers) of which complete data were available for 299 mother-child pairs

Mexico Study: Findings

Author's conclusion	Higher fluoride concentration in mothers was related to lower scores on cognitive tests in the offspring at age 4 and 6-12 years old Study calls for "... additional research on the potential adverse effects of fluoride to ensure benefits of CWF outweigh any potential risks"

***Authors' caution:**

Some evidence suggests that associations with IQ may have been limited to blood fluoride concertation of 0.8 ppm, which is expected to occur at intake concentrations above 1 ppm – higher than what is practiced in the Region of Peel (0.65 ppm)

Mexico Study:

4.1-32

Study Strengths

- Large sample size for this type of study
- Used validated laboratory instruments to measure urinary fluoride
- Used validated tools by trained clinicians to measure cognitive outcomes
- Follow-up time was long enough for outcome to occur

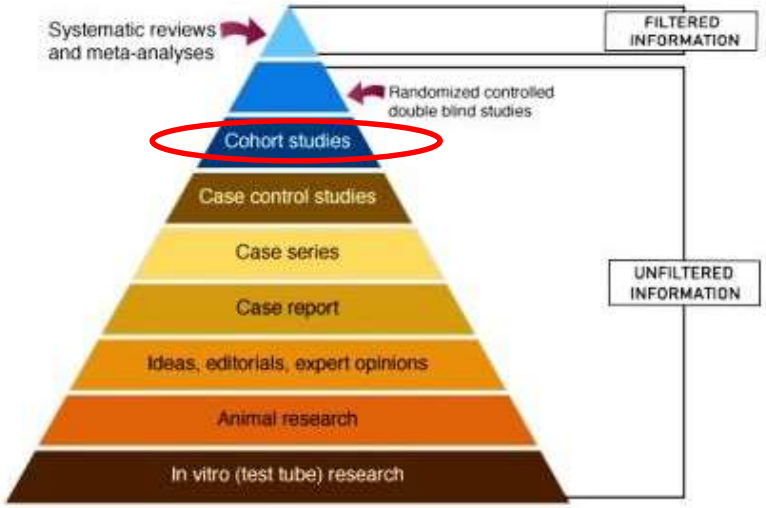


FIGURE 1: The hierarchy of quantitative evidence

Mexico Study:

Study Limitations

- Single study design
  - A limitation of singles study designs is the difficulty of generalizing their results to other populations, because of the small number of subjects and specific context within which they are investigated.
- Lacked non-exposed group
- Unknown exposure level to fluoride
- Important variables not controlled for (e.g. lead and arsenic)
- Variables controlled for had missing data

Mexico Study:

Applicability to Peel

Findings not applicable to Peel context

- The study was not about CWF and its effects on cognitive development in children.
  - The study examined blood fluoride concentration of expecting mothers and the cognitive performance of children at 4 and 6-12 years. The study was not designed in such a way that cause and effect can be studied.
- Study participants were recruited from hospitals in Mexico that serve low-to-moderate income populations.
  - The markedly different socio-economic, cultural and environmental circumstances make applicability to the Peel context limited.
- The total exposure to fluoride was unknown.
  - 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.
  - By virtue of living in Mexico, individuals participating in the study have been exposed to fluoridated salt (at 250 ppm).
- Did not control for exposure to arsenic and may have inappropriately controlled for lead exposure both of which have been associated with cognitive development

Summary

- Peel Public Health is committed to using rigorous, tested scientific methods to monitor and assess evidence. These methods are designed to obtain the highest quality evidence available and reduce bias as much as possible

- These methods are applied to all health issues that addressed by Public Health, including CWF

- The Cochrane and Australian systematic reviews are a part of a body of evidence which support the practice CWF and does not show a link between fluoride in drinking water at the optimal concentration range (0.5 to 0.8 mg/L) and any adverse health effects

- The findings of the Mexico study have important design limitations and are not applicable to the Peel context

- As directed by Council in 2012 and reaffirmed in 2017, Public Health continues to monitor relevant evidence on the effectiveness and safety of CWF and will advise Council, in its capacity as the Board of Health, of any changes to the evidence base

Region of Peel
working with you

REPORT
Meeting Date: 2018-09-27
Community Water Fluoridation Committee

For Information

DATE: September 19, 2018

REPORT TITLE: **COMMUNITY WATER FLUORIDATION – STAFF RESPONSE TO COMMITTEE SELECTED STUDIES**

FROM: Nancy Polsinelli, Commissioner of Health Services
Jessica Hopkins, MD MHSc CCFP FRCPC, Medical Officer of Health

OBJECTIVE

This report addresses direction from the Community Water Fluoridation Committee (CWFC) to review and report on three studies; the Cochrane systematic review[1] regarding Water Fluoridation for the Prevention of Dental Caries, the Australian systematic review[2] regarding the Health Effects of Water Fluoridation, and the Mexico study[3] regarding Prenatal Fluoride Exposure and Cognitive Outcomes in Children 4 and 6-12 years of age in Mexico.

Responses to additional items referred to staff for response at the July 5, 2018 CWFC meeting are provided in Appendix I and include: Lancet Neurology article, EPA list of chemicals with substantial evidence of developmental neurotoxicity, Health Canada's Toxic Substances List, and a comparison of fluoride to lead and arsenic.

REPORT HIGHLIGHTS

- The three studies presented are part of an extensive body of published and unpublished literature on community water fluoridation (CWF).
- The Cochrane and Australian systematic reviews on CWF found the following:
  - Effectiveness: Statistically significant reduction in tooth decay in children and adults.
  - Dental Fluorosis: A small risk of dental fluorosis of aesthetic concern with increased levels of fluoride.
  - Safety: The evidence does not support a link between fluoride in drinking water at 0.7 mg/L* and any adverse health effects.
- The Cochrane and Australian systematic reviews are both strong quality reviews which support the findings of previous systematic reviews that CWF is safe and effective for preventing tooth decay.
- The Mexico study has strong design limitations which may have impacted the findings. Failure to: control for important factors (e.g., iodine, arsenic and nutrition); use a comparison group not exposed to fluoride; and failure to specify the exact level of fluoride exposure.

---

[1] Iheozor-Ejiofor Z, Worthington HV, Walsh T, et al. Water fluoridation for the prevention of dental caries. Cochrane Database Syst Rev [Internet]. 2015 Jun [cited 2018 Aug 15];(6):CD010856.
[2] Jack B, Ayson M, Lewis S, et al. Health effects of water fluoridation [Internet]. Canberra: National Health and Medical Research Council; 2016 [cited 2018 Aug 15]. Available from: http://fluoridealert.org/wp-content/uploads/nhmrc.technical-report.final_.8-24-16.pdf
[3] Bashash M, et al. Prenatal fluoride exposure and cognitive outcomes in children at 4 and 6-12 years of age in Mexico. Environ Health Perspect [Internet]. 2017 Sep [2018 Aug 15];125(9):097017.
* Note that mg/L and parts per million (ppm) are used interchangeably throughout the report.

COMMUNITY WATER FLUORIDATION – STAFF RESPONSE TO COMMITTEE SELECTED STUDIES

DISCUSSION

1. Background

As directed by Council in 2012 and reaffirmed in 2017, Public Health continues to monitor relevant evidence on the effectiveness and safety of community water fluoridation and will advise Council, in its capacity as the Board of Health, of any changes to the evidence base.

In general, the body of reliable, relevant evidence continues to support CWF as a safe and effective public health intervention as part of a comprehensive oral health approach for improving the overall health and well-being of Peel's residents.

2. Study 1: Cochrane Systematic Review (Iheozor-Ejiofor et al. 2015)

The Cochrane systematic review titled "Water Fluoridation to Prevent Tooth Decay," conducted by Iheozor-Ejiofor et al. (2015) examined the effects of fluoride in water (added fluoride or naturally occurring) on the prevention of tooth decay and markings on teeth (dental fluorosis). The review concluded that CWF is effective in the prevention of tooth decay.

a) Study Strengths and Characteristics

i) Strengths

- Clearly focused question and inclusion/exclusion criteria.
- Stringent review process to assess each study for the quality of methods used.
- Assessed the risk of bias in the included studies.
- The Cochrane systematic review was rated "strong" quality by Peel Public Health.

ii) Study characteristics

- Cochrane systematic review included 20 studies which examined the effects of fluoridated water on tooth decay and 135 studies on dental fluorosis with fluoride at any concentration present in drinking water (up to 5 parts per million (ppm) or 5 mg/L).
- Approximately 73 per cent of dental fluorosis studies were conducted in places with naturally occurring fluoride.

b) Findings

The findings of this systematic review were presented to the CWFC in 2016. Amongst children, the introduction of water fluoridation (0.7 ppm) showed:

- 35 per cent reduction in decayed, missing or filled baby teeth (9 studies), 35 per cent reduction in cavities in baby teeth (pooling of nine studies = 44,268 children);
- 26 per cent reduction in cavities in permanent teeth (pooling of 10 studies = 78,764 children); and
- 15 per cent increase in children with no cavities (pooling of 18 studies = 93,504 children).

In areas with a fluoride level of 0.7 ppm in the water, approximately 12 per cent of people had any degree of fluorosis that may cause concern about their appearance.

c) Limitations/Considerations

i) Study design limitations
- Water Fluoridation in Reducing tooth decay in adults:
  - No studies met Cochrane's strict criteria regarding the effectiveness of water fluoridation in adults.
  - Cochrane typically includes studies where the outcomes are evaluated at two points in time in the same sample of adults. Such an evaluation over a long time period can be difficult and unfeasible when assessing population-level interventions such as CWF.
  - Research published in peer-reviewed literature (in Australia and United States) found differences in tooth decay between adults who have access to CWF and those who do not.

ii) Significance of findings
- The authors' statement about being unable to draw conclusions on the effectiveness of CWF in reducing adult tooth decay is related in part to the omission of available, but not included, evidence designed to assess public health programs.
- Due to the strong quality of evidence related to children in the study, Public Health has confidence in the findings that CWF prevents tooth decay in children.

3. Study 2: Australian Systematic Review (Jack et al. 2006)

The Australian systematic review titled Health Effects of Water Fluoridation conducted by Jack et al. (2016) on behalf of the National Health and Medical Research Council (NHMRC) is an update of the evidence from NHMRC's 2007 review to provide guidance on the potential benefits and harms of water fluoridation. The review concluded that CWF is safe and effective in the prevention of tooth decay.

a) Study Strengths and Characteristics

i) Strengths
- Clearly focused question and inclusion/exclusion criteria.
- Level of evidence of the primary studies well described.
- Studies were assessed for quality by two independent reviewers using validated tools.
- Appropriate methods used for comparing results across studies.
- The review was rated "strong" quality by Peel Public Health.

ii) Study characteristics
- This review is an update to the evidence from NHMRC's 2007 review.
- The review examined the effects of water fluoridation (CWF between 0.4 – 1.5 ppm) compared to a non-fluoridated water supply (less than 0.4ppm) on dental caries and dental fluorosis.
- Also looked at the health effects (excluding tooth decay and dental fluorosis) of water fluoridation compared to a non-fluoridated water supply.
- Included three reviews and 25 single studies that reported on tooth decay and one review that also reported on dental fluorosis. Seven single studies reported

on the health effects other than dental outcomes, and 41 single studies reported on 23 health outcomes.

b) Findings

People living in fluoridated areas reported 26-44 per cent less tooth decay than those living in low/non-fluoridated areas. The prevalence of dental fluorosis was associated with an increase in fluoride concentration in water supplies. However, there is insufficient evidence available to predict the prevalence of any dental fluorosis or dental fluorosis of aesthetic concern associated with the current levels of CWF in Australia.

Studies comparing children and adults living in areas with fluoride levels of 0.4, 1.5 and greater than 1.5 ppm with non-/low- fluoridated regions (less than 0.4 ppm) reported:

- No association with intelligence.
- Limited evidence of no association with delayed tooth eruption, tooth wear, osteosarcoma, Ewing sarcoma, total cancer incidence, hip fracture and Down syndrome.
- Insufficient evidence to draw conclusions for kidney stones, chronic kidney disease, gastric discomfort, headache and insomnia.

c) Limitations/Considerations

The systematic review was appraised to be of strong quality; however, the review included poor quality single studies. The one review that showed an association between fluoride at 0.7 ppm and fluorosis was graded low quality for high risk of bias, lack of recent evidence and inconsistency. The review included cases where dental fluorosis can only be detected under clinical conditions and other enamel defects.

The findings of this updated review are reflective with the initial review conducted in 2007 and previous reviews that CWF is safe and effective for preventing tooth decay.

4. Study 3: Mexico Study (Bashash et al. 2017)

The Mexico study titled “Prenatal Fluoride Exposure and Cognitive Outcomes in Children at 4 and 6-12 years of Age in Mexico” conducted by Bashash et al. (2017) examined the association of prenatal exposure to fluoride with offspring neurocognitive development. The study concluded that additional research is needed to examine the potential adverse effects of fluoride to ensure benefits of CWF outweigh any potential risks.

a) Study Strengths and Characteristics

i) Strengths
- Used validated laboratory instruments to measure urinary fluoride.
- Used validated tools by trained clinicians to measure cognitive outcomes.
- Follow-up time was long enough for outcome to occur.

ii) Study characteristics
- Single study (prospective cohort study).
- Measured fluoride in the urine of pregnant mothers and their offspring and examined association with measures of offspring cognitive performance at 4 and 6-12 years old.
- The study had a total of 512 participants (mothers) of which complete data was available for 299 mother-child pairs. Of the 299 mother-child pairs, 287 and 211 had data for General Cognitive Index (GCI) and IQ analyses respectively.
- By living in Mexico, study participants were exposed to fluoridated salt at 250 ppm, and to varying levels of naturally occurring fluoride in drinking water (ranging from 0.15 to 1.38 mg/L).

b) Findings

Among the 299 mother-child pairs living in Mexico City, higher prenatal fluoride exposure was related to lower scores on cognitive tests in the offspring at age 4 and 6-12 years. An increase in urine fluoride of 0.5 mg/L in mothers predicted 3.15 and 2.50 lower offspring scores on the GCI and IQ scores respectively. The GCI is designed to assess the abilities of preschool children (2-8 years of age) based on a six scale scoring system: verbal, perceptual-performance, quantitative, composite (general cognitive), memory, and motor. IQ was measured using a Spanish-version of the Wechsler Abbreviated Scale of Intelligence (WASI), which represents a child's general intellectual ability.

It is important to note that some evidence suggests that associations with IQ may have been limited to fluoride exposures above 0.8 mg/L.

c) Limitations/Considerations

The evidence is based on a prospective cohort study with important design limitations. Prospective cohort studies are single studies and considered lower quality studies compared to systematic reviews. It is unclear if the results of the study are applicable to CWF as practiced in Peel.

i) Study design limitations
- Unclear if cohort (group of people) was representative of the population; hospitals that recruited mothers served low-to-moderate income populations.
- The study did not have a non-intervention group to which study outcomes can be compared to.
- The study did not assess for other plausible explanations of the findings, including the presence of other substances such as iodine or arsenic, deficiencies in nutrition or other possible factors.
- Among variables that may influence the outcome of the study, (e.g., birth weight, gestational age at birth, sex, smoking history, education), data was missing for several variables across participants.
- Study participants were exposed to fluoridated salt (at 250 ppm) and unknown amounts of naturally occurring fluoride in drinking water.
- Of the 512 participants, only 299 had complete data.

ii) Significance of findings

- Despite this study not reaching a clear conclusion, Peel Public Health continues to monitor the evidence on associations between fluoride and IQ and will report to Regional Council if the evidence base changes.
- According to Public Health Ontario's review of this study, "the urinary fluoride levels found in the study are within the range that may be found in some individuals in Canadian communities with fluoridated water supplies."
- Associations with IQ may have been limited to fluoride exposures above 0.8 mg/L, which is higher than Peel's target fluoride concentration of 0.65 mg/L.
- Given the study limitations, particularly the inability to generalize findings, it would be premature to compare the urinary fluoride in study participants to those who live in Canada or elsewhere.
- These findings are not in line with two previous systematic reviews (McDonagh et al. 2000; Jack et al. 2016) that reported no association between fluoride exposure in drinking water and intelligence and other adverse health effects in children or adults.

CONCLUSION

Findings of the systematic reviews indicate that CWF is safe and effective when practiced at a concentration similar to Peel (0.65 mg/L). The Cochrane systematic review found that children living in fluoridated communities have lower incidences and severity of tooth decay compared to those living in low/non-fluoridated communities. The Australian systematic review found that that CWF is effective in reducing tooth decay for both children and adults. The risk of dental fluorosis is slightly higher in fluoridated communities; however this increase represents a small portion of people who experience fluorosis of aesthetic concern. The findings of the Mexico study have important design limitations and are not applicable to the Peel context. Overall, the evidence is consistent with the practice of CWF and does not show a link between fluoride in drinking water at the optimal concentration range (0.5 to 0.8 mg/L) and any adverse health effects.

Nancy Polsinelli, Commissioner of Health Services

Jessica Hopkins, MD MHSc CCFP FRCPC
Medical Officer of Health

COMMUNITY WATER FLUORIDATION – STAFF RESPONSE TO COMMITTEE SELECTED STUDIES

Approved for Submission:

D. Szwarc, Chief Administrative Officer

APPENDICES

Appendix I – Public Health Response to Items Disseminated at the July 5, 2018 CWFC Meeting

For further information regarding this report, please contact Paul Sharma, Director, Chronic Disease and Injury Prevention, Ext. 2013.

Authored By: Fatime Grigorescu, Analyst, Research & Policy, Chronic Disease and Injury Prevention

APPENDIX I
COMMUNITY WATER FLUORIDATION – STAFF RESPONSE TO COMMITTEE SELECTED STUDIES

Public Health Response to Items Disseminated at the July 5, 2018 CWFC Meeting

1. **DOCUMENT:** An email dated May 8, 2017 from Councillor Sprovieri with no subject which asserts that The Lancet has classified fluoride as a neurotoxin. A reference to an article "published in The Lancet Neurology, Volume 13, Issue 3, in the March 2014 edition, by authors Dr. Phillippe Grandjean and Philip J. Landrigan, MD" is included in the email but the article was not provided to staff.

PUBLIC HEALTH RESPONSE: Fluoride has not been classified as a neurotoxin by any governmental body.

- Journals do not declare, or classify substances as a neurotoxin; only governmental organizations are able to make that assertion using published research and other data and regulate those substances accordingly.
- The study was published in the *Lancet Neurology* and introduced no new data on fluoride neurotoxicity.
- The 2012 paper was so misrepresented by some media outlets that the authors had to send out a clarification notice[1] to the press release[2] sent out by Harvard stating that **their results could not be used to assess the levels at which fluoride could become neurotoxic:**
  - "These results do not allow us to make any judgment regarding possible levels of risk at levels of exposure typical for water fluoridation in the U.S. On the other hand, neither can it be concluded that no risk is present. We therefore recommend further research to clarify what role fluoride exposure levels may play in possible adverse effects on brain development, so that future risk assessments can properly take into regard this possible hazard."

2. **DOCUMENT:** A photocopied page with a citation and list of chemicals titled "Chemicals with Substantial Evidence of Developmental Neurotoxicity (n=100)"

PUBLIC HEALTH RESPONSE: Fluoride is not a chemical that causes developmental neurotoxicity.

- Peel Public Health contacted the lead author, Dr. Padilla, to understand its context and the conclusions that can be drawn from it.
- Dr. Padilla stated that the list was intended to inform future research only and does not represent a list of chemicals with proven neurotoxic effect.
- The list was part of a broader poster presentation which clearly states that it does not represent the opinion of the EPA.
- Chemicals were placed on this list of "Substantial Evidence" if more than two laboratories reported evidence of neurotoxic effect. The levels of fluoride in the reports used for classification in the list were substantially higher than that used in Community Water Fluoridation.

3. **DOCUMENT:** A photocopy of the first of ten pages of Schedule 1 of the Canadian Environmental Protection Act (CEPA), 1999 current as of December 22, 2015.

PUBLIC HEALTH RESPONSE: Health Canada recommends the use of drinking water treatment additives (including those used for fluoridation) that have been certified to NSF standards.

---

[1] Statement on fluoride paper [clarification notice on the Internet]. Harvard School of Public Health. 2012 Sep – [cited 2018 Aug 1]. Available from: https://cdn1.sph.harvard.edu/wp-content/uploads/sites/21/2012/07/Media-Statement_Fluoride-9-12-12-Revised2.pdf
[2] Impact of fluoride on neurological development in children. Harvard Chan School News [Internet]. 2012 Jul 25 [cited 2018 Aug 1]. Available from: https://www.hsph.harvard.edu/news/features/fluoride-childrens-health-grandjean-choi/

APPENDIX I
COMMUNITY WATER FLUORIDATION – STAFF RESPONSE TO COMMITTEE SELECTED STUDIES

CEPA 1999 is an Act respecting pollution prevention and the protection of the environment and human health in order to contribute to sustainable development. It provides the Government of Canada with instruments to protect the environment and/or human health, establishes strict timelines for managing substances found toxic under the Act, and requires the virtual elimination of releases to the environment from substances found toxic under the Act that are bioaccumulative, persistent and anthropogenic.

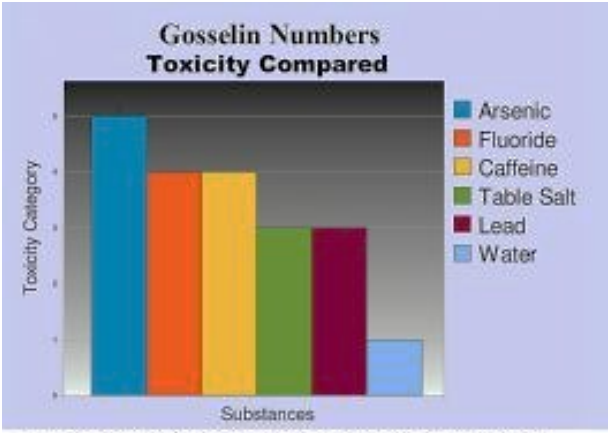
- The Government of Canada's Toxic Substances Management Policy puts forward a precautionary and preventive approach to deal with substances that enter the environment and could harm the environment and/or human health. It provides a framework for making science-based decisions on the effective management of toxic substances. Under this process, Environment Canada and Health Canada prepare a Risk Management Strategy which outlines the proposed approach for reducing risks to human health or the environment posed by a substance found toxic under the Act.

4. DOCUMENT: A photocopied page titled "How Toxic is Fluoride compared to Lead & Arsenic" noting the source *Clinical Toxicology of Commercial Products LD50 data - 1984*

PUBLIC HEALTH RESPONSE: Staff were unable to obtain the complete source of the document provided so is unable to provide comment on the context or accuracy of the information.

However, the American Fluoridation Society did provide comment on this source on its website providing the complete chart included in the source.

"According to Gosselin, et al., both fluoride and caffeine have a toxicity rating of 4 (Very Toxic). Substances at this classification are toxic to humans at the level of 50-500mg/kg. As 1 kg = 2.2 pounds, a 200 pound individual would weigh 90.7 kg. Therefore, the range of toxicity for a substance at the industrial toxicity level of 4 would be 4,535 mg – 45,350 mg. One would have to ingest over 6,000 liters of optimally fluoridated water in a short period of time to even reach the threshold of toxicity of fluoride. As can plainly be seen, the level of daily fluoride intake is so minuscule that a comparison of such toxicity ratings is entirely irrelevant to optimally fluoridated water."



TOXICITY RATING FOR HUMANS (70 KG BODY WEIGHT)

Rating/Class	Dose
6. Super toxic	<5 mg/kg
5. Extremely toxic	5–50 mg/kg
4. Very toxic	50–500 mg/kg
3. Moderately toxic	0.5–5 g/kg
2. Slightly toxic	5–15 g/kg
1. Practically nontoxic	>15 g/kg

Gosselin, et al. (1984). *Clinical Toxicology of Commercial Products.* Williams & Wilkens.

Gosselin, et al. (1984) *Clinical Toxicology of Commercial Products*

From: Sprovieri, John Councillor [mailto:John.Sprovieri@brampton.ca]
Sent: August 22, 2018 1:48 PM
To: West, Helena
Cc: Sprovieri, John; John Sprovieri; Downey, Johanna; Palleschi, Michael; Kovac, John; Dale, Frank; Szwarc, David; Lockyer, Kathryn; O'Connor, Patrick
Subject: FW: Water Fluoridation Committee agenda

Hi Helena,
Can you place the attached information and information from Gilles Parent below on the September 27, 2018 Community Water Fluoridation Committee agenda.
Regards, John.

REFERRAL TO _____
RECOMMENDED
DIRECTION REQUIRED _____
RECEIPT RECOMMENDED ✓_____

From: Gilles Parent, ND
Sent: July 5, 2018 5:40 PM
To: Sprovieri, John Councillor <John.Sprovieri@brampton.ca>
Subject: RE: Water Fluoridation Committee agenda

Dear John,

Yes, I have seen it but this information is brought up for the first time.

Health Canada developed the Guidelines for Canadian Drinking Water Quality: Guideline Technical Document – Fluoride ("Guidelines"), which identifies the Maximum Acceptable Concentration for fluoride (1.5 mg/L). This *Guideline* relies on rigorous evaluation of high quality evidence examining the toxicological effects of fluoridated water. It reviewed over 430 studies, including chronic toxicological studies, to determine that the consumption of water fluoridated at the optimal level did not pose a risk to human health. (By petitions and Freedom of information request, Health Canada was incapable to supply any toxicological review even if in its answers, Health Canada has stated that toxicological review existed, that they were essential to assure the safety of fluoridation chemicals and that they were available in the document of the National Institute of Environmental Health Sciences entitled «Sodium Hexafluorosilicate [CASRN 16893-85-9] And Fluorosilicic Acid [CASRN 16961-83-4] Review of Toxicological Literature». In Quebec, the Public Health referred us to the same document that surprisingly and explicitly states that these toxicological reviews have not been done and that they aren't available. Same for the Quebec Ministry of Health does not have any toxicological review and is incapable to supply any reference to any document on the subject. Any health authority that claims being an expert and that has not been aware of what is found in the document of National Institute of Environmental Health Sciences cannot pretend being so.
Inhalation: No data
Oral: LD50, rat, 125 mg/kg (Sodium Hexafluorosilicate)
Dermal: No data
Irritation: No data
Sensitization: No data
Comments: None
Chronic toxicity: No data
Carcinogenic Designation: None
Environmental Fate: No information found.
Environmental Toxicity: No information found.
It is strange that now, still without these toxicological review, long considered as essential, aren't required anymore because they don't exist.)

> The Guideline development also included a comprehensive peer-review process with international experts in relevant fields and approval by the Federal/Provincial/Territorial Committee on Drinking Water and the Federal/Provincial/Territorial Committee on Health and Environment.

For the purposes of drinking water treatment chemicals, toxicology reviews are conducted for substances that are ingested with drinking water. Health Canada has not conducted toxicology reviews on HFSA because it completely dissociates, leaving fluoride in the water,

not HFSA. (Strangely, Health Canada has stated in our Petitions 299, 299B and 299 C that a toxicological review was required.)

From: Sprovieri, John Councillor [mailto:John.Sprovieri@brampton.ca]
Sent: August 22, 2018 1:48 PM
To: West, Helena
Cc: Sprovieri, John; John Sprovieri; Downey, Johanna; Palleschi, Michael; Kovac, John; Dale, Frank; Szwarc, David; Lockyer, Kathryn; O'Connor, Patrick
Subject: FW: Water Fluoridation Committee agenda

Hi Helena,
Can you place the attached information and information from Gilles Parent below on the September 27, 2018 Community Water Fluoridation Committee agenda.
Regards, John.

REFERRAL TO _____
RECOMMENDED
DIRECTION REQUIRED _____
RECEIPT RECOMMENDED ✓_____

EPA/635/R-00/007

TOXICOLOGICAL REVIEW

OF

CHLORINE DIOXIDE

AND

CHLORITE

(CAS Nos. 10049-04-4 and 7758-19-2)

In Support of Summary Information on the Integrated Risk Information System (IRIS)

September 2000

U.S. Environmental Protection Agency
Washington, DC

DISCLAIMER

This document has been reviewed in accordance with U.S. Environmental Protection Agency policy. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

This document may undergo revisions in the future. The most up-to-date version will be made electronically via the IRIS Home Page at http://www.epa.gov/iris.

CONTENTS

CONTENTS (continued)

FOREWORD

The purpose of this Toxicological Review is to provide scientific support and rationale for the hazard and dose-response assessment in IRIS pertaining to chronic exposure to chlorine dioxide and chlorite. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of chlorine dioxide and chlorite.

In Section 6, EPA has characterized its overall confidence in the quantitative and qualitative aspects of hazard and dose response. Matters considered in this characterization include knowledge gaps, uncertainties, quality of data, and scientific controversies. This characterization is presented in an effort to make apparent the limitations of the assessment and to aid and guide the risk assessor in the ensuing steps of the risk assessment process.

For other general information about this assessment or other questions relating to IRIS, the reader is referred to EPA's Risk Information Hotline at 513-569-7254.

AUTHORS, CONTRIBUTORS, AND REVIEWERS

Chemical Managers/Authors

Yogendra Patel, Ph.D.
OST/HECD
Office of Water
U.S. Environmental Protection Agency
Washington, DC

Diana Wong, Ph.D., D.A.B.T.
OST/HECD
Office of Water
U.S. Environmental Protection Agency
Washington, DC

Contributing Authors

Lisa Ingerman, Ph.D., D.A.B.T.
Senior Scientist
Syracuse Research Corporation
Portland, OR

Patricia McGinnis, Ph.D., D.A.B.T.
Senior Scientist
Syracuse Research Corporation
Philadelphia, PA

Mark Osier, Ph.D.
Senior Scientist
Syracuse Research Corporation
North Syracuse, NY

Reviewers

This document and summary information on IRIS have received peer review both by EPA scientists and by independent scientists external to EPA. Subsequent to external review and incorporation of comments, this assessment has undergone an Agencywide review process whereby the IRIS Program Manager has achieved a consensus approval among the Office of Research and Development; Office of Air and Radiation; Office of Prevention, Pesticides, and Toxic Substances; Office of Solid Waste and Emergency Response; Office of Water; Office of Policy, Planning, and Evaluation; and the Regional Offices.

AUTHORS, CONTRIBUTORS, AND REVIEWERS (continued)

Internal EPA Reviewers

Annie J. Jarabek
ORD / NCEA
Research Triangle Park, NC

Ginger Moser, Ph.D., D.A.B.T.
ORD / NTD/NHEERL
Research Triangle Park, NC

External Peer Reviewers

Paul E. Brubaker, Ph.D.
Consultant
Brubaker and Associates

James Edward Klaunig, Ph.D.
Division of Toxicology, Department of Pharmacology and Toxicology
Indiana University School of Medicine

June Dunnick, Ph.D.
Scientist
National Institute of Environmental Health Sciences

Calvin C. Willhite, Ph.D.
State of California, Department of Toxic Substances Control

Summaries of the external peer reviewers' comments and the disposition of their recommendations are in the Appendix.

1. INTRODUCTION

This document presents background and justification for the hazard and dose-response assessment summaries in the U.S. Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS). IRIS summaries may include an oral reference dose (RfD), inhalation reference concentration (RfC), and a carcinogenicity assessment.

The RfD and RfC provide quantitative information for noncancer dose-response assessments. The RfD is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis but may not exist for other toxic effects such as some carcinogenic responses. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer effects during a lifetime. The inhalation RfC is analogous to the oral RfD, but it provides a continuous inhalation exposure estimate. The inhalation RfC considers toxic effects for the respiratory system (portal of entry) and for effects peripheral to the respiratory system (extra respiratory or systemic effects). It is generally expressed in units of mg/m^3.

The carcinogenicity assessment provides information on the carcinogenic hazard potential of the substance in question and quantitative estimates of risk from oral exposure and inhalation exposure. The information includes a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen and the conditions under which the carcinogenic effects may be expressed. Quantitative risk estimates are presented in three ways. The *slope factor* is the result of application of a low-dose extrapolation procedure and is presented as the risk per mg/kg-day. The *unit risk* is the quantitative estimate in terms of either risk per ：g/L drinking water or risk per ：g/m^3 air breathed. Another form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000.

Development of these hazard identification and dose-response assessments for chlorine dioxide and chlorite has followed the general guidelines for risk assessment as set forth by the National Research Council (1983). EPA guidelines that were used in the development of this assessment may include the following: *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986a); *Guidelines for the Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 1986b); *Guidelines for Mutagenicity Risk Assessment* (U.S. EPA, 1986c); *Guidelines for Developmental Toxicity Risk Assessment* (U.S. EPA, 1991); *Guidelines for Neurotoxicity Risk Assessment* (U.S. EPA, 1998a); *Proposed Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1996a); *Reproductive Toxicity Risk Assessment Guidelines* (U.S. EPA, 1996b); *Recommendations for and Documentation of Biological Values for Use in Risk Assessment* (U.S. EPA, 1988); (proposed) *Interim Policy for Particle Size and Limit Concentration Issues in Inhalation Toxicity* (U.S. EPA, 1994a); *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994b); *Peer Review and Peer Involvement at the U.S. Environmental Protection Agency* (U.S. EPA, 1994c); *Use of the Benchmark Dose Approach in Health Risk Assessment* (U.S. EPA, 1995); *Science Policy Council Handbook: Peer Review* (U.S.

EPA, 1998b); and a memorandum from EPA Administrator, Carol Browner, dated March 21, 1995, Subject: Guidance on Risk Characterization.

Literature search strategies employed for these compounds were based on the CASRN and at least one common name. At a minimum, the following databases were searched: RTECS, HSDB, TSCATS, CCRIS, GENETOX, EMIC, EMICBACK, DART, ETICBACK, TOXLINE, CANCERLINE, MEDLINE, and MEDLINE backfiles. Any pertinent scientific information submitted by the public to the IRIS Submission Desk was also considered in the development of this document.

2. CHEMICAL AND PHYSICAL INFORMATION RELEVANT TO ASSESSMENTS

Chlorine dioxide (ClO_2; CASRN 10049-04-4) is a yellow to reddish-yellow gas at room temperature that is stable in the dark but is unstable in light. It is a strong oxidizing agent that under oxidant demand conditions is readily reduced to chlorite (ClO_2^-; CASRN 7758-19-2), another strong oxidizing agent. The *Drinking Water Criteria Document on Chlorine Dioxide, Chlorite, and Chlorate* (U.S. EPA, 1994d) provides the relevant information concerning dissociation byproducts of chlorine dioxide in water. The strong oxidizing ability of chlorine dioxide makes it useful as a drinking water disinfectant. Other uses of chlorine dioxide include bleaching textiles and wood pulp for paper manufacturing, antimicrobial applications, and reducing loads of adsorbable organic halogenated compounds in industrial effluents. Chlorite is also used for etching printed circuit boards. The physical and chemical properties of chlorine dioxide and chlorite are presented in Table 1.

Chlorine dioxide and chlorite are characterized together in this report because studies conducted with chlorite, the predominant degradation product of chlorine dioxide, are likely relevant to characterizing the toxicity of chlorine dioxide. In addition, studies conducted with chlorine dioxide may be relevant to characterizing the toxicity of chlorite. Chlorine dioxide is fairly unstable and rapidly dissociates, predominantly into chlorite and chloride, and to a lesser extent, chlorate. There is a ready interconversion among these species in water (before administration to animals) and in the gut (after ingestion) (U.S. EPA, 1994d). Therefore, what exists in water or the stomach is a mixture of these chemical species (i.e., chlorine dioxide, chlorite, chlorate) and possibly their reaction products with the gastrointestinal contents.

Table 1. Physical and chemical properties of chlorine dioxide and chlorite

Properties	Chlorine dioxide	Chlorite (sodium salt)
CAS registry number	10049-04-4	7758-19-2
Molecular formula	ClO_2	$NaClO_2$
Molecular weight	67.46	90.45
Melting point, °C	-59	decomposes at 180–200
Boiling point, °C	11	no data
Water solubility, g/L	3.0 at 25°C and 34 mmHg	39 at 30°C
Specific gravity	1.642 at 0°C	no data

Source: Budavari et al., 1989.

3. TOXICOKINETICS RELEVANT TO ASSESSMENTS

3.1. ABSORPTION

3.1.1. Gastrointestinal Absorption

3.1.1.1. *Chlorine Dioxide*

After ingestion, chlorine dioxide is rapidly absorbed from the gastrointestinal tract. Levels of radioactive chlorine in plasma peaked 1 hour after Sprague-Dawley rats were administered a single gavage dose of 100 mg/L $^{36}ClO_2$ (approximately 1.4 mg/kg) (Abdel-Rahman et al., 1979a). Peak plasma levels were achieved 2 hours after Sprague-Dawley rats received a gavage dose of 300 mg/L $^{36}ClO_2$ after a 15-day exposure to 100 mg/L chlorine dioxide in drinking water (Abdel-Rahman et al., 1979a). Approximately 30% of the 100 mg/L single gavage dose was excreted in the urine after 72 hours, indicating that at least 30% of the dose was absorbed (Abdel-Rahman et al., 1979a); the absorption rate constant and half time were 3.77/hour and 0.18 hours, respectively (Abdel-Rahman et al., 1982). Since total radioactivity was measured rather than identification of individual chemical entities, it was not clear from these reports whether the parent chlorine dioxide itself or the chlorite, chlorate, or chloride ion degradation products were absorbed.

3.1.1.2. *Chlorite*

Chlorite is also rapidly absorbed from the gastrointestinal tract. Peak plasma levels of radiolabeled chlorine were reached 2 hours after administration of a single gavage dose of 10 mg/L $^{36}ClO_2^-$ (approximately 0.13 mg/kg) to Sprague-Dawley rats. Using 72-hour urinary

excretion data, it can be assumed that at least 35% of the initial dose was absorbed (Abdel-Rahman et al., 1984a). The absorption rate constant and half-time were 0.198/hour and 3.5 hours, respectively (Abdel-Rahman et al., 1982). Since total radioactivity was measured rather than identification of individual chemical entities, it was not clear from these reports whether the parent chlorine dioxide itself or the chlorite, chlorate, or chloride ion degradation products were absorbed.

3.1.2. Respiratory Tract Absorption

No data were located on respiratory tract absorption of chlorine dioxide or chlorite.

3.1.3. Dermal Absorption

Scatina et al. (1984) reported on the dermal absorption of Alcide, an antimicrobial compound consisting of solutions of sodium chlorite and lactic acid, which when mixed immediately before use result in the formation of chlorine dioxide. 0.6 g ^{36}Cl-labeled sodium chlorite as part of the Alcide was used to monitor absorption following application to the shaved backs of 10 female Sprague-Dawley rats. Maximum absorption of ^{36}Cl into plasma was observed after 72 hours, where a plasma concentration of 69.4 µg% ^{36}Cl was reached. The absorption half-life was calculated to be 22.1 hours, which corresponds to a rate constant of 0.0314 hr^{-1}.

3.2. DISTRIBUTION

3.2.1. Chlorine Dioxide

Following a single 100 mg/L gavage dose of $^{36}ClO_2$, the ^{36}Cl was slowly cleared from the blood; the rate constant and half-time for elimination from blood were 0.0156/hour and 43.9 hours, respectively (Abdel-Rahman et al., 1982). Elimination from blood was shortened in Sprague-Dawley rats exposed to chlorine dioxide in drinking water for 2 weeks prior to receiving the 300 mg/L gavage dose of $^{36}ClO_2$; the rate constant and half time were 0.022/hour and 31.0 hours, respectively (Abdel-Rahman et al., 1979a). After removal from the blood, the radiolabel appeared to be widely distributed throughout the body, although the highest concentrations were found in the blood, stomach, and small intestines. The lung, kidney, liver, testes (assessed only in the 300 mg/L group), spleen, thymus, and bone marrow also had high concentrations of radiolabel 72 hours after dosing with 100 mg/L (single dose) or 300 mg/L (with 2-week drinking water exposure to 100 mg/L) (Abdel-Rahman et al., 1979a). Seventy-two hours after a single gavage dose of 100 mg/L $^{36}ClO_2$, most of the ^{36}Cl label in the plasma was in the form of chloride ion (Cl^-) and chlorite; the ratio of chloride to chlorite was 4 to 1 (Abdel-Rahman et al., 1979b).

3.2.2. Chlorite

Removal of chlorite from the blood is slow; the rate constant and half-time for elimination of ^{36}Cl from the blood were 0.0197/hour and 35.2 hours in Sprague-Dawley rats receiving a single gavage dose of 10 mg/L $^{36}ClO_2^-$ (Abdel-Rahman et al., 1982). Seventy-two hours after dosing, the highest concentrations of radiolabel were found in the blood, stomach,

testes, skin, lung, kidneys, small intestine, carcass, spleen, brain, bone marrow, and liver (Abdel-Rahman et al., 1982, 1984a).

3.3. METABOLISM

3.3.1. Chlorine Dioxide

Chloride ion is the ultimate metabolite of chlorine dioxide. Approximately 87% and 80% of radiolabeled chlorine in the urine (collected 0–72 hours after administration) and plasma (collected 72 hours after administration), respectively, are in the form of chloride ion following administration of a single gavage dose of 100 mg/L $^{36}ClO_2$ in rats (Abdel-Rahman et al., 1979b). Chlorite was a major metabolite, accounting for approximately 11% and 21% of urine and plasma ^{36}Cl, respectively; approximately 2% of the urinary ^{36}Cl was in the form of chlorate. An in vivo recovery study by Bercz et al. (1982) suggests that ingested chlorine dioxide is rapidly reduced in the stomach to nonoxidizing species (presumably chloride). Five minutes after chlorine dioxide was instilled into the stomach of a monkey, only 8% of the total oxidizing capacity equivalents of chlorine dioxide was recovered. Bercz et al. (1982) also reported that in vitro chlorine dioxide was rapidly reduced to chloride ion by saliva obtained from anesthetized monkeys.

3.3.2. Chlorite

Although fewer data are available on metabolism of chlorite, it is likely that metabolism of chlorite is similar to that of chlorine dioxide. Approximately 85% of the ^{36}Cl recovered in the urine of Sprague-Dawley rats 0–72 hours after administration of a single gavage of 10 mg/L $^{36}ClO_2^-$ was in the form of chloride; the remaining 15% was present as chlorite (Abdel-Rahman et al., 1984a).

3.4. ELIMINATION

3.4.1. Chlorine Dioxide

The radioactive chlorine label was primarily excreted in the urine of rats administered a single gavage dose of 100 mg/L $^{36}ClO_2$ (Abdel-Rahman et al., 1979a). During the first 24 hours after dosing, 18% of the label was excreted in the urine and 4.5% in the feces. Seventy-two hours after dosing, 31% and 10% of the label were excreted in the urine and feces, respectively; the label was not detected in expired air. The parent compound was not detected in the urine; most of the label was in the form of chloride, with smaller amounts as chlorite. The ratio of $^{36}Cl^-$ to $^{36}ClO_2^-$ was 5 to 1 during the first 24 hours and 4 to 1 during the first 72 hours (Abdel-Rahman et al., 1979b).

3.4.2. Chlorite

Urine was the primary route of excretion in rats administered a single gavage dose of 10 mg/L $^{36}ClO_2^-$. Twenty-four hours after dosing, 14% of the label was excreted in the urine and

0.9% in the feces; 35% and 5% of the label were excreted in the urine and feces, respectively, 72 hours after dosing (Abdel-Rahman et al., 1984a). Approximately 90% of the excreted label was in the form of chloride.

4. HAZARD IDENTIFICATION

4.1. STUDIES IN HUMANS—EPIDEMIOLOGY, CASE REPORTS, CLINICAL CONTROLS

4.1.1. Oral Exposure

4.1.1.1. *Chlorine Dioxide*

The short-term toxicity of chlorine dioxide was assessed in two human studies conducted by Lubbers and associates (Lubbers et al., 1981, 1982, 1984a; Bianchine et al., 1981). In the first study (Lubbers et al., 1981; also published as Lubbers et al., 1982), a group of 10 healthy male adults drank 1,000 mL (divided into two 500 mL portions, separated by 4 hours) of a 0 or 24 mg/L chlorine dioxide solution (0.34 mg/kg, assuming a 70 kg reference body weight). In the second study (Lubbers et al., 1984a), groups of 10 adult males were given 500 mL distilled water containing 0 or 5 mg/L chlorine dioxide (0.04 mg/kg-day assuming a reference body weight of 70 kg) for 12 weeks. Neither study found any physiologically relevant alterations in general health (observations and physical examination), vital signs (blood pressure, pulse rate, respiration rate, and body temperature), serum clinical chemistry parameters (including glucose, urea nitrogen, phosphorus, alkaline phosphatase, and aspartate and alanine aminotransferases), serum triiodothyronine (T3) and thyroxine (T4) levels, or hematologic parameters.

4.1.1.2. *Chlorite*

Lubbers et al. (1981, 1982, 1984a) also examined the toxicity of chlorite in normal healthy adults in studies that were run concurrently with the chlorine dioxide studies. In the single exposure study (Lubbers et al., 1981, 1982), 10 male adults consumed two 500 mL (separated by 4 hours) solutions containing 2.4 mg/L chlorite (0.034 mg/kg assuming a reference body weight of 70 kg). In a 12-week study (Lubbers et al., 1984a), groups of 10 men drank 500 mL solutions of 0 or 5 mg/L chlorite (0.04 mg/kg-day assuming a 70 kg body weight). No physiologically relevant alterations in general health (observations and physical examination), vital signs, hematologic (including erythrocyte and total and differential leukocyte counts, hemoglobin, hematocrit, and methemoglobin) or serum clinical chemistry (including glucose, electrolytes, calcium, urea nitrogen, enzyme levels, and cholesterol) parameters, or serum T3 or T4 levels were found in either study.

In a companion study, three healthy glucose-6-phosphate dehydrogenase deficient male subjects were given deionized water containing 5 mg/L chlorite (0.04 mg/kg-day assuming a reference body weight of 70 kg) for 12 weeks (Lubbers et al., 1984b). Compared with the

control group in Lubbers et al. (1984a), the chlorite exposure did not alter general health, vital signs, hematologic parameters (including erythrocyte and total and differential leukocyte counts, hemoglobin, hematocrit, and methemoglobin) or serum clinical chemistry (including glucose, electrolytes, calcium, urea nitrogen, enzyme levels, and cholesterol) parameters.

4.1.1.3. *Chlorine Dioxide–Disinfected Water*

Michael et al. (1981), Tuthill et al. (1982), and Kanitz et al. (1996) have examined communities with chlorine dioxide disinfected water. The focus of the Tuthill et al. (1982) and Kanitz et al. (1996) studies was developmental toxicity. Michael et al. (1981) measured hematologic (erythrocyte, leukocyte, and reticulocyte counts, hemoglobin and methemoglobin levels, hematocrit, mean corpuscular volume, and osmotic fragility) and serum chemistry (blood urea nitrogen and total bilirubin levels) parameters in 198 individuals 1 week before the community initiated the chlorine dioxide water treatment program and 10 weeks after initiation. Blood samples were collected at the same times from a control group of 118 individuals not exposed to chlorine dioxide–treated drinking water. The water treatment facility operated only 8 hours/day; water was drawn from storage tanks for the rest of the day. Chlorine dioxide rapidly disappeared from the stored water (within 2–4 hours), and chlorite levels concomitantly increased. Weekly average concentrations (presumably measured during plant operation hours) of chlorine dioxide ranged from 0.25 to 1.11 ppm, and chlorite concentrations ranged from 3.19 to 6.96 ppm (daily mean chlorite concentration was 5.21 ppm). Using measured water consumption rates (1.98 L/day), the study authors estimated that daily chlorite intakes ranged from 0 to 39.4 mg/day (0–0.56 mg/kg-day assuming a 70 kg reference body weight); the mean intake was 10.3 mg/day (0.15 mg/kg-day). The difference between pre- and posttreatment blood urea nitrogen levels was lower in the community with chlorine dioxide–disinfected water than in the control community. However, the study authors noted that this difference was probably because mild dehydration had occurred in the control community, the postinitiation sample was taken during extremely hot weather, and more individuals in the control group had active, outdoor jobs. No other hematologic or serum chemistry alterations were found.

Tuthill et al. (1982) retrospectively compared infant morbidity and mortality data for a community that had utilized “high” levels of chlorine dioxide as a drinking water disinfectant in the 1940s with data of a neighboring community using conventional drinking water chlorination practices. The authors reported average monthly levels of 0.32 ppm of sodium chlorite added post-treatment, but they did not report chlorine dioxide levels in the treated water. Exposure to chlorine dioxide–treated water did not adversely affect fetal, neonatal, postneonatal, or infant mortality, nor did it affect birthweight, sex ratio, or birth condition. Incidence of newborns judged premature by physician assessment was significantly higher in the community with chlorine dioxide–treated water. In reviewing this study, EPA (1994d) concluded there was no increase in the proportion of premature infants when the age of the mother was controlled and that there was a greater postnatal weight loss in infants from the exposed community.

Kanitz et al. (1996) followed 548 births at Galliera Hospital, Genoa, and 128 births at Chiavari Hospital, Chiavari, Italy, during 1988–1989. Data on infant birthweight, body length, cranial circumference, and neonatal jaundice and on maternal age, smoking, alcohol

consumption, education, and preterm delivery were collected from hospital records. Women in Genoa were exposed to filtered water disinfected with chlorine dioxide, sodium hypochlorite, or both; trihalomethane levels varied from 8 to 16 ppb in sodium hypochlorite-treated water and 1 to 3 ppb in chlorine dioxide–disinfected water. Levels of chlorine dioxide in the water immediately after treatment were less than 0.3 mg/L, while chlorine residue was less than 0.4 mg/L. Women residing in Chiavari used water pumped from wells, without any disinfection treatment, and served as the comparison group (controls). Odds ratios were determined for the somatic parameters by comparison of groups exposed to chlorine dioxide, sodium hypochlorite, or both with controls and adjusted for maternal education level, income, age, and smoking and for sex of the child. Neonatal jaundice occurred more frequently (odds ratio [OR] = 1.7; 95% confidence interval [CI] = 1.1–3.1) in infants whose mothers resided in the area where surface water was disinfected with chlorine dioxide, when compared with infants with mothers using nondisinfected well water. Infants born to mothers residing in areas where surface water was disinfected had smaller cranial circumference (# 35 cm) (OR = 2.2, 95% CI = 1.4–3.9 for chlorine dioxide; OR = 3.5, 95% CI = 2.1–8.5 for sodium hypochlorite vs. untreated well water; OR = 2.4, 95% CI = 1.6–5.3 for both vs. untreated well water). In addition, these infants had a smaller body length (# 49.5 cm) (OR = 2.0, 95% CI = 1.2–3.3 for chlorine dioxide vs. untreated well water; OR = 2.3, 95% CI = 1.3–4.2 for sodium hypochlorite vs. untreated well water). Risks for low-birthweight infants (# 2,500 g) were reported to be increased in mothers residing in areas using water disinfected with chlorite and chlorine dioxide, but these associations were not statistically significant. For preterm delivery (# 37 weeks), small but not statistically significant increased risks were found among mothers residing in the area using chlorine dioxide. The study authors concluded that infants of women who consumed drinking water treated with chlorine compounds during pregnancy were at higher risk for neonatal jaundice, cranial circumference # 35 cm, and body length # 49.5 cm.

Interpretability of the results of Kanitz et al. (1996) is limited by lack of consideration of exposure and potential confounding variables such as quantity of water consumed during pregnancy, lack of quantitative exposure information, exposure to other chemicals in the water, and nutritional and smoking habits and age distribution of the women. In addition, baseline values for the infant sex ratio and percentage of low-weight births for the comparison group deviate from values presented by the World Health Organization for Italy. For example, the sex ratio (male/female live births * 100) used in the study for the comparison group was 86, but most recent data (for 1996, as cited in WHO, 2000) for Italy indicate a sex ratio value of 113. Although the percentage of low-weight births in the control group for the Kanitz et al. (1996) study was 0.8%, the percentage of low-weight births (< 2,500 g) in Italy for 1994 is 6%. The quality of the untreated well water is not known (i.e., whether it contained any chemical or biological contaminants). The atypical baseline data raise concerns about the control population selected for this study and render any comparison to them by the exposed group difficult to interpret, thereby precluding the ability to draw conclusions (Selevan, 1997).

4.1.2. Inhalation Exposure

4.1.2.1. *Chlorine Dioxide*

Several case reports of accidental inhalation exposure to chlorine dioxide have been reported in the literature. Elkins (1959) described the case of a bleach tank worker who died after being exposed to 19 ppm chlorine dioxide (52 mg/m^3) for an unspecified amount of time; another worker exposed at the same time survived. Elkins also stated that 5 ppm (14 mg/m^3) was definitely irritating to humans. In a case reported by Exner-Freisfeld et al. (1986), a woman experienced coughing, pharyngeal irritation, and headache after inhaling an unknown amount of chlorine dioxide inadvertently generated while bleaching flowers. Seven hours after exposure, the woman was hospitalized with cough, dyspnea, tachypnea, tachycardia, rales on auscultation, and marked leukocytosis; a decrease in lung function (reduced vital capacity and 1-second forced expiratory volume) was also reported. Most of these symptoms were alleviated with corticosteroid treatment.

Meggs et al. (1996) examined 13 individuals (1 man and 12 women) 5 years after they were occupationally exposed to chlorine dioxide from a leak in a water purification system pipe. The long-term effects of the accident included development of sensitivity to respiratory irritants (13 subjects), disability with loss of employment (11 subjects), and chronic fatigue (11 subjects). Nasal abnormalities (including injection, telangectasia, paleness, cobblestoning, edema, and thick mucus) were found in all 13 individuals. Nasal biopsies taken from the subjects revealed chronic inflammation with lymphocytes and plasma cells present within the lamina propria in 11 of the 13 subjects; the inflammation was graded as mild in 2 subjects, moderate in 8 subjects, and severe in 1 subject. Nasal biopsies from three control subjects showed chronic inflammation in one subject. The average inflammation grading was statistically higher in the subjects compared with the controls. The number of nerve fibers in the biopsies was higher in the subjects (rare fibers in three subjects, moderate fibers in two subjects, and many fibers in three subjects) than controls, but the difference was not statistically significant.

Gloemme and Lundgren (1957), Ferris et al. (1967), and Kennedy et al. (1991) examined workers occasionally exposed to high concentrations of chlorine dioxide that resulted from equipment failure. Concurrent exposure to chlorine gas and, in some cases, sulfur dioxide confounds interpretation of the results of these studies. Gloemme and Lundgren (1957) examined the respiratory health of 12 workers employed at a sulfite-cellulose production facility. Under normal working conditions, the atmospheric chlorine content was less than 0.1 ppm (chlorine dioxide levels were not measured); however, occasional equipment leakages would result in high levels of chlorine dioxide, chlorine, and/or sulfur dioxide. The workers reported respiratory discomfort (breathlessness, wheezing, irritant cough) and ocular discomfort (conjunctivitis and “halo phenomena”) connected with these leakage exposures. A slight, nonspecific chronic bronchitis was diagnosed in 7 of the 12 men. An earlier-observed bronchitis disappeared in one case, suggesting to the study authors that improved working conditions might entail reversal of this disorder.

In the Ferris et al. (1967) study, no significant alterations in pulmonary function (forced vital capacity, maximum expiratory flow, forced expiratory flow, and forced expiratory volume) were observed in 147 men employed (length of employment not reported) at a pulp mill, compared with 124 men employed at a paper mill. The pulp mill workers were exposed to sulfur dioxide or chlorine dioxide and chlorine; the chlorine dioxide concentrations ranged from trace amounts to 2 ppm (average concentrations ranged from trace amounts to 0.25 ppm), and chlorine concentrations ranged from trace amounts to 64 ppm (average concentrations ranged from trace amounts to 7.4 ppm). When the pulp mill workers were divided into workers exposed to sulfur dioxide and those exposed to chlorine or chlorine dioxide, significantly higher incidences of shortness of breath and excess phlegm were found in the chlorine/chlorine dioxide workers.

In the Kennedy et al. (1991) study of 321 pulp mill workers exposed to chlorine and chlorine dioxide, significant increases in the incidence of wheezing, wheezing accompanied by breathlessness, and work-related wheezing were observed, compared with 237 workers at a rail maintenance yard. Personal time-weighed average (TWA) exposure concentration for chlorine at the pulp mill ranged from 5 to 14 ppm, whereas TWA for chlorine dioxide was below 0.1 ppm. However, 60% of the pulp mill workers reported one or more chlorine or chlorine dioxide "gassing" incidents. No significant differences in tests of pulmonary function were observed between the two groups. The pulp mill workers were divided into two groups based on self-reported accidental exposures to high levels of chlorine/chlorine dioxide gas ("gassing"). In the workers reporting one or more incidents of gassing, the prevalence of wheezing and missed work because of chest illness was higher than in the pulp mill workers not reporting gassing incidents. Additionally, the incidence of airflow obstruction (as measured by a decrease in midmaximal flow rate and the ratio of 1-second forced expiratory volume to forced vital capacity) was higher in nonsmokers and former smokers reporting gassing incidents compared with smokers also reporting gassing incidents.

4.1.2.2. *Chlorite*

No human inhalation exposure data for chlorite were located.

4.2. PRECHRONIC AND CHRONIC STUDIES AND CANCER BIOASSAYS IN ANIMALS—ORAL AND INHALATION

4.2.1. Oral Exposure

4.2.1.1. *Chlorine Dioxide*

Although the subchronic/chronic toxicity of chlorine dioxide has been investigated in a number of studies, only Daniel et al. (1990) and Haag (1949) examined a wide range of endpoints. The other studies (Bercz et al., 1982; Abdel-Rahman et al., 1984b; Couri and Abdel-Rahman, 1980; Moore and Calabrese, 1982) focused on the hematologic system. To date, no studies have examined the carcinogenic potential of chlorine dioxide.

Daniel et al. (1990) exposed groups of 10 male and 10 female Sprague-Dawley rats to chlorine dioxide in drinking water for 90 days at concentrations of 0, 25, 50, 100, or 200 mg/L. These concentrations correspond to administered doses of 0, 2, 4, 6, or 12 mg/kg-day chlorine dioxide for males and 0, 2, 5, 8, or 15 mg/kg-day chlorine dioxide for females (calculated by the study authors using water consumption and body weight data). No exposure-related deaths were reported. Exposure to 200 mg/L resulted in significant reductions in terminal body weights and body weight gain (26%–29% lower than controls). Significant reductions in water consumption were observed in the males exposed to $ 50 mg/L and in females exposed to $ 25 mg/L; decreases in food consumption were also observed in the 200 mg/L males. Absolute liver weights were decreased in males at $ 50 mg/L, and absolute spleen weights were decreased in females at $ 25 mg/L. No consistent alterations in hematologic parameters (erythrocyte and total and differential leukocyte counts, hemoglobin levels, hematocrit, and mean corpuscular volume measured) were observed. Serum lactate dehydrogenase and aspartate aminotransferase levels were decreased and serum creatinine levels were increased in the males exposed to 100 or 200 mg/L; no other alterations in serum chemistry parameters were consistently found. A significant increase in incidence of nasal lesions (goblet cell hyperplasia and inflammation of nasal turbinates) was found in males exposed to $ 25 mg/L and in females at $100 mg/L. The study authors postulated that these lesions were likely caused by inhalation of chlorine dioxide vapors at the drinking water sipper tube or from off-gassing of the vapors after drinking rather than ingestion of the drinking water. Thus, 25 mg/L (2 mg/kg-day) can be described as a lowest-observed-adverse-effect level (LOAEL), but the toxicological significance of the nasal lesions is not known. Respiratory tract pathologies have not been reported in other oral studies and the effect may possibly be an artifact of treatment.

In a chronic toxicity study by Haag (1949), groups of seven male and seven female rats were exposed to 0, 0.5, 1, 5, 10, or 100 mg/L chlorine dioxide in drinking water (0.07, 0.13, 0.7, 1.3, or 13 mg/kg-day as calculated by U.S. EPA, 1994d) for 2 years. Survival in the 100 mg/L group was significantly decreased. No chlorine dioxide-related alterations were observed in the histopathologic examination of representative animals (2–6/sex) from each group. Thus, a no-observed-adverse-effect level (NOAEL) of 10 mg/L (1.3 mg/kg-day) and a frank effect level (FEL) (based on decreased survival) of 100 mg/L (13 mg/kg-day) can be identified from this study.

The Bercz et al. (1982) study used a rising-dose design in which each animal served as its own control. Five male and seven female adult African green monkeys (*Cercopithecus aethiops*) were exposed to 0, 30, 100, and 200 mg/L chlorine dioxide for 4–6 weeks. The study authors estimated chlorine dioxide administered doses to be 3.5 and 9.5 mg/kg-day in the 30 and 100 mg/L groups, respectively. Exposure to 200 mg/L resulted in erythema and ulceration of the oral mucosa, mucous nasal discharge, and avoidance of drinking water; exposure to 200 mg/L was terminated after 1 week because some of the animals showed signs of dehydration. No significant alterations in hematologic clinical chemistry (erythrocyte, total and differential leukocyte, and reticulocyte counts, hemoglobin levels, hematocrit, osmotic fragility, and methemoglobin levels) or serum clinical chemistry (creatinine, blood urea nitrogen [BUN], alkaline phosphatase, lactate dehydrogenase, and alanine and aspartate aminotransferase) parameters or body weight gain were observed. Serum T4 levels were significantly decreased in

the 100 mg/L chlorine dioxide-exposed monkeys after 6 weeks of exposure. Thus, this study identifies a NOAEL of 30 mg/L (3.5 mg/kg-day) and a LOAEL of 100 mg/L (9.5 mg/kg-day) for alterations in thyroid hormone levels in monkeys exposed to chlorine dioxide in the drinking water for 4–6 weeks.

Abdel-Rahman et al. (1984b) exposed groups of four male Sprague-Dawley rats to 0, 1, 10, 100, or 1,000 mg/L chlorine dioxide in the drinking water 20 hours/day for 11 months (doses of 0.10, 1, 10, and 100 mg/kg-day are estimated using a reference body weight of 0.523 kg and reference water intake of 0.062 L/day and adjusting for intermittent exposure). Significant reductions in body weight gain were observed in the 1,000 mg/L group at 2, 5, 7, 10, and 11 months and in all groups during months 10 and 11. A number of statistically significant hematologic alterations were observed; however, the magnitude of the alterations does not appear to be dose related. Osmotic fragility was decreased in the 100 and 1,000 mg/L groups after 2, 4, 7, or 9 months of exposure and in the 10 mg/L group only after 9 months of exposure. Erythrocyte counts were decreased in the 1 and 1,000 mg/L groups after 9 months of exposure, but not after 7 months. Reduced hematocrit and hemoglobin levels were observed in all groups at 9 months; hematocrit levels were significantly increased the 100 and 1,000 mg/L groups at 7 months. Mean corpuscular hemoglobin concentrations were increased in the 100 and 1,000 mg/L groups after 9 months. Blood glutathione levels were significantly reduced in the 1, 10, and 1,000 mg/L groups at 2 months; the 1 and 10 mg/L groups after 4 months; the 1 mg/L group after 7 months; and the 100 mg/L group after 9 months. DNA synthesis (assessed using ^{3}H-thymidine incorporation) was significantly reduced in the kidneys of rats exposed to 100 mg/L, decreased in the testes of rats in the 10 and 100 mg/L groups, and increased in the intestinal mucosa of rats exposed to 10 or 100 mg/L chlorine dioxide; thymidine incorporation was not significantly altered in the liver. The lack of a consistent relationship between dose and hematologic alterations and the small number of animals (four males/group) confound interpretation of the study.

Couri and Abdel-Rahman (1980) found significant increases in blood glutathione reductase levels in Sprague-Dawley rats (four males/group) exposed to 10, 100, or 1,000 mg/L chlorine dioxide in drinking water 20 hours/day, 7 days/week for up to 1 year (0, 0.1, 1, 10, or 100 mg/kg-day using reference body weights and drinking water intakes of 0.523 kg and 0.062 L/day, respectively, and adjusting for intermittent exposure). After 12 months of exposure, the erythrocyte glutathione reductase levels in rats exposed to 1, 10, 100, or 1,000 mg/L were similar to those of controls, but the levels of erythrocyte glutathione peroxidase were significantly increased at 100 and 1,000 mg/L. Erythrocyte glutathione concentrations were significantly decreased at 1, 10, and 100 mg/L after 6 months and at 1,000 mg/L after 12 months of exposure. Erythrocyte catalase levels were increased in the 1,000 mg/L group after 6 and 12 months of exposure and decreased in the 1 and 10 mg/L groups after 6 months of exposure.

In similarly exposed Swiss Webster mice (six males/group) (estimated doses of 0.18, 1.8, 18, and 180 mg/kg-day [as calculated by U.S. EPA, 1994d] for 1, 10, 100, and 1,000 mg/L chlorine dioxide, respectively, drinking water concentrations), glutathione peroxidase levels were decreased at 100 mg/L and increased at 1,000 mg/L after 12 months of exposure, and glutathione levels were decreased at 10 and 100 mg/L after 12 months (Couri and Abdel-Rahman, 1980).

Catalase levels were increased in the 10, 100, and 1,000 mg/L groups after 12 months of exposure. As with the Abdel-Rahman et al. (1984b) study, the inconsistent relationship between the dose and the magnitude of the alterations in the glutathione-dependent system makes interpretation of the results of this study difficult; additionally, it is not clear if these effects are biologically significant, precluding determination of a NOAEL and LOAEL for these studies.

Moore and Calabrese (1982) exposed groups of 10 A/J or C57L/J mice (sex not specified) to 0 or 100 ppm chlorine dioxide in drinking water for 30 days (0 or 19 mg/kg-day using a reference body weight of 0.0316 kg and water intake of 0.0078 L/day). No significant alterations in hematologic parameters (complete blood count, reticulocyte count, glucose-6-phosphate activity, and osmotic fragility) were observed in either mouse strain.

4.2.1.2. *Chlorite*

The database for chlorite subchronic/chronic systemic toxicity consists of the Harrington et al. (1995a) subchronic study, the Haag (1949) chronic study, and the Bercz et al. (1982), Abdel-Rahman et al. (1984b), Couri and Abdel-Rahman (1980), and Moore and Calabrese (1982) studies, which examined a limited number of endpoints. Kurokawa et al. (1986) is the only study that examined the carcinogenic potential of ingested chlorite.

Harrington et al. (1995a) administered doses of 0, 10, 25, or 80 mg/kg-day sodium chlorite (equivalent to 0, 7.4, 19, or 60 mg chlorite/kg-day, respectively) via gavage to Crl:CD (SD) BR rats (15/sex/group) for 13 weeks. In the 60 mg/kg-day group, four animals died during treatment and both sexes exhibited salivation, significantly decreased erythrocyte counts, and decreased total serum protein levels. The males receiving 60 mg/kg-day exhibited significantly decreased hematocrit and hemoglobin levels and increased methemoglobin and neutrophil levels, whereas in the females, methemoglobin levels were significantly decreased. Possible reasons for the decrease in methemoglobin in females, which is unexpected considering the known oxidative effects of sodium chlorite, were not discussed by the study authors. The following observations were also noted in the 60 mg/kg-day group: morphological changes in erythrocytes in some animals of both sexes, significant increases in relative adrenal and spleen weights in the males, increases in absolute and relative spleen and adrenal weight in females, and increases in relative liver and kidney weights in the females. Body weight and food consumption were not affected by treatment. Histopathologic alterations in the 60 mg/kg-day group included squamous epithelial hyperplasia, hyperkeratosis, ulceration, chronic inflammation, and edema in the stomachs of seven males and eight females. At 19 mg/kg-day, the following alterations were reported: occasional salivation in two males, hematologic alterations in males (increased methemoglobin levels and neutrophil count, decreased lymphocyte count), increases in absolute and relative spleen and adrenal weights in females, and histologic alterations in the stomach of two males, similar to those seen in the high-dose group. The increase in absolute splenic weight was attributed to morphological alterations in erythrocytes, but no explanation was provided for alterations in absolute adrenal weight. The NOAEL in this study is determined to be 7.4 mg/kg-day, and the LOAEL is 19 mg/kg-day for stomach lesions and increases in spleen and adrenal weights in rats subchronically treated with sodium chlorite.

In a chronic study by Haag (1949), groups of rats (seven/sex/group) were exposed to 0, 1, 2, 4, 8, 100, or 1,000 mg/L chlorite in the drinking water (0, 0.09, 0.18, 0.35, 0.7, 9.3, or 81 mg/kg-day, as calculated by U.S. EPA, 1994d) for 2 years. Animals exposed to chlorite concentrations of 100 or 1,000 mg/L exhibited treatment-related renal pathology, characterized by distention of the glomerular capsule and appearance of a pale pinkish staining material in the renal tubules. These effects were also observed in a group of animals administered sodium chloride at a concentration equimolar to 1,000 mg sodium chlorite/L. The study author concluded that the renal pathology was a nonspecific salt effect, but this observation does not alter the observation that concentrations of 100 mg/L or higher led to adverse effects. Based on renal effects, this study identifies a NOAEL of 8 mg/L (0.7 mg/kg-day) and a LOAEL of 100 mg/L (9.3 mg/kg-day). The study was limited because an insufficient number of animals were tested per group, pathology was conducted on a small number of animals, and it did not provide adequate evaluations of more sensitive parameters, which would have been more useful in the overall assessment of chronic toxicity.

Two similarly designed studies, by Abdel-Rahman et al. (1984b) and Couri and Abdel-Rahman (1980), tested the hematotoxicity of chlorite in rats. Groups of four male Sprague-Dawley rats were exposed to 0, 10, or 100 mg/L chlorite in drinking water 20 hours/day, 7 days/week for up to 1 year (0, 1, or 10 mg/kg-day using a reference body weight of 0.523 kg and water intake rate of 0.062 L/day) and adjusting for intermittent exposure. At all measuring periods (after 2, 5, 7, 10, and 11 months of exposure), there were significant decreases in body weight gain in the 100 mg/L group; body weight gain also was decreased in the 10 mg/L group at 10 and 11 months. The study authors do not note whether water consumption was affected. No consistent alterations in erythrocyte count, hematocrit, or hemoglobin levels were observed. Mean corpuscular hemoglobin concentration was increased at both exposure levels after 7 months of exposure, but not after 9 months. Osmotic fragility was significantly decreased at 10 and 100 mg/L after 7 and 9 months of exposure. DNA synthesis (as measured by ^{3}H-thymidine incorporation) was decreased in the liver and testes at 10 and 100 mg/L, decreased in the intestinal mucosa at 100 mg/L, and increased in the intestinal mucosa at 10 mg/L. Blood glutathione reductase activity was significantly increased at 10 and 100 mg/L after 6 months of exposure and decreased at 10 mg/L after 12 months. Blood glutathione peroxidase was not altered after 6 months of exposure, but after 12 months it was decreased in both groups. Significant decreases in blood glutathione levels were observed in both groups. Blood catalase activity was decreased after 6 months of exposure in the 10 and 100 mg/L groups and increased in the 10 mg/L groups after 12 months. The lack of a consistent dose-effect relationship, small numbers of animals, and small magnitude of effects complicate interpretation of the results.

Moore and Calabrese (1982) also examined the hematotoxicity of chlorite. In this study, groups of 11–23 A/J or C57L/J mice (sex not specified) were exposed to 0, 1, 10, or 100 ppm sodium chlorite (0, 0.75, 7.5, or 75 ppm chlorite) in drinking water for 30 days. Significant increases in mean corpuscular volume, osmotic fragility, and glucose-6-phosphate activity were observed in both strains of mice exposed to 100 ppm; no other alterations in hematologic parameters were observed. This study identifies a NOAEL of 10 ppm sodium chlorite (1.9 mg/kg-day chlorite using a reference body weight of 0.0316 kg and water intake of 0.0078 L/day)

and a LOAEL of 100 ppm sodium chlorite (19 mg/kg-day) for hematologic effects in mice exposed to chlorite in drinking water for 30 days.

Using a rising-dose study protocol, Bercz et al. (1982) examined the effects of subchronic exposure to sodium chlorite in drinking water on hematologic and serum clinical chemistry parameters. Five male and seven female adult African green monkeys (*C. aethiops*) were exposed to 0, 25, 50, 100, 200, or 400 mg/L chlorite in drinking water for 4–6 weeks; the study authors estimated the dose for the 400 mg/L group to be 58.4 mg/kg-day. Each animal served as its own control. A number of statistically significant, dose-related alterations in hematologic and serum clinical chemistry parameters were observed. These included decreases in erythrocyte levels and cell indices, increases in aspartate aminotransferase (increases were subclinical), slight decreases in hemoglobin levels, and slight increases in reticulocyte count and methemoglobin levels. The data were not presented in a manner that would allow identification of threshold doses for the hematologic alterations. Other hematologic and clinical chemistry parameters and body weight were not affected. Serum T4 levels were significantly reduced in the 400 mg/L group.

To assess the renal toxicity of sodium chlorite, Moore and Calabrese (1982) exposed groups of 55–60 male C57L/J mice to 0, 4, 20, or 100 ppm sodium chlorite (0, 3, 15, or 75 ppm chlorite) in the drinking water for 30, 90, or 190 days. No significant alterations in body weight gain, absolute or relative kidney weights, water consumption, or kidney histology were observed.

In an oral carcinogenicity study conducted by Kurokawa et al. (1986) (mouse data were also presented in Yokose et al., 1987), groups of male and female F344 rats and B6C3F1 mice (50/sex/species/group) were exposed to sodium chlorite in the drinking water for 85 or 80 weeks (with a 5-week recovery period) (Yokose et al., 1987). The sodium chlorite concentrations were 0, 300, or 600 ppm for rats and 0, 250, or 500 ppm for mice. Using water consumption and body weight data, the study authors estimated the doses to be 18 and 32 mg/kg-day in male rats and 28 and 41 mg/kg-day in female rats. All groups of rats were infected with the Sendai virus. No adverse effect on survival was observed in the rats. A slight dose-related decrease in body weight gain was observed (body weight gain in the high-dose group was within 10% of controls). No chlorite-related increases in tumor incidence were observed in the rats.

For mice, daily doses of 0, 48, and 95 mg sodium chlorite/kg-day (0, 36, and 71 mg chlorite/kg-day) were calculated by EPA (1994d). In the mice, there were no significant chlorite-related alterations in survival or body weight gain; increased mortality was observed in the male control group, which was attributed to severe fighting. Significant increases in liver and lung tumors were observed in the male mice. Incidence of hyperplastic nodules in the liver was significantly increased in the low- and high-dose groups relative to controls (3/35 [reported as 6/35 in Yokose et al., 1987], 14/47, 11/43, in the control, low-, and high-dose groups, respectively) and combined incidence of liver hyperplastic nodules and hepatocellular carcinoma was increased in the low-dose group (7/35, 22/47, and 17/43, respectively). Incidence of lung adenoma (0/35, 2/47, and 5/43, respectively) and combined incidence for lung adenoma and adenocarcinoma (0/35, 3/47, and 7/43, respectively) were significantly increased in the high-dose group compared with controls. The study authors noted that incidences of liver hyperplastic

nodules and lung adenomas in the treated animals were within the range of historical controls in their laboratory and in the National Toxicology Program laboratories. The high mortality in the control males because of fighting may have contributed to the low tumor incidence in the concurrent control group, making statistical comparisons between concurrent controls and treated animals difficult to interpret. In the female mice, the only significant alteration in tumor incidence was a significantly lower incidence of malignant lymphoma/leukemia in the high-dose group (7/47, 5/50, 1/50, respectively). This study is considered inadequate for assessing carcinogenicity because of the relatively short exposure duration (80 weeks) and the high incidence of early mortality in the concurrent control males from excessive fighting.

4.2.2. Inhalation Exposure

4.2.2.1. *Chlorine Dioxide*

Paulet and Desbrousses (1970) conducted four studies to investigate toxicity of inhaled chlorine dioxide in rats and rabbits (strains not specified): (1) 5 male and 5 female rats were exposed to 10 ppm chlorine dioxide (28 mg/m^3) 2 hours/day for 30 days; (2) 10 male rats, 10 female rats, and 4 rabbits were exposed to 5 ppm chlorine dioxide (14 mg/m^3) 2 hours/day for 30 days; (3) 10 male and 10 female rats were exposed to 2.5 ppm chlorine dioxide (6.9 mg/m^3) 7 hours/day for 30 days; and (4) 8 rabbits were exposed to 2.5 ppm chlorine dioxide (6.9 mg/m^3) 4 hours/day for 45 days. The weekly exposure frequency was not reported—presumably it was 5 days/week. Control groups with equal numbers of animals were used for each study. The following adverse effects were observed at 10 ppm: nasal discharge and red eyes, localized bronchopneumonia with desquamation of the alveolar epithelium, and significantly increased blood erythrocyte and leukocyte levels. Similar, but less severe, respiratory tract effects were observed at 5 ppm; there were no alterations in erythrocyte or leukocyte levels at this concentration. Lymphocytic infiltration of the alveolar spaces, alveolar vascular congestion, hemorrhagic alveoli, epithelial erosions, and inflammatory infiltrations of the bronchi were observed in the rats exposed to 2.5 ppm. The study authors noted that body weight gain was "slightly slowed" (data not presented) and the erythrocyte and leukocyte levels were 85% and 116% of controls, respectively (statistical analysis not reported), in the rats exposed to 2.5 ppm. In rabbits exposed to 2.5 ppm chlorine dioxide, hemorrhagic alveoli and congested capillaries were observed in the lungs. Body weight gain was not adversely affected, and erythrocyte and leukocyte levels were 80% and 116% of controls (statistical analysis not reported; the study authors state that the cell counts "changed very little"). Another group of rats and rabbits were sacrificed 15 days after termination of the 2.5 ppm exposure regimens. Recovery from the pulmonary lesions was evident in these animals. The liver was not adversely affected in the rats or rabbits following exposure to 2.5, 5, or 10 ppm chlorine dioxide. This study identifies a LOAEL of 2.5 ppm (6.9 mg/m^3) for thoracic effects (alveolar congestion and hemorrhage and bronchial inflammation) in rats (7 hours/day for 30 days) and pulmonary effects (alveolar hemorrhage and capillary congestion) in rabbits (4 hours/day for 45 days).

In a follow-up study by Paulet and Desbrousses (1972), groups of eight Wistar rats (sex not reported) were exposed to 1 ppm chlorine dioxide (2.8 mg/m^3) 5 hours/day, 5 days/week for 2 months. The study authors noted that weight gain and erythrocyte and leukocyte levels were

not affected, but they did not present concurrent control data. Vascular congestion and peribronchiolar edema were observed in the lungs of chlorine dioxide-exposed rats; no alterations in the epithelium or parenchyma were observed. This subchronic study identifies a LOAEL of 1 ppm (2.8 mg/m^3) for respiratory effects in rats.

In a second series of studies conducted by Paulet and Desbrousses (1974), groups of 10–15 rats (sex and strain not reported) were exposed to 5, 10, or 15 ppm chlorine dioxide (14, 28, or 41 mg/m^3) for 15-minute periods two or four times/day for 1 month. Control groups were similarly exposed to room air. At 15 ppm, 1/10 and 1/15 rats exposed two or four times/day, respectively, died; body weight loss was observed in both groups. Histologic alterations observed at this exposure level included nasal and ocular inflammation and discharge, bronchitis, and catarrhous lesions of the alveoli with peribronchiolar infiltrations (more pronounced in the four times/day group). The alveolar lesions were reversible; 15 days after exposure termination, the lung histology was similar to that of controls. No histologic alterations were observed in the liver. At 10 ppm, alveolar irritation and decreases in body weight gain were observed. No adverse effects on clinical signs, body weight gain, or histopathology of the lungs were observed at 5 ppm. Exposure to chlorine dioxide did not adversely affect hematologic parameters. This study identifies a NOAEL of 5 ppm (14 mg/m^3) and LOAEL of 10 ppm (28 mg/m^3) for lung damage following intermittent exposure for 15-minute periods, two or four times/day for 4 weeks.

Dalhamn (1957) conducted a series of inhalation studies to assess toxicity of chlorine dioxide in the rat (sex and strain not reported). In the first study, a group of three rats was exposed once a week for 3 minutes to decreasing concentrations of chlorine dioxide (3,400 ppm [9,500 mg/m^3] in week 1, 1,100 ppm [3,000 mg/m^3] in week 2, and 800 ppm [2,200 mg/m^3] in week 3); a second group of three rats served as controls. Respiratory distress and decreased body weight were observed in the chlorine dioxide-exposed rats. Bronchopneumonia and hyperemia of the renal corticomedullary junction were observed in two of three rats; the renal hyperemia was also observed in the control group (2/3). In the second study, exposure to 260 ppm (720 mg/m^3) chlorine dioxide for 2 hours resulted in ocular discharge, epistaxis, death (1/4 rats), pulmonary edema, and circulatory engorgement. In the third study, groups of five rats were exposed to 0 or approximately 10 ppm chlorine dioxide (28 mg/m^3) 4 hours/day for 9 days in a 13-day period. Death (3/5 rats), rhinorrhea, “embarrassed respiration,” and weight loss were observed in the chlorine dioxide-exposed rats. Respiratory infection with acute renal and hepatic congestion also were observed. The fourth study involved exposure of groups of five rats to 0 or approximately 0.1 ppm chlorine dioxide (0.28 mg/m^3) 5 hours/day for 10 weeks (frequency of exposure not reported). No effects on body weight gain were observed and no histologic alterations were observed in the lungs, kidneys, or liver. The Dalhamn studies identified a NOAEL of 0.1 ppm (0.28 mg/m^3) in rats exposed 5 hours/day for 10 weeks and a LOAEL of 10 ppm (28 mg/m^3) for respiratory tract irritation in rats exposed 4 hours/day for approximately 2 weeks.

4.2.2.2. *Chlorite*

No animal inhalation or intratracheal installation data were located for chlorite.

4.3. REPRODUCTIVE/DEVELOPMENTAL STUDIES—ORAL AND INHALATION

4.3.1. Chlorine Dioxide

Carlton et al. (1991) administered daily gavage doses of 0, 2.5, 5, or 10 mg/kg chlorine dioxide in deionized water to groups of 12 male Long-Evans rats for 56 days prior to mating and throughout the 10-day mating period. Groups of 24 female rats received the same gavage doses for 14 days prior to mating, during the mating period, and throughout gestation and lactation. No significant alterations in mortality, clinical signs, fertility rates, sperm parameters, length of gestation, prenatal deaths, mean litter size, or mean pup weights were observed. A statistically significant delay in the day of eye opening was observed in pups from the 10 mg/kg-day group, but the study authors did not consider this effect to be biologically significant because it was not dose related (16.70, 15.59, 16.26, and 15.95 days in the 0, 2.5, 5, and 10 mg/kg-day groups, respectively). No significant alterations in reproductive tract organ weights were observed in the F1 male rats. In the F1 female rats, there were statistically significant decreases in absolute and relative vagina weights in the 10 mg/kg-day group, but no differences in terminal body weights or uterine and ovarian weights. No consistent chlorine dioxide-related alterations in T3 or T4 levels were measured in the F0 male and female rats and F1 male rats (hormone levels measured on postnatal days 17, 28, and 40). This study identifies a NOAEL of 10 mg/kg-day for reproductive effects in rats receiving gavage doses of chlorine dioxide.

In a developmental toxicity study by Suh et al. (1983), groups of six to eight female Sprague-Dawley rats were administered 0, 1, 10, or 100 mg/L chlorine dioxide in the drinking water (0, 0.1, 1, and 10 mg/kg-day using a reference body weight of 0.35 kg and water intake of 0.046 L/day) for 2.5 months prior to mating with unexposed males and during gestational days 0–20; the dams were killed on gestational day 20. A slight, nonsignificant decrease in maternal body weight gain was observed in the 10 and 100 mg/L groups. There was a statistically significant trend for decreasing number of implants per litter and number of live fetuses per dam. Total fetal weights and male fetal weights were significantly increased in the 100 mg/L group compared with controls; crown-rump length was not significantly affected. Incidences of skeletal anomalies did not significantly differ between groups. This study identifies a NOAEL of 10 mg/L (1 mg/kg-day) and LOAEL of 100 ppm (10 mg/kg-day) for developmental effects in the offspring of rats exposed to chlorine dioxide in the drinking water.

Toth et al. (1990) examined the neurodevelopmental toxicity of chlorine dioxide in the postnatally exposed Long-Evans hooded rats. Groups of four male and four female pups per litter received daily gavage doses of 0 or 14 mg/kg chlorine dioxide on postnatal days 1–20. The chlorine dioxide pups weighed significantly less than controls at ages 11, 21, and 35 days. No significant alterations in cerebellum or olfactory bulb weights were observed on postnatal days 11, 21, or 35. Forebrain weights were significantly lower in the chlorine dioxide-exposed pups on postnatal days 21 and 35. This reduction in forebrain weight was accompanied by reductions

in protein content on postnatal days 21 and 35 and reduced DNA content on postnatal day 35. The ratio of protein content to forebrain weight was decreased on postnatal days 11, 21, and 35; the protein content to cerebellum weight was increased on postnatal day 35. The ratio of DNA content to brain part weight was not significantly affected in the chlorine dioxide-exposed pups. No alterations in counts of branches of apical dendrites of cerebral cortical layer 5 pyramidal cells were observed, but dendritic spine counts in the Krieg's area 18 (a visual association region of the cortex) were significantly decreased. No gross lesions, loss of myelin, or changes in cells staining positive for Nissl substance in the forebrain, cerebellum, or brainstem were observed in the brains of chlorine dioxide-exposed pups. No significant alterations in T3 or T4 levels or free T4 index were observed on postnatal days 11, 21, and 35. This study identifies a LOAEL of 14 mg/kg-day for altered brain development (decreased forebrain weight and protein content) in postnatally exposed rats.

Mobley et al. (1990) exposed groups of 12 female Sprague-Dawley rats to 0 or 100 ppm chlorine dioxide in the drinking water (0 or 14 mg/kg-day using a reference body weight of 0.35 kg and water intake of 0.046 L/day) for 10 days prior to mating with unexposed males and during the gestation and lactation periods (until postconception days 35–42). No significant alterations in litter size were observed. At birth, the litter weight of the chlorine dioxide-exposed group was significantly lower than that of controls. Chlorine dioxide exposure significantly decreased exploratory activity on postconception days 36–39, but not on days 39–41. Although serum T3 and T4 levels were not significantly altered in the chlorine dioxide-exposed pups (assessed on postconception days 37 and 38), a significant decrease in T3 uptake was observed. Free T3 and T4 levels were lower in the chlorine dioxide group, but the difference was not statistically significant. On postconception day 42, there were no significant alterations in total T3 or T4, free T4, or T3 uptake. The day of eye opening was not significantly affected by chlorine dioxide exposure. Thus, 100 ppm (14 mg/kg-day) is a LOAEL for decreased litter weight and exploratory activity.

In a study conducted by Orme et al. (1985) designed to assess toxicity of chlorine dioxide on the thyroid, groups of female Sprague-Dawley rats were exposed to 0, 2, 20, or 100 mg/L in the drinking water (doses of 0, 1, 3, and 14 mg/kg-day were estimated by U.S. EPA, 1994d) for 2 weeks prior to mating and throughout gestation and lactation. In a companion study, groups of 5-day-old Sprague-Dawley pups (dams were not exposed) received gavage doses of 0 or 14 mg/kg-day chlorine dioxide on postnatal days 5–20. No significant alterations in pup weight were observed in the pups exposed in utero; the postnatally exposed pups weighed significantly less than controls on postnatal days 14–21. Age of eye opening was not affected by chlorine dioxide exposure. Locomotor activity was consistently decreased in the 100 mg/L group, but the decrease was not statistically significant. In the 14 mg/kg-day gavaged group, activity was significantly decreased on postnatal days 18–19; on days 15–17 and 20, activity levels were similar to controls. In the 100 mg/L group, there was a significant decrease in T3 and T4 levels; T4 levels were also significantly decreased in the 14 mg/kg-day group. In all groups, there was a significant correlation between T4 levels and locomotor activity. T4 levels were not significantly altered in the chlorine dioxide–exposed dams. This study identifies a NOAEL of 20 mg/L (3 mg/kg-day) and a LOAEL of 100 mg/L (14 mg/kg-day) for neurobehavioral effects (decreased

T3 and T4 levels and delayed development) in the offspring of rats exposed to chlorine dioxide in drinking water.

Taylor and Pfohl (1985) exposed groups of 13–16 female Sprague-Dawley rats to 0 or 100 ppm chlorine dioxide in drinking water (0 or 14 mg/kg-day calculated using a reference body weight of 0.35 kg and water intake of 0.046 L/day) for 14 days prior to breeding and throughout gestation and lactation. Groups of male pups from unexposed dams were administered 0 or 14 mg/kg chlorine dioxide via gavage from postnatal days 5 to 20. No significant alterations in maternal or pup body weights were observed in the group receiving 100 ppm in the drinking water. A significant decrease in whole brain weight, primarily because of a decrease in cerebellar weight, was observed in the 21-day-old offspring of dams receiving 100 ppm in the drinking water. A decrease in cerebellar total DNA content also was observed; the difference was caused by a decrease in total number of cells rather than in cell density. A nonsignificant decrease in locomotor activity (assessed at 10–20 days of age) was observed in the 100 ppm offspring. A significant decrease in exploratory behavior was observed in the 100 ppm offspring at 60 days of age. In the pups receiving gavage doses of chlorine dioxide, significant decreases in body weight, absolute and relative whole brain and forebrain weights, and forebrain DNA content and total cell number were observed in the 21-day-old pups; cerebellum and forebrain DNA content and total cell number were also significantly decreased in the 11-day-old pups. Significant decreases in home cage and wheel-running activity at ages 18–19 and 10 days, respectively, also were observed in the pups receiving gavage doses of chlorine dioxide. Thus, the LOAEL for neurobehavioral effects, decreased brain weight, and cell number in the offspring of rats exposed to chlorine dioxide in drinking water and in rats postnatally exposed to chlorine dioxide via gavage is 14 mg/kg-day.

4.3.2. Chlorite

The Chemical Manufacturers Association (CMA) conducted a two-generation study to examine reproductive, developmental neurotoxicity, and hematologic endpoints in rats exposed to sodium chlorite (CMA, 1996). Thirty male and 30 female Sprague-Dawley rats of the OFA(SD)IOPS-Caw strain (F0) generation received drinking water containing 35, 70, or 300 ppm sodium chlorite (concentrations of sodium chlorite in the drinking water were apparently adjusted to compensate for the 81.4% purity of the test material) for 10 weeks and were then paired (1M:1F) for mating. A similar group received purified water and served as controls. Males were exposed throughout mating and then were sacrificed. Exposure for the females continued through mating, pregnancy, and lactation until necropsy following weaning of their litters. Sodium chlorite concentrations were adjusted downward during lactation to offset increases in the volume of water consumed so that a constant intake (mg/kg-day) could be maintained. Twenty-five males and females from each of the first 25 litters to be weaned in a treatment group were chosen to produce the F1 generation. The F1 pups were continued on the same treatment regimen as their parents. At approximately 14 weeks of age, they were mated to produce the F2a generation. Because of a reduced number of litters in the 70 ppm F1-F2a generation, the F1 animals were remated following weaning of the F2a to produce the F2b generation. Pregnant F1 females were allowed to litter and rear the F2a and F2b generations until weaning at postnatal day 21. Based on sodium chlorite intake (in mg/kg-day) calculated by

the study authors from measured water consumption and body weight, and adjusting for the molecular weight of sodium in sodium chlorite, doses for the F0 animals were 0, 3, 5.6, and 20 and 0, 3.8, 7.5, and 28.6 mg/kg-day chlorite for males and females, respectively. For the F1 animals, doses were 0, 2.9, 5.9, and 22.7 mg/kg-day chlorite for the males and 0, 3.8, 7.9, and 28.6 mg/kg-day chlorite for the females. Numerous parameters were measured or calculated, including body weight, food and water consumption, estrus cycle in the F0 and F1 rats, and hematology and T3 and T4 levels in the F1 rats (blood samples collected from 1 male and 1 female from the first 20 F1 litters at age 25 days and another group at 13 weeks). Other parameters measured were gestation duration, litter size, pup sex, pup body weight, pup developmental landmarks, number alive/dead pups in the F1 and F2 generations, total caudal sperm number and percent motile, morphology by computer-assisted sperm motility analysis in the F0 and F1 rats, and organ weight and histopathologic examination of the brain, pituitary gland, liver, adrenal gland, spleen, thymus, kidneys, and reproductive organs of all F0 and F1 controls and high-dose animals. An additional group of F1 pups was chosen for neurohistopathology on postnatal day 11 (examination of the brain and spinal cord) or postnatal day 60 (sensory ganglia, dorsal and ventral nerve roots, and several peripheral nerves and muscles). Another group of F1 rats was examined for neurotoxicological endpoints (motor activity in a “Figure 8" Activity System and neuropathology on postnatal day 60, auditory startle in the SR-Screening System, learning and memory retention in a water E-maze). A functional observational battery (FOB) was also conducted on the pups undergoing auditory and learning assessments. This group was composed of 2 males and 2 females from 20 litters, and exposure was discontinued after weaning. Reevaluation of the auditory startle response was conducted in 20 males and 20 females in the F2a and F2b generations.

There were reductions in water consumption, food consumption, and body weight gain in both sexes in all generations at various times throughout the experiment (e.g., during premating, pregnancy, gestation, postweaning), primarily in the 70 and 300 ppm groups. The authors attributed these reductions to lack of palatability of the drinking water solution, but did not show data to support this contention. Significant alterations related to treatment at 300 ppm include reduced absolute and relative liver weight in F0 females and F1 males and females, reduced pup survival (increase in number of pups found dead and/or killed prematurely during lactation) and reduced body weight at birth and throughout lactation in F1 and F2 rats, lower thymus and spleen weight in both generations, lowered incidence of pups exhibiting normal righting reflex and with eyes open on postnatal day 15, alteration in clinical condition in F2 animals chosen for neurotoxicity, decrease in absolute brain weight for F1 males and F2 females, delay in sexual development in males (preputial separation) and females (vaginal opening) in F1 and F2 rats, and lower red blood cell parameters in F1 rats. The reported alterations in pup sexual maturation measures might be due to reduced pup body weight, but a definitive conclusion cannot be drawn. In the 70 ppm groups, reduced absolute and relative liver weight in F0 females and F1 males was observed. Minor, statistically significant changes in hematologic data at the 35 and 70 ppm concentrations (generally 1%–7%) in the F1 rats appear to be within normal ranges based on historical data and are therefore not considered clinically or biologically significant or adverse. In addition, a significant decrease in maximum response to an auditory startle stimulus was noted in the 70 and 300 ppm groups on postnatal day 24, but not on postnatal day 60. Analysis of the

E-maze data by EPA personnel indicated possible alterations in learning behavior in the 70 ppm group, but the differences from the conclusions of the report could not be resolved.

The CMA (1996) study is adequate in that it was conducted with sufficient numbers of animals of both sexes and examined numerous endpoints. The study is acceptable and consistent with EPA testing guidelines that were in effect at the time of the study (U.S. EPA, 1991). However, there are several limitations to this study. Lack of pair-watered and pair-fed control animals confounds the results and precludes definitive conclusions as to whether the alterations in food and water consumption and body weight are related to water palatability or a direct toxic effect of the agent. Developmental landmarks (e.g., vaginal opening in F2a group) were not reported for all groups. Grip strength and landing foot splay were not included in the FOB. Discontinuation of exposure for the animals undergoing neurotoxicity testing minimizes the likelihood of finding a positive effect and precludes comparison of the data with those of other rats with continued exposure. Although the study employed an exposure regimen consistent with testing guidelines and should potentially detect adverse effects on the developing nervous system, discontinuation of exposure after weaning reduces the opportunity to detect neurological effects from continuous or lifetime exposures similar to those expected from lifetime drinking water exposure in humans.

Interpretation of the neurobehavioral tests is limited. The report lacks detailed descriptions of experimental methods (e.g., size of the arena, length of observations) and positive control data (including estimates of variability) for the FOB. Positive control studies for the motor activity and E-maze studies used high doses of the validation chemicals, were not adequate to show the sensitivity of the methods, and showed only that effects of the chemicals at maximally toxic doses could be recognized. Variability in the startle response data was high. The high variability and problems in calibrating and operating the automated startle apparatus (as presented in the report) would tend to decrease the sensitivity of the test to detect a difference between control and treated groups, because differences in startle amplitude would have to be larger to attain statistical significance. In some cases, inappropriate statistical analyses were applied. For example, repeated-measures techniques were apparently not used to account for the fact that the rats were tested repeatedly, and it is not clear how nonparametric rank data were analyzed or why a log transformation was applied to the learning data. The NOAEL for this study is 35 ppm (2.9 mg/kg-day chlorite) and the LOAEL is 70 ppm (5.9 mg/kg-day chlorite) based on lowered auditory startle amplitude and altered liver weights in two generations.

Groups of 12 male Long-Evans rats were exposed to 0, 1, 10, or 100 ppm sodium chlorite (0, 0.7, 7, and 70 ppm chlorite) in the drinking water for 56 days prior to mating and throughout a 10-day mating period (Carlton and Smith, 1985; Carlton et al., 1985, 1987). Groups of 24 female rats were exposed to the same sodium chlorite drinking water concentrations for 14 days prior to mating, during the mating period, and throughout gestation and lactation. Doses of 0, 0.075, 0.75, and 7.5 mg/kg-day were estimated by EPA (1994d). No significant alterations in body weight gain or water consumption were observed. There was a wide degree of variability among fertility rates for the different groups (67%–96%), but no dose-related alterations in fertility rates were observed. No significant alterations in litter survival rates, median day of eye opening, or median day of observed vaginal patency were observed. Additionally, no alterations

were observed in gross and histopathologic examination of reproductive tract tissues, hematologic parameters, or testis, epididymis, and caudal epididymis weights. No significant alterations in sperm count or percentage of sperm mobility were observed. A trend toward decreased sperm mean progressive movement was observed in the 100 ppm group, but the velocity was not significantly different from controls. The percentage of abnormal sperm in sodium chlorite-exposed rats did not differ from controls. No significant alterations in T3 and T4 hormone levels were observed in the F0 males or females. T3 and T4 levels were measured in the F1 males and females on postnatal days 17 (males only), 21, and 40; significant decreases in hormone levels were consistently observed at 100 ppm at days 21 and 40. This study identifies a NOAEL of 10 ppm (0.75 mg/kg-day) and a LOAEL of 100 ppm (7.5 mg/kg-day) for altered thyroid hormone levels in the offspring of rats exposed to sodium chlorite in drinking water.

Carlton and Smith (1985) and Carlton et al. (1985, 1987) conducted two follow-up studies to further investigate the effect of sodium chlorite on sperm parameters. In these studies, groups of 12 male rats received drinking water containing 0, 100, or 500 ppm sodium chlorite (0, 70, and 370 ppm chlorite) or 0, 1, 10, or 100 ppm sodium chlorite (0, 0.7, 7, and 70 ppm chlorite) for 72–76 days. Water consumption was significantly decreased (28%) in the 500 ppm group; in other groups, water consumption was similar to that of controls. Estimated doses of 0.075, 0.75, 7.5, and 27 mg/kg-day were calculated for the 1, 10, 100, and 500 ppm groups, respectively. No significant alterations in body weight gain were observed in the sodium chlorite-exposed rats. As in the first experiment, there were no significant alterations in sperm count, percentage of sperm mobility, or mean progressive movement. However, there was a trend toward decreased progressive movement in the 100 and 500 ppm groups. When the three experiments were combined, there was a statistically significant reduction of direct progressive movement at 100 and 500 ppm. A significant increase in abnormal sperm was observed in the 100 and 500 ppm groups; the most common morphological abnormalities were frayed tails, open hooks, and amorphous sperm heads. Collectively, these studies identify a NOAEL of 10 ppm (0.75 mg/kg-day) and LOAEL of 100 ppm (7.5 mg/kg-day) for reproductive effects in rats exposed to sodium chlorite in drinking water.

Couri et al. (1982) exposed groups of 7–13 pregnant Sprague-Dawley rats to 0%, 0.1%, 0.5%, or 2% sodium chlorite (0%, 0.07%, 0.4%, and 1.5% chlorite) in the drinking water during gestational days 8–15. The litters were either delivered at term or by cesarean section on gestational day 22. Using the daily doses of 0, 34, 163, and 212 mg sodium chlorite/rat/day calculated by the study authors and an estimated body weight (midpoint of gestation day 1 body weights [0.280 kg] plus one-half of the body weight gain), doses of 0, 95, 590, and 820 mg/kg-day sodium chlorite (0, 70, 440, and 610 mg/kg-day chlorite) were calculated. Another group of four pregnant rats received daily gavage doses of 200 mg/kg sodium chlorite on gestational days 8–15. Profuse vaginal and urethral bleeding and 100% mortality were observed in the rats receiving 200 mg/kg gavage doses. No deaths were observed in the rats receiving sodium chlorite via drinking water. Weight loss and decreases in food and water consumption were observed at the 0.5% and 2% concentrations; decreased water consumption was also observed in the 0.1% group. Irregular blood cells, ruptured cells, and hemolysis were observed in the 2% and 200 mg/kg-day groups. Significant decreases in crown-rump length were observed in litters

term-delivered in the 0.1%, 0.5%, and 2% groups and in the 0.5% group cesarean-delivered on gestational day 22. Fetal weights were not adversely affected. An increase in the number of resorbed and dead fetuses was observed in litters delivered on gestational day 22 in the 0.1%, 0.5%, and 2% groups; two litters out of five were totally resorbed in the 2% group. Postnatal growth and the incidences of soft tissue and skeletal malformations were not adversely affected by in utero exposure to sodium chlorite. This study identifies a FEL of 0.1% for resorbed and dead fetuses and decreases in crown–rump length in the offspring of rats exposed to 0.1% sodium chlorite (70 mg/kg-day chlorite) in drinking water.

Groups of six to nine female Sprague-Dawley rats were administered 0, 1, or 10 mg/L chlorite in the drinking water (0, 0.1, or 1 mg/kg-day calculated using a reference body weight of 0.35 kg and water intake of 0.046 L/day) for 2.5 months prior to mating with unexposed males and during gestational days 0–20; the dams were killed on gestational day 20 (Suh et al., 1983). No significant alterations in general appearance or maternal body weight gain were observed. No significant alterations in number of implants (total and per dam), resorptions, or dead fetuses were observed. No difference in fetal body weights was observed. Crown-rump length was significantly higher in the 10 mg/L group compared with controls, but the difference was very small and is probably not biologically significant. Chlorite exposure did not significantly alter incidence of skeletal anomalies. This study identifies a NOAEL of 10 mg/L (1 mg/kg-day) for developmental toxicity in the offspring of rats exposed to chlorite in the drinking water.

Mobley et al. (1990) exposed groups of 12 female Sprague-Dawley rats to 0, 20, or 40 ppm chlorite in the drinking water (doses of 0, 3, and 6 mg/kg-day were estimated by U.S. EPA, 1994d) for 10 days prior to mating with unexposed males and during gestation and lactation until postnatal days 42–53. Chlorite exposure did not adversely affect litter size or pup weight gain. Significant, consistent decreases in exploratory activity were observed in the 40 ppm group on postnatal days 36–39, but not on days 39–41. In the 20 ppm group, there were significant decreases in activity on days 36 and 37, but not on days 38–40. No significant alterations in serum T3 or T4 levels were observed in the 37–38- or 42-day-old postconception pups. However, the free T4 levels were significantly increased in the 40 ppm group. The day of eye opening in the 20 and 40 ppm groups was similar to that of controls. A review of the results of this study relative to the findings of the newer developmental studies in the database suggests that the NOAEL for neurodevelopmental behavioral effects in rats exposed to chlorite in drinking water for this study is 20 ppm (3 mg/kg-day) and the LOAEL is 40 ppm (6 mg/kg-day).

Moore et al. (1980) (data also presented in Moore and Calabrese, 1982) exposed groups of pregnant female A/J mice to 0 or 100 ppm sodium chlorite in drinking water throughout gestation and lactation; 21 control and 12 exposed dams had litters. EPA (1994d) estimated that the 100 ppm sodium chlorite (75 ppm chlorite) concentration corresponds to a dose of 22 mg/kg-day. A decrease in the conception rate (number of females positive for vaginal plug/number of females producing litters) was observed in the chlorite group (39% vs. 56% in controls); the statistical significance was not reported. No statistically significant alterations in gestation length, litter size, number of pups dead at birth, and number of pups alive at weaning were observed. Pup growth was adversely affected, as shown by significant decreases in average pup weaning weight and birth to weaning growth rate. This study identifies a LOAEL of 100 ppm

(22 mg/kg-day) for developmental effects in the offspring of mice exposed to chlorite in the drinking water.

Harrington et al. (1995b) treated groups of 16 female New Zealand white rabbits with technical-grade sodium chlorite (80.6% purity) via their drinking water at levels of 0, 200, 600, or 1,200 ppm from gestation days 7–20, followed by terminal sacrifice at day 28. Water concentrations were maintained at the same levels throughout pregnancy and were not adjusted for changes in volume of water consumed. Based on measured water consumption, the study authors calculated a mean daily intake of approximately 0, 10, 26, or 40 mg/kg-day chlorite (corrected for purity and adjusted by the weight of the salt). Clinical condition, maternal body weight, and food and water consumption were measured daily. At necropsy, gravid uterine weights, number of corpora lutea, number of implantation sites, and live and dead fetuses were recorded. Live fetuses were weighed, examined for external abnormalities, sexed, and dissected, and a gross visceral examination was performed. Skeletal examinations were also performed. Abnormalities were categorized as minor or major, and the latter were thought to impair survival or fitness. Commonly observed variations were also recorded. The study authors did not state which malformations fell into each of these categories. There was no mortality, although two rabbits (one from each of the control and 26 mg/kg-day groups) were sacrificed in extremis because of a clinical condition unrelated to treatment. A significant decrease in water consumption during the treatment period was observed in the 26 and 40 mg/kg-day groups, and a decrease during treatment days 16–20 of pregnancy was observed in the 10 mg/kg-day group. The study authors attributed the decreases in consumption to lack of palatability of the drinking water solution, although no supporting data were presented. Food consumption was decreased in the 26 and 40 mg/kg-day groups during days 7–11 of pregnancy. Body weight gain of treated animals was decreased on days 7–19, although by day 26 these groups showed no differences from controls in body weight gain.

The authors concluded there were no treatment-related effects on pregnancy incidence, number of implantations, number of preimplantation losses, fetal sex ratio, number of live fetuses, or fetal visceral or structural abnormalities. Data for specific malformations and variations were not shown; instead, data were presented as the number or mean percentage of fetuses with major or minor external and visceral or skeletal abnormalities. The number and mean percentage of major external and visceral and skeletal abnormalities were increased in the 26 and 40 mg/kg-day groups (external/visceral: 6.6% and 2.9%, respectively, vs. 1.5% in controls; skeletal: 5.4% and 0%, respectively, vs. 0% in controls). Mean fetal weights in the 26 and 40 mg/kg-day groups were slightly decreased (< 9% relative to controls). In the 26 and 40 mg/kg-day groups, the incidence of minor skeletal abnormalities (13.9 and 14.2 for the 26 and 40 mg/kg-day groups, respectively, vs. 7.7% in controls) and skeletal variants related to incomplete fetal bone ossification (such as of the pubis and sternebrae) was higher than for controls. The authors state in their discussion that these alterations in fetal body weight and delayed ossification indicate embryonic growth retardation. The NOAEL for this study is 200 ppm (10 mg/kg-day chlorite) and the LOAEL is 600 ppm (26 mg/kg-day chlorite) based on decreased fetal weight and delayed skeletal ossification, decreased food and water consumption in the dams, and decreased body weight gain in the dams. Although this study employed sufficient numbers of animals and administered chlorite by a route relevant to human exposure, uncertainties exist in

interpretation of the results because of inadequate reporting of the number and types of specific abnormalities and variations. There is additional uncertainty as to whether the decreases in food and water consumption and body weight gain in the dams are caused by unpalatability or a direct toxic effect of the chlorite.

4.4. OTHER STUDIES

4.4.1. Other Carcinogenicity Studies

4.4.1.1. *Chlorine Dioxide*

The potential for chlorine dioxide to induce proliferative epidermal hyperplasia was examined by Robinson et al. (1986). Groups of five dorsally shaved female SENCAR mice were placed in chambers filled with 0, 1, 10, 100, 300, or 1,000 ppm liquid chlorine dioxide; the chambers were designed to prevent the head from getting wet and to prevent inhalation of vapors. The animals were exposed 10 minutes/day for 4 days. A significant increase in interfollicular epidermal thickness was observed in the 1,000 ppm group, but not at the lower concentrations. Increases in total cell numbers and basal cell numbers in skin sections were observed in both the 300 and 1,000 ppm groups. In a second study, groups of 40 mice were immersed in 0 or 1,000 ppm chlorine dioxide for 10 minutes; animals (5/group) were killed 1, 2, 3, 4, 5, 8, 10, or 12 days postexposure. A significant increase in interfollicular epidermis thickness was observed at all time periods, with the highest values at 10 and 12 days postexposure. The authors concluded that even short-term dermal exposure to high concentrations of chlorine dioxide is capable of inducing hyperplastic responses in the mouse skin.

Miller et al. (1986) tested the carcinogenic potential of drinking water disinfected with chlorine dioxide using three short-term assays. Following disinfection with chlorine dioxide, the water samples (containing 0.5 mg/L chlorine dioxide residue) were concentrated 2,000× or 4,000× using a macroreticular resin process. In a mouse initiation-promotion assay, groups of 14–34 SENCAR mice (sex not specified) were orally administered 0.5 mL of the 4000× concentrate in 2% emulphor 3 times/week for 2 weeks followed by topical exposure to 1.0 ：g 12-tetradecanylphorbal-13-acetate (TPA) in acetone applied to the dorsal skin 3 times/week for 20 weeks and then sacrificed. No significant increases, compared with vehicle controls, in the number of skin tumors or the number of tumors per animal were observed.

In a lung adenoma assay (Miller et al., 1986), groups of 20 male and 20 female Strain A mice received 0.25 mL gavage doses of 2000× or 4000× concentrates in 2% emulphor 3 times/week for 8 weeks followed by a 16-week observation period. The number of animals with lung adenomas and the number of adenomas per animal were not significantly altered compared with vehicle controls.

Miller et al. (1986) also examined the development of liver foci in rats in a short-term assay. In this study, groups of partially hepatectomized rats received a single dose of concentrated water (chlorine dioxide concentration not reported) in 2% emulphor followed 1 week later by administration of 500 ppm sodium phenobarbital in drinking water for 56 days;

animals were sacrificed on day 70. A control group received nondisinfected water. No significant increases in incidence of (-glutamyltranspeptidase foci were observed.

4.4.1.2. *Chlorite*

Kurokawa et al. (1984) also conducted dermal carcinogenicity studies. In a study to assess the ability of chlorite to act as a complete carcinogen, groups of 20 female SENCAR mice were exposed twice weekly for 51 weeks to 20 mg/mL sodium chlorite in acetone. The solution (0.2 mL; 100 mg/kg sodium chlorite per application) was applied to the shaved backs of the mice. The sodium chlorite exposure did not result in increased tumor incidence. To test the ability of chlorite to act as a tumor promoter, a single initiating dose of 20 :mol of dimethylbenzanthracene (DMBA) was applied to the skin of 20 SENCAR mice. The DMBA application was followed by a 51-week exposure to sodium chlorite (as described for the complete carcinogen study). Tumor incidence was 6/20 (30%) compared with 0/20 in mice that received DMBA followed by acetone treatments for 51 weeks. Squamous cell carcinomas were observed in 5/20 animals in the chlorite group. However, the results were not statistically significant.

4.4.2. Genotoxicity Studies

4.4.2.1. *Chlorine Dioxide*

Both positive and negative results have been found in in vitro genotoxicity studies. Chlorine dioxide did not increase chromosome aberrations in Chinese hamster fibroblast cells but did increase reverse mutation in *Salmonella typhimurium* (with activation) (Ishidate et al., 1984). However, water samples disinfected with chlorine dioxide did not induce reverse mutations in *S. typhimurium* with or without activation (Miller et al., 1986). In vivo micronucleus and bone marrow chromosomal aberration assays in Swiss CD-1 mice administered 0.1–0.4 mg chlorine dioxide via gavage for 5 consecutive days were negative, as was a sperm-head abnormality assay in B6C3F1 mice administered 0.1–0.4 mg via gavage for 5 consecutive days (0, 3.2, 8, and 16 mg/kg-day) (Meier et al., 1985). Hayashi et al. (1988) reported positive results in the micronucleus assay in ddY mice following a single intraperitoneal injection of 3.2–25 mg/kg chlorine dioxide.

4.4.2.2. *Chlorite*

Genotoxicity of chlorite was assessed in several in vitro and in vivo assays. In in vitro assays, chlorite induced reverse mutations in *S. typhimurium* (with activation) and chromosome aberrations in Chinese hamster fibroblast cells (Ishidate et al., 1984). In general, the results of the in vivo assays were negative. In the micronucleus assays, negative results were found in ddY mice following an oral gavage dose of 37.5–300 mg/kg chlorite single injection (Hayashi et al., 1988) and in Swiss CD-1 mice administered 0.25–1 mg chlorite via gavage for 5 consecutive days (0, 8, 20, and 40 mg/kg-day) (Meier et al., 1985). Using the same dosages, Meier et al. also reported negative results in the bone marrow chromosomal aberration assay in Swiss CD-1 mice and in the sperm-head abnormality assay in B6C3F1 mice. Positive results were found in the

micronucleus assay in ddY mice when the chlorite was administered via intraperitoneal injection (7.5–60 mg/kg) (Hayashi et al., 1988).

4.4.3. Mechanistic Studies

EPA (1994d) has extensively discussed the mechanism of action whereby chlorine dioxide and chlorite produce hematologic and systemic effects. The mechanisms are still incompletely understood. Oxidative damage to the erythrocyte and production of methemoglobin are most likely related to their properties as oxidants (U.S. EPA, 1994d). Chlorite is thought to be the intermediate species responsible in many of the hematologic effects of chlorine dioxide because of its more efficient production of methemoglobin, depletion of red blood cell (RBC) glutathione, and alteration of erythrocyte fragility.

In a series of experiments, Bercz and co-workers (1982, 1986); and Harrington et al. (1986) suggested that chlorine dioxide increases binding of dietary iodide to gastrointestinal tissue and contents, producing a functional iodide deficiency. Bercz et al. (1982) found decreased levels of circulating thyroxine in monkeys drinking water containing > 9.5 mg/kg-day chlorine dioxide, but not 44 mg/kg-day chlorite, for 4–6 weeks. In a follow-up study, Harrington et al. (1986) demonstrated increases in thyroid iodide uptake and a rebound in thyroxine levels in monkeys 1 year after an 8-week exposure to approximately 5 mg/kg-day chlorine dioxide in drinking water. Unlike monkeys, rats showed dose-related declines in thyroxine levels and no alteration in thyroid iodide uptake following an 8-week exposure to 10 mg/kg-day chlorine dioxide in drinking water.

Whether either or both of these mechanisms are operable in inducing reproductive, developmental, and neurodevelopmental effects is not known. One could also speculate that hypothyroidism, induced by chlorine dioxide alteration of iodide uptake in the gastrointestinal tract, might contribute to alterations in maternal or neonatal behavior. Alternative, as yet unknown mechanisms are also plausible because few definitive mechanistic data are available. Additional research is needed to understand whether the parent chlorine dioxide and/or its oxychlorine degradation products induce delays and alterations in fetal/neonatal neurodevelopment and behavior through disturbance in maternal thyroid function or directly within the embryo itself.

4.5. SYNTHESIS AND EVALUATION OF MAJOR NONCANCER EFFECTS AND MODE OF ACTION (IF KNOWN)—ORAL AND INHALATION

4.5.1. Oral Exposure

4.5.1.1. *Chlorine Dioxide*

The subchronic/chronic toxicity of chlorine dioxide has not been adequately assessed. The Haag (1949) chronic drinking water study reported decreases in survival in rats exposed to 13 mg/kg-day chlorine dioxide for 2 years, but the cause of death was not reported and no effects were observed at lower concentrations. The small number of animals tested and the limited

number and lack of sensitive endpoints examined make interpretation of this study difficult. Daniel et al. (1990) found increases in incidence of nasal lesions in rats exposed to $ 25 mg/L chlorine dioxide (2 mg/kg-day) in drinking water for 90 days; no other adverse effects were observed. However, it is not known if the nasal lesions resulted from inhaling chlorine dioxide vapors at the drinking water sipper tube or from off-gassing of the vapors after drinking. No other studies have reported similar effects. Other subchronic/chronic studies primarily examined hematologic parameters. Bercz et al. (1982) found significant decreases in serum T4 levels in monkeys exposed to 9.5 mg/kg-day chlorine dioxide in the drinking water for 4–6 weeks. Adverse hematologic effects could not be discerned in Abdel-Rahman et al. (1984b) because there was no consistent dose-effect relationship. Additionally, Daniel et al. (1990), Bercz et al. (1982), and Moore and Calabrese (1982) did not find hematologic alterations in rats, monkeys, or mice, respectively. Abdel-Rahman et al. (1984b) and Couri and Abdel-Rahman (1980) reported alterations in the glutathione-dependent system, in particular, decreases in erythrocyte glutathione levels, increases in glutathione peroxidase activity, and increases in erythrocyte catalase levels. However, as with the hematologic effects this group found, consistent relationships between dose and magnitude of the alterations were lacking.

A number of studies have consistently found developmental effects following in utero exposure or postnatal gavage administration of 14 mg/kg-day chlorine dioxide. The effects include altered brain development (decreases in forebrain and/or cerebellum DNA content, ratio of protein content to forebrain weight, and dendritic spine counts in a visual association area of the cerebral cortex) (Toth et al., 1990; Taylor and Pfohl, 1985), decreased locomotor or exploratory activity (Orme et al., 1985; Taylor and Pfohl, 1985), and increased T3 uptake (Mobley et al., 1990). Orme et al. (1985) found decreases in T3 and T4 levels in in utero and postnatally exposed pups; however, other studies did not find alterations in T3 and T4 levels in similarly exposed animals (Toth et al., 1990; Carlton et al., 1991).

The available data indicate that the critical effect of chlorine dioxide is neurodevelopmental toxicity.

4.5.1.2. *Chlorite*

A number of studies have examined the subchronic/chronic toxicity of chlorite; however, only the Harrington et al. (1995a) study examined a wide range of endpoints. This study identified a NOAEL and LOAEL of 7.4 and 19 mg/kg-day, respectively, for stomach lesions and alterations in spleen and adrenal weights in rats receiving gavage doses of sodium chlorite. The bolus administration of sodium chlorite might have contributed to the stomach lesions; these effects might not have been observed if the sodium chlorite had been administered in the drinking water. Haag (1949) found renal effects in rats drinking 9.3 mg/kg-day chlorite (NOAEL of 0.7 mg/kg-day); interpretation of the results of this study is limited by the small numbers of animals that underwent pathological examination and the limited number of endpoints examined. Abdel-Rahman et al. (1984b) and Couri and Abdel-Rahman (1980) found decreases in osmotic fragility, blood glutathione levels, and blood catalase activity in rats exposed to 1 and 10 mg/kg-day chlorite in drinking water. It is unclear, however, if these effects are statistically or biologically significant. In contrast, Moore et al. (1980) and Moore and Calabrese (1982) found

increases in osmotic fragility in mice exposed to 22 mg/kg-day chlorite in drinking water. Bercz et al. (1982) found decreases in erythrocyte and hemoglobin levels and decreases in T4 levels in monkeys exposed to 58.4 mg/kg-day chlorite.

As with chlorine dioxide, developmental toxicity appears to be the most sensitive effect of oral chlorite exposure. At exposure levels of 3 mg/kg-day and 6 mg/kg-day, Mobley et al. (1990) found significant decreases in exploratory activity in rat pups exposed to chlorite in utero. The changes at 3 mg/kg-day were small, whereas changes observed at 6 mg/kg-day were more consistent with findings from several other studies. Similarly, lowered auditory startle response and reduced liver weight were observed at 6 mg/kg-day, but not at 3 mg/kg-day, in rats in a two-generation study (CMA, 1996). At higher concentrations (19–28 mg/kg-day), decreases in fetal/pup body weight have been observed in mice and rabbits (Moore et al., 1980; Moore and Calabrese, 1982; Harrington et al., 1995b). Data from Carlton and Smith (1985) and Carlton et al. (1987) suggest that sperm may be a sensitive target of toxicity. Reductions in sperm progressive movement and increases in abnormal sperm have been observed in rats exposed to 7.5 mg/kg-day chlorite in drinking water for 72–76 days. However, the CMA (1996) two-generation study did not find any alterations in reproductive performance in rats exposed to 22.7 mg/kg-day chlorite in drinking water.

4.5.2. Inhalation Exposure

4.5.2.1. *Chlorine Dioxide*

Several human studies have examined the toxicity of inhaled chlorine dioxide (Gloemme and Lundgren, 1957; Elkins, 1959; Ferris et al., 1967; Exner-Freisfeld et al., 1986; Kennedy et al., 1991; Meggs et al., 1996). Despite the limitations of these studies (including poor exposure assessment, small number of subjects, and concomitant exposure to chlorine and/or sulfur dioxide), they consistently demonstrate that the respiratory tract is a very sensitive target of toxicity.

A series of studies by Paulet and Desbrousses (1970, 1972, 1974) and Dalhamn (1957) examined the acute and subchronic toxicity of chlorine dioxide in rats and rabbits. As with the human studies, the respiratory tract is the most sensitive target of toxicity. The effects include alveolar congestion and hemorrhage, bronchial inflammation, and peribronchiolar edema. A NOAEL for these effects has not been identified; the lowest LOAEL is 1 ppm (2.8 mg/m^3) in rats exposed to chlorine dioxide 5 hours/day, 5 days/week for 2 months (Paulet and Desbrousses, 1972).

4.5.2.2. *Chlorite*

No data are available on the toxicity of inhaled chlorite.

4.6. WEIGHT-OF-EVIDENCE EVALUATION AND CANCER CHARACTERIZATION—SYNTHESIS OF HUMAN, ANIMAL, AND OTHER SUPPORTING EVIDENCE, CONCLUSIONS ABOUT HUMAN CARCINOGENICITY, AND LIKELY MODE OF ACTION

4.6.1. Chlorine Dioxide

Under the current guidelines (U.S. EPA, 1986a), chlorine dioxide is classified as Group D, not classifiable as to human carcinogenicity because of inadequate data in humans and animals. Under the draft Carcinogen Assessment Guidelines (U.S. EPA, 1996a), the human carcinogenicity of chlorine dioxide cannot be determined because no satisfactory human or animal studies assessing the chronic carcinogenic potential of chlorine dioxide were located.

No human or animal studies assessing the carcinogenic potential of chlorine dioxide were located. The carcinogenic potential of concentrates prepared from drinking water treated with chlorine dioxide was tested by Miller et al. (1986). The concentrates did not increase incidence of lung adenomas in Strain A mice, skin tumor frequency in mice, or incidence of gamma-glutamyl transpeptidase positive foci (a measure of preneoplastic changes) in rat livers. Robinson et al. (1986) found significant increases in skin thickness in SENCAR mice immersed in chlorine dioxide, suggesting that high concentrations of chlorine dioxide are capable of inducing hyperplastic responses in the mouse skin.

Both positive and negative results have been found in genotoxicity studies of chlorine dioxide. Exposure to chlorine dioxide did not induce chromosomal aberrations in vitro, but it did increase occurrence of reverse mutations (Ishidate et al., 1984). In vivo assays did not find increases in micronucleus induction, chromosomal aberrations, or sperm-head abnormalities following oral exposure (Meier et al., 1985), but they did find increases in micronuclei induction after intraperitoneal injection (Hayashi et al., 1988).

4.6.2. Chlorite

Under the current guidelines (U.S. EPA, 1986a), chlorite is classified as Group D, not classifiable as to human carcinogenicity because of inadequate data in humans and animals. Under the draft Carcinogen Assessment Guidelines (U.S. EPA, 1996a), the human carcinogenicity of chlorite cannot be determined because of a lack of human data and limitations in animal studies.

No human studies assessing the carcinogenic potential of chlorite were located. Chlorite was tested for potential carcinogenicity in rat and mouse drinking water studies (Kurokawa et al., 1986; Yokose et al., 1987). These studies do not provide sufficient evidence to draw conclusions as to the carcinogenic potential of chlorite in humans. In the rat study (Kurokawa et al., 1986), exposure to sodium chlorite did not significantly increase the incidence of tumors. The short exposure duration (85 weeks) and high incidence of Sendai viral infection in control and exposed rats limit the use of this study to assess carcinogenicity.

In the mouse drinking water study (Kurokawa et al., 1986; Yokose et al., 1987), significant increases in liver and lung tumors were observed in male mice. Combined incidence of hepatocellular nodules and hepatocellular carcinomas was increased in the low-dose group, and combined incidence of lung adenomas and adenocarcinomas was elevated in the high-dose group relative to concurrent controls. However, these tumor incidences were within the range of values of historical controls in the study laboratory and in the National Toxicology Program laboratories (Kurokawa et al., 1986). This study is considered inadequate for assessing carcinogenicity because of the relatively short exposure duration (80 weeks) and the high incidence of early mortality in the concurrent control males from excessive fighting, making statistical comparisons between concurrent controls and treated animals difficult to interpret. No increases in tumor incidence were seen in female mice in this study.

Chlorite has been shown to be mutagenic in in vitro assays for reverse mutations and chromosome aberrations (Ishidate et al., 1984) and in an in vivo assay of micronucleus induction in which mice received an intraperitoneal injection of sodium chlorite (Hayashi et al., 1988). In vivo assays for micronucleus induction, chromosome aberrations, and sperm-head abnormalities were negative in mice receiving gavage doses of chlorite for 5 days (Meier et al., 1985; Hayashi et al., 1988).

4.7. SUSCEPTIBLE POPULATIONS

4.7.1. Possible Childhood Susceptibility

4.7.1.1. *Chlorine Dioxide and Chlorite*

Developmental delays have been observed in animal studies following in utero and postnatal exposure to ingested chlorine dioxide or chlorite, suggesting that infants and children may be more likely than adults to experience adverse effects following exposure to these chemicals, although the reasons for this increased sensitivity are not fully understood. It is well recognized that neurological development continues after birth and that gastrointestinal uptake of many nutrients and chemicals is greater in the neonate than the adult.

4.7.2. Possible Gender Differences

4.7.1.2. *Chlorine Dioxide and Chlorite*

No data are available to suggest there are gender differences in the toxicity of chlorine dioxide or chlorite.

5. DOSE-RESPONSE ASSESSMENTS

5.1. ORAL REFERENCE DOSE (RfD)

5.1.1. Choice of Principal Study and Critical Effect—With Rationale and Justification

In general, human studies have not found adverse effects in individuals consuming low concentrations (0.04–0.15 mg/kg-day) of chlorine dioxide or chlorite in experimental studies (Lubbers et al., 1981, 1982, 1984a) or consuming drinking water disinfected with chlorine dioxide (Michael et al., 1981; Tuthill et al., 1982). An epidemiology study by Kanitz et al. (1996) found increases in the risk of several developmental effects (neonatal jaundice, small cranial circumference, and shorter body length) in a community with chlorine dioxide-disinfected drinking water. However, the Kanitz et al. (1996) study has numerous limitations (including multiple chemical exposures; lack of exposure data; lack of control for smoking, age, and nutritional habits; and atypical control data), making it difficult to interpret the study findings.

In animals, the most sensitive effect following oral exposure to chlorine dioxide or chlorite is neurodevelopmental delay. In utero exposure to chlorine dioxide or postnatal gavage administration of chlorine dioxide has resulted in altered brain development (decreases in brain weight, protein content, and cell number) (Taylor and Pfohl, 1985; Toth et al., 1990) and decreased locomotor or exploratory activity (Orme et al., 1985; Taylor and Pfohl, 1985; Mobley et al., 1990). The LOAEL for these effects is 14 mg/kg-day chlorine dioxide (Orme et al., 1985; Taylor and Pfohl, 1985; Mobley et al., 1990; Toth et al., 1980); Orme et al. (1985) identified a NOAEL of 3 mg/kg-day.

Neurobehavioral effects (lowered auditory startle amplitude, decreased brain weight, and decreased exploratory activity) are also the most sensitive endpoints following oral exposure to chlorite (Mobley et al., 1990; CMA, 1996). The LOAEL identified in the Mobley et al. (1990) developmental toxicity study and the CMA (1996) two-generation developmental toxicity study is 6 mg/kg-day chlorite; Mobley et al. (1990) also found significant decreases in exploratory activity at 3 mg/kg-day, but the difference between activity in this group and the controls was small. Thus, the NOAEL for neurobehavioral effects is 3 mg/kg-day chlorite. At higher concentrations (22–28 mg/kg-day chlorite), decreases in fetal/pup body weight have also been observed in mice and rabbits (Moore and Calabrese, 1982; Moore et al., 1980; Harrington et al., 1995b).

Chlorine dioxide in drinking water rapidly degrades to chlorite; in the Michael et al. (1981) study, chlorine dioxide rapidly disappeared from the stored water (within 2–4 hours) and chlorite levels concomitantly increased. Once absorbed, chlorine dioxide and chlorite are cleared from the blood at similar rates and are similarly distributed throughout the body (Abdel-Rahman et al., 1979b, 1982). Additionally, chloride is the major in vivo degradation product of both chlorine dioxide and chlorite. Available data suggest that chlorine dioxide and chlorite have similar targets of toxicity and potencies. Therefore, the toxicity information for chlorite is relevant to deriving an RfD for chlorine dioxide.

The CMA (1996) two-generation study was selected as the critical study for the development of an RfD for both chlorine dioxide and chlorite. Both in its study report (CMA 1996) and in a later journal article (Gill et al., 2000), CMA reported that the study defined a NOAEL of 70 ppm (6 mg/kg-day chlorite) and a LOAEL of 300 ppm (28.6 mg/kg-day chlorite) based on hematologic toxicity. For the reasons outlined below, EPA disagrees with CMA's choice of NOAEL and LOAEL values. Alterations in multiple endpoints define the LOAEL-NOAEL boundary in the CMA study. Effects observed included statistically significant decreases in pup body weight, absolute brain weight, liver weight, and lowered startle amplitude at the 28.6 mg/kg-day dose. Statistically significant decreases in auditory startle amplitude (F1 and F2 generations) and absolute and relative liver weights (F0 and F1) occurred at 6 mg/kg-day. Although different responses were found for auditory startle (as indicated by measures of amplitude, latency, and habituation), this is not unexpected given that these measures examine different aspects of nervous system function and thus can be differently affected. Transient alterations in neurofunctional (or neurochemical) measures, such as in the auditory startle response, can occur without neuropathological changes and are considered of neurotoxic concern (U.S. EPA, 1998a). Some of effects observed at 6 mg/kg-day and 28.6 mg/kg-day occurred in both sexes and in more than one generation. These effects are considered toxicologically significant, which is consistent with EPA guidelines for reproductive, developmental, and neurotoxicity risk assessment (U.S. EPA, 1991, 1996b, 1998a). The NOAEL for this study is 3 mg/kg-day chlorite and the LOAEL is 6 mg/kg-day chlorite based on lowered auditory startle amplitude and decreased liver weight.

Although the CMA (1996) study is adequate, having been conducted with sufficient numbers of animals of both sexes at multiple dose levels showing a range of effects, and having examined numerous endpoints, there are several limitations. Lack of pair-watered and pair-fed control animals confounds the results and precludes making definitive conclusions as to whether the alterations in food and water consumption and body weight are related to water palatability or a direct toxic effect of the agent. Discontinuation of exposure for the animals undergoing neurotoxicity testing limits the likelihood of finding a positive effect, precludes comparison of the data with those of other rats with continued exposure, and does not reflect the expected lifetime exposure by humans to these chemicals in drinking water. In addition, a lack of detailed description of experimental methods and positive control data (including estimates of variability), and in some cases inappropriate statistical analysis, limits interpretation of the neurobehavioral tests.

The principal study is supported by the developmental studies by Orme et al. (1985), Taylor and Pfohl (1985), Mobley et al. (1990), and Toth et al. (1990), wherein rats administered chlorite or chlorine dioxide at similar dosages in drinking water also showed alterations in exploratory and locomotor behavior and reduced brain weights (NOAELs of 3 mg/kg-day; LOAELs of 14 mg/kg-day).

5.1.2. Methods of Analysis—Including Models (PBPK, BMD, etc.)

The NOAEL/LOAEL approach was used to derive RfDs for chlorine dioxide and chlorite. The RfD was derived using the NOAEL of 3 mg/kg-day identified in the CMA (1996)

study. This dose was determined from the nominal water concentration based on measured water consumption and adjusted for the molecular weight of the salt, so that doses are expressed as the chlorite ion. (For example, males administered 35 ppm had intakes of sodium chlorite equivalent to 3.9 mg/kg-day. Adjusting for the molecular weight of sodium chlorite [MW = 90.5] relative to the chlorite ion [MW = 67.5] gives the NOAEL dose of 3 mg/kg-day chlorite.)

5.1.3. RfD Derivation—Including Application of Uncertainty Factors and Modifying Factors

The RfDs for chlorine dioxide and chlorite were derived by dividing the NOAEL of 3 mg/kg-day by an uncertainty factor of 100. This composite factor includes a factor of 10 to account for uncertainties associated with interspecies extrapolation and a factor of 10 for intrahuman variability. Because the critical effect is a developmental effect in a database that includes chronic studies, it is not necessary to use an uncertainty factor to account for use of a less-than-lifetime study. A default modifying factor of 1 is applied. The resultant RfD is 3×10^{-2} mg/kg-day:

$$\text{RfD} = 3 \text{ mg/kg-day} \div 100 = 3 \times 10^{-2} \text{ mg/kg-day}.$$

5.2. INHALATION REFERENCE CONCENTRATION (RfC)

5.2.1. Choice of Principal Study and Critical Effect—With Rationale and Justification

5.2.1.1. *Chlorine Dioxide*

Human studies examining toxicity of inhaled chlorine dioxide are limited to several case reports (Elkins, 1959; Exner-Freisfeld et al., 1986; Meggs et al., 1996) and occupational exposure studies (Gloemme and Lundgren, 1957; Ferris et al., 1967; Kennedy et al., 1991) that involved concurrent exposure to chlorine and possibly sulfur dioxide. Although these studies cannot be used to establish risk assessment values, the results of these studies consistently demonstrate that the respiratory tract is a very sensitive target of chlorine dioxide toxicity.

A series of studies by Paulet and Desbrousses (1970, 1972, 1974) and Dalhamn (1957) examined the acute and subchronic toxicity of chlorine dioxide in rats and rabbits. The earliest Paulet and Desbrousses (1970) study identified a LOAEL of 2.5 ppm chlorine dioxide (6.9 mg/m^3) for thoracic effects (alveolar congestion and hemorrhage; bronchial inflammation) in rats exposed 7 hours/day (presumably 5 days/week) for 30 days and pulmonary effects (alveolar hemorrhage and capillary congestion) in rabbits exposed 4 hours/day (presumably 5 days/week) for 45 days; a NOAEL was not identified. A follow-up study by this group attempted to identify a threshold for respiratory effects (Paulet and Desbrousses, 1972). This study identified a LOAEL of 1 ppm (2.8 mg/m^3) for pulmonary effects (vascular congestion and peribronchiolar edema) in rats exposed 5 hours/day, 5 days/week for 2 months; a NOAEL was not identified. The Dalhamn (1957) study identified a NOAEL of 0.1 ppm chlorine dioxide (0.28 mg/m^3) for lung damage in rats exposed 5 hours/day (frequency of weekly exposure not reported) for 10

weeks; a LOAEL of 10 ppm (28 mg/m^3) for respiratory tract irritation was identified in rats exposed 4 hours/day for 9 days in a 13-day period.

Collectively, the results of the human and animal studies suggest that the respiratory tract is the critical target. The Paulet and Desbrousses (1970, 1972) studies were selected as cocritical studies. The 1972 study identified the lowest LOAEL for a sensitive endpoint (respiratory tract effects); however, the study duration (2 months) is shorter than the typical subchronic study (approximately 90 days) and only one exposure concentration was tested. The 1970 study is used to support the identification of the critical effect and critical concentrations; this study tested several concentrations in two species for durations of 30 or 45 days.

5.2.1.2. *Chlorite*

An RfC for chlorite is not recommended at this time. No human or animal studies examining the toxicity of inhaled chlorite were located. Although the available human and animal data on inhaled chlorine dioxide support the derivation of an RfC for this chemical, these data cannot be used to derive an RfC for chlorite. Under ambient conditions, airborne chlorite is likely to exist as a particulate, whereas inhalation exposure to chlorine dioxide is as a gas. Based on their physical and chemical properties, it is anticipated that inhaled chlorine dioxide and chlorite would have very different modes of exposure. Therefore, the potential hazards associated with exposure to these two chemicals are also very different. In the absence of data demonstrating parallels in pharmacokinetic behavior following inhalation exposure—as are available following oral exposure—derivation of an RfC for chlorite from the available data for chlorine dioxide is not recommended.

5.2.2. Methods of Analysis—NOAEL/LOAEL

5.2.2.1. *Chlorine Dioxide*

The NOAEL/LOAEL approach was used to calculate the RfC for chlorine dioxide. A benchmark concentration (BMC) analysis could not be conducted because the report of the Paulet and Desbrousses (1970, 1972) studies did not include incidence data.

The RfC was derived using the Paulet and Desbrousses (1970, 1972) studies as co-critical studies. From the LOAEL of 1 ppm for pulmonary effects in rats identified in the Paulet and Desbrousses (1972) study, concentration in mg/m^3 was calculated using a molecular weight of 67.46 and the assumption of 25°C and 760 mmHg:

$$\text{LOAEL} = 1 \text{ ppm} \times 67.46/24.45 = 2.8 \text{ mg/m}^3 \text{ (Paulet and Desbrousses, 1972 - rats).}$$

The duration-adjusted LOAEL ($\text{LOAEL}_{\text{ADJ}}$) was calculated by multiplying the LOAEL by the daily exposure duration (5 hours/day) and the weekly exposure frequency (5 days/week):

$$\text{LOAEL}_{\text{ADJ}} = 2.8 \text{ mg/m}^3 \times 5 \text{ hours}/24 \text{ hours} \times 5 \text{ days}/7 \text{ days} = 0.41 \text{ mg/m}^3 \text{ (rat).}$$

The human equivalent concentration (HEC) for the LOAEL ($LOAEL_{HEC}$) was calculated by multiplying the $LOAEL_{ADJ}$ by the regional gas dose ratio for the thoracic region of the respiratory tract ($RGDR_{TH}$). The $RGDR_{TH}$ was calculated using the following equation:

$$RGDR_{TH} = \frac{\left[\frac{MV}{SA}\right]_A}{\left[\frac{MV}{SA}\right]_H}$$

where MV is the minute volume in rats (0.118 m^3/min; 0.17 m^3/day) and humans (13.8 m^3/min; 20 m^3/day) and SA is the surface area of the thoracic region in rats (3461.6 cm^2) and humans (640,581 cm^2).

$LOAEL_{HEC}$ = 0.41 mg/m^3 × [(0.118 m^3/min / 3461.6 cm^2) / (13.8 m^3/min / 640,581 cm^2);

$LOAEL_{HEC}$ = 0.41 mg/m^3 × 1.57 = 0.64 mg/m^3.

Similarly, for the Paulet and Desbrousses (1970) study, using values of 1.10 m^3/min for the minute volume and 59,100 cm^2 for the surface area of the thoracic region of rabbits, the calculation of the $LOAEL_{HEC}$ is as follows:

LOAEL = 2.5 ppm × 67.46/24.45 = 6.9 mg/m^3.

$LOAEL_{ADJ}$ = 6.9 mg/m^3 × 4 hours/24 hours × 5 days/7 days = 0.82 mg/m^3.

$LOAEL_{HEC}$ = 0.82 mg/m^3 × [(1.10 m^3/min / 59,100 cm^2) / (13.8 m^3/min / 640,581 cm^2);

$LOAEL_{HEC}$ = 0.82 mg/m^3 × 0.596 = 0.49 mg/m^3.

5.2.3. RfC Derivation—Including Application of Uncertainty Factors and Modifying Factors

5.2.3.1. *Chlorine Dioxide*

The RfC for chlorine dioxide is derived by dividing the $LOAEL_{HEC}$ thoracic effects by an uncertainty factor of 3,000. This uncertainty factor comprises a factor of 10 to account for extrapolation of a chronic RfC from a subchronic study, 3 for interspecies extrapolation using dosimetric adjustments, 10 for intrahuman variability, and 10 to account for extrapolation from a LOAEL for mild effects and for the lack of inhalation developmental and reproductive toxicity studies. EPA's policy is to limit the size of the composite uncertainty factor to 3,000 in recognition of the lack of independence of these factors (U.S. EPA, 1994b). The LOAEL to NOAEL and database uncertainties are therefore coalesced into one uncertainty factor of 10. The composite uncertainty factor for this RfC is therefore 3,000. No modifying factor is used for this assessment.

$$RfC = 0.64 \text{ mg/m}^3 \div 3{,}000 = 2 \times 10^{-4} \text{ mg/m}^3.$$

or

$$RfC = 0.49 \text{ mg/m}^3 \div 3{,}000 = 2 \times 10^{-4} \text{ mg/m}^3.$$

As can be seen, the same value for the RfC can be calculated using the LOAEL from either of the key studies. Note that this is the same value as was verified by the RfC workgroup in 1990, as no new data were available.

5.3. CANCER ASSESSMENT

5.3.1. Chlorine Dioxide

The oral and inhalation databases are inadequate to assess the carcinogenicity of chlorine dioxide in humans or animals; thus, derivation of an oral slope factor and inhalation unit risk level is precluded.

5.3.2. Chlorite

The oral and inhalation databases are inadequate to assess the carcinogenicity of chlorite in humans or animals; thus, derivation of an oral slope factor and inhalation unit risk level is precluded.

6. MAJOR CONCLUSIONS IN THE CHARACTERIZATION OF HAZARD AND DOSE RESPONSE

6.1. HUMAN HAZARD POTENTIAL

Chlorine dioxide and chlorite are strong oxidizing agents used as drinking water disinfectants and to bleach textile and wood pulp for paper manufacturing. Chlorine dioxide and chlorite are rapidly absorbed from the gastrointestinal tract and slowly cleared from the blood. Chlorine dioxide and chlorite, primarily in the form of chloride, are widely distributed throughout the body and predominantly excreted in the urine. Chloride is the major urinary "metabolite" for both chlorine dioxide and chlorite. No data are available on the pharmacokinetics of inhaled or dermally applied chlorine dioxide or chlorite.

In general, human ingestion studies have found no adverse effects in adults and neonates living in areas with chlorine dioxide-disinfected water. However, these studies are fraught with methodological problems, such as lack of characterization of exposure to other agents in the drinking water and control of potential confounding factors. These studies do little to confirm a possible association between exposure to chlorine dioxide and chlorite and adverse reproductive or developmental outcome in humans. Inhalation exposure to chlorine dioxide results in

respiratory irritation in humans. However, these studies also poorly characterize exposure, and the occupational exposure studies involve concomitant exposure to chlorine and/or sulfur dioxide.

Animal toxicity databases for chlorine dioxide and chlorite is fairly comprehensive, composed of subchronic and chronic studies, reproductive and developmental studies, and toxicokinetic and mechanistic information. Multiple animal studies have shown similar alterations in neurodevelopmental endpoints, such as brain weight and behavioral measures. The majority of these studies have used sufficient numbers of animals and employed routes of exposure (gavage and drinking water) relevant to human exposure. The majority of the developmental studies have utilized rats and have shown a fairly consistent definition of the NOAEL/LOAEL.

Reproductive studies in male animals are not consistent in demonstrating alterations in spermatogenic indices, that is, abnormal morphology or motility; however, reported effects seem to appear at doses higher than the adverse developmental effects. Similarly, clinically or toxicologically significant alterations in hematologic parameters occur at higher doses.

The mode of action for induction of adverse neurodevelopmental effects is not known. It is also not known whether the rat is an adequate model for toxicity of chlorine dioxide and chlorite in humans. However, this species is widely used to characterize reproductive and developmental effects in humans.

Animal studies have demonstrated that the respiratory tract is the most sensitive target of toxicity following inhalation exposure to chlorine dioxide. No animal inhalation studies are available for chlorite.

No human studies assessing the carcinogenic potential of chlorine dioxide or chlorite were located. Chlorine dioxide carcinogenicity has not been tested in animal bioassays. Chlorite was not shown to increase tumor incidences in rats and mice; these studies are considered inadequate for assessing human carcinogenicity because the exposure was for less than a lifetime, a high incidence of Sendai virus was found in the rats, and mortality was high in the mouse control group because of excessive fighting.

Areas of scientific uncertainty in this assessment include the mode of action of chlorine dioxide and chlorite in producing adverse effects on multiple organ systems, including reproductive, developmental, and hematologic effects. Inherent in the uncertainty over the mode of action is identification of the susceptible populations or subgroups, and additional research in this area would help to better quantify the additional risk to these groups. Well-designed and conducted epidemiologic studies in communities with drinking water disinfected with these chemicals would decrease uncertainty in the utilization of animal models for determination of human health effects.

6.2. DOSE RESPONSE

Quantitative estimates of human risk as a result of low-level chronic chlorine dioxide or chlorite oral exposure are based on animal experiments, because no adequate human exposure data are available. Neurodevelopmental toxicity is the primary effect in offspring of rats exposed to chlorine dioxide or chlorite in drinking water. Quantitative estimates of human risk as a result of low-level chronic chlorine dioxide inhalation exposure are based on animal experiments, because no adequate human inhalation data are available. The respiratory tract appears to be the primary target of toxicity in human and animal studies.

The oral RfD for chlorine dioxide or chlorite is 3×10^{-2} mg/kg-day. This is 1/100 of the NOAEL, using neurodevelopmental toxicity in a two-generation rat study as the indicator of adverse effects. Overall confidence in this RfD assessment is medium to high. Confidence in the CMA (1996) principal study is medium. Although the study design and analytical approaches are consistent with EPA testing guidelines, some limitations in the design and conduct of the study exist. Confidence in the database is high because there are studies in multiple species, chronic duration studies in males and females, reproductive/developmental toxicity studies, and a multigenerational study. The threshold for adverse effects is consistently defined among the animal studies.

The inhalation RfC for chlorine dioxide is 2×10^{-4} mg/m^3. This concentration is 1/3,000 of the HEC for thoracic effects in rats (Paulet and Desbrousses, 1970, 1972). No human or animal data were located for chlorite that could be used to derive an RfC. Overall confidence in the RfC for chlorine dioxide is low. The studies by Paulet and Desbrousses (1970, 1972) identify only a LOAEL in rats and rabbits for adverse lung effects in 60- and 45-day studies and lack experimental detail. There were no adequate subchronic or chronic inhalation studies that examined extrarespiratory effects, and no acceptable developmental or reproductive studies on inhaled chlorine dioxide.

7. REFERENCES

Abdel-Rahman, MS; Couri, D; Bull, RJ. (1979a) Kinetics of ClO_2 and effects of ClO_2, ClO_2^-, and ClO_3 in drinking water on blood glutathione and hemolysis in rat and chicken. J Environ Pathol Toxicol 3:431-449.

Abdel-Rahman, MS; Couri, D; Jones, JD. (1979b) Chlorine dioxide metabolism in rat. J Environ Pathol Toxicol 3:421-430.

Abdel-Rahman, MS; Couri, D; Bull, RJ. (1982) Metabolism and pharmacokinetics of alternate drinking water disinfectants. Environ Health Perspect 46:19-23.

Abdel-Rahman, MS; Couri, D; Bull, RJ. (1984a) The kinetics of chlorite and chlorate in the rat. J Am Coll Toxicol 3:261-267.

Abdel-Rahman, MS; Couri, D; Bull, RJ. (1984b) Toxicity of chlorine dioxide in drinking water. J Am Coll Toxicol 3:277-284.

Bercz, JP; Jones, LL; Garner, L; et al. (1982) Subchronic toxicity of chlorine dioxide and related compounds in drinking water in the nonhuman primate. Environ Health Perspect 46:47-55.

Bercz, JP; Jones, LL; Harrington, RM; et al. (1986) Mechanistic aspects of ingested chlorine dioxide on thyroid function: impact of oxidants on iodide metabolism. Environ Health Perspect 69:249-255.

Bianchine, JR; Lubbers, JR; Chauhan, S; et al. (1981) Study of chlorine dioxide and its metabolites in man. Final report on EPA Grant No. 805643. EPA-600/1-82-068. Available from: National Technical Information Service, Springfield, Virginia; PB82-109356.

Budavari, S; O'Neil, MJ; Smith, A; et al. (eds). (1989) The Merck index: an encyclopedia of chemicals, drugs, and biologicals, 11th ed. Whitehouse Station, NJ: Merck and Co, Inc.

Carlton, BD; Smith, MK. (1985) Reproductive effects of alternate disinfectants and their by-products. In: Jolley, RL, et al., eds. Water chlorination: environmental impact and health effects, vol. 5. Chelsea, MI: Lewis Publications, pp. 295-305.

Carlton, BD; Habash, DL; Barsaran, AH; et al. (1987) Sodium chlorite administration in Long-Evans rats: reproductive and endocrine effects. Environ Res 42:238-245.

Carlton, BD; Basaran, AH; Mezza, LE; et al. (1991) Reproductive effects in Long-Evans rats exposed to chlorine dioxide. Environ Res 56:170-177.

Chemical Manufacturers Association. (CMA) (1996) Sodium chlorite: drinking water rat two-generation reproductive toxicity study. Quintiles Report Ref. CMA/17/96.

Couri, D; Abdel-Rahman, MS. (1980) Effect of chlorine dioxide and metabolites on glutathione dependent system in rat, mouse and chicken blood. J Environ Pathol Toxicol 3:451-460.

Couri, D; Miller, CH; Bull, RJ; et al. (1982) Assessment of maternal toxicity, embryotoxicity and teratogenic potential of sodium chlorite in Sprague-Dawley rats. Environ Health Perspect 46:25-29.

Dalhamn, T. (1957) Chlorine dioxide: toxicity in animal experiments and industrial risks. Arch Ind Health 15:101-107.

Daniel, FB; Condie, LW; Robinson, M; et al. (1990) Comparative subchronic toxicity studies of three disinfectants. J Am Water Works Assoc 82:61-69.

Elkins, HB. (1959) The chemistry of industrial toxicology, 2nd ed. New York: Wiley and Sons, pp. 89-90.

Exner-Freisfeld, H; Kronenberger, H; Meier-Sydow, J; et al. (1986) Intoxication from bleaching with sodium chlorite. The toxicology and clinical course [German with English abstract]. Dtsch Med Wochenschr 111(50):1927-1930.

Ferris, BG, Jr; Burgess, WA; Worcester, J. (1967) Prevalence of chronic respiratory disease in a pulp mill and a paper mill in the United States. Br J Ind Med 24(1):26-37.

Gill, MW, Swanson, MS; Murphy, SR, et al. (2000) Two-generation reproduction and developmental neurotoxicity study with sodium chlorite in the rat. J Appl Toxicol 20:291-303.

Gloemme, J; Lundgren, KD. (1957) Health hazards from chlorine dioxide. Arch Ind Health 16:169-176.

Haag, HB. (1949) The effect on rats of chronic administration of sodium chlorite and chlorine dioxide in the drinking water. Report to the Mathieson Alkali Works from H.B. Haag of the Medical College of Virginia. February 7, 1949.

Harrington, RM; Shertzer, HG; Bercz, JP. (1986) Effects of chlorine dioxide on thyroid function in the African green monkey and the rat. J Toxicol Environ Health 19:235-242.

Harrington, RM; Romano, RR; Gates, D; et al. (1995a) Subchronic toxicity of sodium chlorite in the rat. J Am Coll Toxicol 14:21-33.

Harrington, RM; Romano, RR; Irvine, L. (1995b) Developmental toxicity of sodium chlorite in the rabbit. J Am Coll Toxicol 14:109-118.

Hayashi, M; Kishi, M; Sofuni, T; et al. (1988) Micronucleus test in mice on 39 food additives and eight miscellaneous chemicals. Food Chem Toxicol 26:487-500.

Ishidate, M; Sofuni, T; Yoshikawa, K; et al. (1984) Primary mutagenicity screening of food additives currently used in Japan. Food Chem Toxicol 22:623-636.

Kanitz, S; Franco, Y; Patrone, V; et al. (1996) Associations between drinking water disinfection and somatic parameters at birth. Environ Health Perspect 104:516-520.

Kennedy, SM; Enarson, DA; Janssen, RG; Chan-Yeung, M. (1991) Lung health consequences of reported accidental chlorine gas exposures among pulpmill workers. Am Rev Respir Dis 143:74-79.

Kurokawa, Y; Takamura, N; et al. (1984) Studies on the promoting and complete carcinogenic activities of some oxidizing chemicals in skin carcinogenesis. Cancer Lett 24:299-304.

Kurokawa, Y; Takamura, S; Konishi, Y; et al. (1986) Long-term in vivo carcinogenicity tests of potassium bromate, sodium hypochlorite, and sodium chlorite conducted in Japan. Environ Health Perspect 69:221-235.

Lubbers, JR; Chauhan, S; Bianchine, JR. (1981) Controlled clinical evaluations of chlorine dioxide, chlorite and chlorate in man. Fundam Appl Toxicol 1:334-338.

Lubbers, JR; Chauhan, S; Bianchine, JR. (1982) Controlled clinical evaluations of chlorine dioxide, chlorite and chlorate in man. Environ Health Perspect 46:57-62.

Lubbers, JR; Chauhan, S; Miller, JK; et al. (1984a) The effects of chronic administration of chlorine dioxide, chlorite and chlorate to normal healthy adult male volunteers. J Environ Pathol Toxicol Oncol 5:229-238.

Lubbers, JR; Chauhan, S; Miller, JK; et al. (1984b) The effects of chronic administration of chlorite to glucose-6-phosphate dehydrogenase deficient healthy adult male volunteers. J Environ Pathol Toxicol Oncol 5:239-242.

Meggs, WJ; Elsheik, T; Metzger, WJ; et al. (1996) Nasal pathology and ultrastructure in patients with chronic airway inflammation (RADS and RUDS) following an irritant exposure. Clin Toxicol 34:383-396.

Meier, JR; Bull, RJ; Stober, JA; et al. (1985) Evaluation of chemicals used for drinking water disinfection for production of chromosomal damage and sperm-head abnormalities in mice. Environ Mutagen 7:201-211.

Michael, GE; Miday, RK; Bercz, JP; et al. (1981) Chlorine dioxide water disinfection: a prospective epidemiology study. Arch Environ Health 36:20-27.

Miller, RG; Kopler, FC; Condie, LW; et al. (1986) Results of toxicological testing of Jefferson Parish pilot plant samples. Environ Health Perspect 69:129-139.

Mobley, SA; Taylor, DH; Laurie, RD; et al. (1990) Chlorine dioxide depresses T3 uptake and delays development of locomotor activity in young rats. In: Jolley, RL, et al., eds. Water chlorination: chemistry, environmental impact and health effects, vol. 6. Chelsea, MI: Lewis Publications, pp. 347-358.

Moore, GS; Calabrese, EJ. (1982) Toxicological effects of chlorite in the mouse. Environ Health Perspect 46:31-37.

Moore, GS; Calabrese, EJ; Leonard, DA. (1980) Effects of chlorite exposure on conception rate and litters of A/J strain mice. Bull Environ Contam Toxicol 25:689-696.

Orme, J; Taylor, DH; Laurie, RD; et al. (1985) Effects of chlorine dioxide on thyroid function in neonatal rats. J Toxicol Environ Health 15:315-322.

Paulet, G; Desbrousses, S. (1970) On the action of ClO_2 at low concentrations on laboratory animals. Arch Mal Prof 31(3):97-106.

Paulet, G; Desbrousses, S. (1972) On the toxicology of chlorine dioxide. Arch Mal Prof 33(1-2):59-61.

Paulet, G; Desbrousses, S. (1974) Action of a discontinuous exposure to chlorine dioxide (ClO_2) on the rat [French with English translation.]. Arch Mal Prof 35:797-804.

Robinson, M; Bull, RJ; Schmaer, M; Long, RF. (1986) Epidermal hyperplasia in the mouse skin following treatment with alternate drinking water disinfectants. Environ Health Perspect 69:293-300.

Scatina, J; Abdel-Rahman, MS; Gerges, SE; et al. (1984) Pharmacodynamics of Alcide, a new antimicrobial compound, in rat and rabbit. Fundam Appl Toxicol 4:479-484.

Selevan, S. (1997) Comments on Italian study: association between drinking water disinfection and somatic parameters by Kanitz et al., Environ Health Perspect 104(5):516-520, 1996. Memorandum to J. Wiltse, U.S. EPA, Washington, DC, May 7.

Suh, DH; Abdel-Rahman, MS; Bull, RJ. (1983) Effect of chlorine dioxide and its metabolites in drinking water on fetal development in rats. J Appl Toxicol 3:75-79.

Taylor, DH; Pfohl, RJ. (1985) Effects of chlorine dioxide on the neurobehavioral development of rats. In: Jolley, RL, et al., eds. Water chlorination: chemistry, environmental impact and health effects, vol. 6. Chelsea, MI: Lewis Publications, pp. 355-364.

Toth, GP; Long, RE; Mills, TS; et al. (1990) Effects of chlorine dioxide on the developing rat brain. J Toxicol Environ Health 31:29-44.

Tuthill, RW; Giusti, RA; Moore, GS; et al. (1982) Health effects among newborns after prenatal exposure to ClO_2-disinfected drinking water. Environ Health Perspect 46:39-45.

U.S. Environmental Protection Agency. (1986a) Guidelines for carcinogen risk assessment. Federal Register 51(185):33992-34003.

U.S. Environmental Protection Agency. (1986b) Guidelines for the health risk assessment of chemical mixtures. Federal Register 51(185):34014-34025.

U.S. Environmental Protection Agency. (1986c) Guidelines for mutagenicity risk assessment. Federal Register 51(185):34006-34012.

U.S. Environmental Protection Agency. (1988) Recommendations for and documentation of biological values for use in risk assessment. Prepared by Environmental Criteria and Assessment

Office, Office of Health and Environmental Assessment, Cincinnati, OH. EPA 600/6-87/008. Available from: National Technical Information Service, Springfield, VA, PB88-179874/AS.

U.S. Environmental Protection Agency. (1991) Guidelines for developmental toxicity risk assessment. Federal Register 56(234):63798-63826.

U.S. Environmental Protection Agency. (1994a) Interim policy for particle size and limit concentration issues in inhalation toxicity: notice of availability. Federal Register 59(206):53799.

U.S. Environmental Protection Agency. (1994b) Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. Prepared by Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Research Triangle Park, NC. EPA/600/8-90/066F.

U.S. Environmental Protection Agency. (1994c) Peer review and peer involvement at the U.S. Environmental Protection Agency. Signed by the U.S. EPA Administrator, Carol M. Browner, dated June 7, 1994.

U.S. Environmental Protection Agency. (1994d) Final draft of the drinking water criteria document on chlorine dioxide, chlorite, and chlorate. Office of Science and Technology, Office of Water, Washington, DC. Office of Research and Development, Washington, DC.

U.S. Environmental Protection Agency. (1995) Use of the benchmark dose approach in health risk assessment. EPA/630/R-94/007.

U.S. Environmental Protection Agency. (1996a) Proposed guidelines for carcinogen risk assessment. Federal Register 61(79):17960-18011. http://www.epa.gov/nceawww1/cancer.htm

U.S. Environmental Protection Agency. (1996b) Reproductive toxicity risk assessment guidelines. Federal Register 61(212):56274-56322. http://www.epa.gov/ORD/WebPubs/repro/

U.S. Environmental Protection Agency. (1998a) Guidelines for neurotoxicity risk assessment. Federal Register 63(93):26926-26954. http://www.epa.gov/nceawww1/nurotox.htm

U.S. Environmental Protection Agency. (1998b) Science policy council handbook: peer review. Prepared by the Office of Science Policy, Office of Research and Development, Washington, DC. EPA 100-B-98-001.

World Health Organization, Regional Office for Europe. (2000) Health for All Statistical Database. Online. European Public Health Information Network for Eastern Europe. http://www.euphin.dk/hfa/Phfa.asp

Yokose, Y; Uchida, K; Nakae, D; et al. (1987) Studies of carcinogenicity of sodium chlorite in B6C3F1 mice. Environ Health Perspect 76:205-210.

APPENDIX A. EXTERNAL PEER REVIEW— SUMMARY OF COMMENTS AND DISPOSITION

The support document and IRIS summary for chlorine dioxide and chlorite have undergone both internal peer review performed by scientists within EPA and a more formal external review performed by scientists in accordance with EPA guidance on peer review (U.S. EPA, 1994c). Comments made by the internal reviewers were addressed prior to submitting the documents for external peer review and are not part of this appendix. The external peer reviewers were tasked with providing written answers to general questions on the overall assessment and on chemical-specific questions in areas of scientific controversy or uncertainty. A summary of significant comments made by the external reviewers and EPA's response to these comments follows.

Question 1. Are you aware of any other data/studies that are relevant (i.e., useful for hazard identification or dose-response assessment) for the assessment of the adverse health effects, both cancer and noncancer, of this chemical?

Comments: Two reviewers did not find any new relevant studies that would have any impact on the conclusions of this document. Four additional references were mentioned by the two other reviewers. One reviewer concurred that the results of the EPA evaluation agree with IARC (vol. 52, 1991), and there is inadequate evidence for the carcinogenicity of sodium chlorite in experimental animals. One reviewer commented on sensitive subgroups of the population and potential effects on blood chemistry parameters in renal dialysis patients when chlorine dioxide was used as a disinfectant. Also, one reviewer suggested a statement should be made on whether chlorite can be designated as a tumor promoter based on an initiation/promotion study on mouse skin (Kurokawa et al., 1984) and if the promoting activity is related to epidermal hyperplasia induction after topical exposure to sodium chlorite.

Response to Comments: The effects of chlorine dioxide and chlorite on human subjects and blood chemistry are described in the *Drinking Water Criteria Document on Chlorine Dioxide, Chlorite, and Chlorate* (U.S. EPA, 1994d) and in this Toxicological Review. All relevant ingestion studies, including the additional studies mentioned by the reviewers, have been evaluated in the drinking water criteria document, which was used in preparing this Toxicological Review. Changes seen in the tumor promoter study on mouse skin were not statistically significant.

Question 2. For RfD, RfC, and cancer, where applicable, have the most appropriate critical effects been chosen? For the cancer assessment, are the tumors observed biologically significant?

Comments: Two reviewers reiterated that it would appear that NOAELs around 3 mg/kg-day for the neurodevelopmental and behavioral effects are the most appropriate to develop the RfD for the oral exposure route, that the selection of the Paulet and Desbrousses (1972) study

for developing the RfC for chlorine dioxide is appropriate, and also that there is still no adequate evidence for the carcinogenicity of chlorine dioxide or chlorite. Other reviewers also stated that there are inadequate cancer data for risk assessment. One reviewer commented that an independent pathology group should review the histopathology diagnoses in the CMA (1996) study.

Response to Comments: The CMA (1996) study was vigorously subjected to independent peer review at EPA and by external reviewers. It was also reviewed by the stakeholders. Additional review of the histopathology diagnoses was not performed because the most sensitive endpoints (neurofunctional effects) were not histologic in nature.

Question 3. For RfD and RfC and cancer, have the appropriate studies been chosen as principal?

Comments: The external reviewers reiterated that appropriate studies were chosen for chlorine dioxide and chlorite. One reviewer stated that actual study reports cited were not available for review; the reviewer also suggested review of additional studies for irritating effects of chlorine dioxide in humans and questioned whether humans were more sensitive than rodents to chlorine dioxide.

Response to Comments: EPA cited the suggested studies as appropriate within the text. Studies describing irritating effects of chlorine dioxide in humans are described in the text. Data on the comparative sensitivity of rodents and humans to chlorine dioxide are not available. The 10-fold uncertainty factor for animal to human extrapolation was deemed an appropriate adjustment for this data gap.

Question 4. Studies included in the RfD and RfC and cancer under the heading "Supporting/Additional Studies" are meant to lend scientific justification for the designation of critical effect by including any relevant pathogenesis in humans, any applicable mechanistic information, any evidence corroborative of the critical effects, or to establish the comprehensiveness of the data base with respect to various endpoints. Should some studies be removed?

Comments: Reviewers indicated that additional and supporting studies cited for the RfD, RfC, and cancer assessments are appropriate and that no studies should be removed. One reviewer commented that he would question the quality and utility of studies that were conducted 50 years ago when quality assurance procedures and chemical production procedures and specifications were not what they are today. One reviewer asked whether any attempts were made to obtain histopathology slides from the unpublished Haag et al. (1949) studies.

Response to Comments: EPA agrees that no additional and supporting studies should be removed from this document. EPA did not attempt to acquire the histopathology slides from the unpublished Haag et al. (1949) chronic studies of chlorine dioxide in rats since they are older studies.

Question 5. Are there other data that should be considered in developing the uncertainty factors or the modifying factor? Do you consider that the data support use of different (default) values than those proposed?

Comments: One reviewer was unaware of any additional or other data that should be considered in developing the uncertainty factors for chlorine dioxide or chlorite. One reviewer questioned whether it would be useful to review/discuss the risk analysis that supports the use of chlorine dioxide and sodium chlorite as indirect food additives or as components of consumer products such as mouthwash or toothpaste. A comment was made that the report should compare lifetime animal and human oral exposures to chlorine dioxide or chlorite on the basis of mg/kg body weight and mg/mL body surface. One reviewer commented that patients on extracorporeal hemodialysis using home equipment may be potentially exposed to 70–90 times the residues exposed by adults who merely consume the water. A question was raised on the data available to support selection of an uncertainty factor that takes into account for those individuals with deficient glucose-6-phosphate dehydrogenase activity and neonates with sluggish methemoglobin reductase activity.

Response to Comments: EPA agrees with a reviewer that additional or other data are not warranted for this risk assessment. EPA followed the customary guideline for risk assessment for development of an RfD derivation. EPA did not examine chlorine dioxide or chlorite as indirect food additives or as components of consumer products such as mouthwash or toothpaste. EPA discussed individuals with deficiency in glucose-6-phosphate dehydrogenase and methemoglobin reductase as a potential susceptible subpopulation in the drinking water criteria document (U.S. EPA, 1994d). EPA thinks that an uncertainty factor of 100 is adequate to protect this group as well as the 80,000 Americans on renal dialysis.

Question 6. Do the confidence statements and weight-of-evidence statements present a clear rationale and accurately reflect the utility of the principal study and the comprehensiveness of the data? Do these statements make sufficiently apparent all the underlying assumptions and limitations of these assessments? If not, what needs to be added?

Comments: External reviewers indicated that the confidence and weight-of-evidence statements were clearly and rationally presented. One reviewer indicated that the comprehensiveness of the data was adequately presented and the underlying assumptions and limitations of the assessments were sufficently presented. One reviewer mentioned that the confidence statements for the RfC for chlorine dioxide should indicate whether humans are more susceptible to chlorine dioxide.

Response to Comments: Adequate information is not available to determine if humans are more susceptible. EPA has applied a 10-fold uncertainty factor for extrapolation from animals to humans to address this area of uncertainty.

Question 7. Is the weight of evidence for cancer assigned at the appropriate level (where applicable)?

Comments: External reviewers indicated that cancer assessment was not applicable for chlorine dioxide and chlorite, as the data are inadequate. One reviewer commented that a statement should be made concerning the designation of sodium chlorite as a tumor promoter in mouse skin under the conditions examined in the Kurokawa et al. (1984) study.

Response to Comments: The reviewers agreed that the cancer assessment was assigned at the appropriate level. EPA does not agree that such a statement should be made as the increased tumor incidence did not attain statistical significance.

From: Sprovieri, John Councillor [mailto:John.Sprovieri@brampton.ca]
Sent: August 22, 2018 1:48 PM
To: West, Helena
Cc: Sprovieri, John; John Sprovieri; Downey, Johanna; Palleschi, Michael; Kovac, John; Dale, Frank; Szwarc, David; Lockyer, Kathryn; O'Connor, Patrick
Subject: FW: Water Fluoridation Committee agenda

Hi Helena,
Can you place the attached information and information from Gilles Parent below on the September 27, 2018 Community Water Fluoridation Committee agenda.
Regards, John.

REFERRAL TO _____
RECOMMENDED
DIRECTION REQUIRED _____
RECEIPT RECOMMENDED ✓_____

Review

Neurobehavioural effects of developmental toxicity

Philippe Grandjean, Philip J Landrigan

Lancet Neurol 2014; 13: 330–38

Published Online
February 15, 2014
http://dx.doi.org/10.1016/S1474-4422(13)70278-3

Department of Environmental Medicine, University of Southern Denmark, Odense, Denmark (P Grandjean MD); **Department of Environmental Health, Harvard School of Public Health, Boston, MA, USA** (P Grandjean); **and Icahn School of Medicine at Mount Sinai, New York, NY, USA** (P J Landrigan MD)

Correspondence to:
Dr Philippe Grandjean, Environmental and Occupational Medicine and Epidemiology, Harvard School of Public Health, 401 Park Drive E-110, Boston, MA 02215, USA
pgrand@hsph.harvard.edu

Neurodevelopmental disabilities, including autism, attention-deficit hyperactivity disorder, dyslexia, and other cognitive impairments, affect millions of children worldwide, and some diagnoses seem to be increasing in frequency. Industrial chemicals that injure the developing brain are among the known causes for this rise in prevalence. In 2006, we did a systematic review and identified five industrial chemicals as developmental neurotoxicants: lead, methylmercury, polychlorinated biphenyls, arsenic, and toluene. Since 2006, epidemiological studies have documented six additional developmental neurotoxicants—manganese, fluoride, chlorpyrifos, dichlorodiphenyltrichloroethane, tetrachloroethylene, and the polybrominated diphenyl ethers. We postulate that even more neurotoxicants remain undiscovered. To control the pandemic of developmental neurotoxicity, we propose a global prevention strategy. Untested chemicals should not be presumed to be safe to brain development, and chemicals in existing use and all new chemicals must therefore be tested for developmental neurotoxicity. To coordinate these efforts and to accelerate translation of science into prevention, we propose the urgent formation of a new international clearinghouse.

Introduction

Disorders of neurobehavioural development affect 10–15% of all births,[1] and prevalence rates of autism spectrum disorder and attention-deficit hyperactivity disorder seem to be increasing worldwide.[2] Subclinical decrements in brain function are even more common than these neurobehavioural developmental disorders. All these disabilities can have severe consequences[3]—they diminish quality of life, reduce academic achievement, and disturb behaviour, with profound consequences for the welfare and productivity of entire societies.[4]

The root causes of the present global pandemic of neurodevelopmental disorders are only partly understood. Although genetic factors have a role,[5] they cannot explain recent increases in reported prevalence, and none of the genes discovered so far seem to be responsible for more than a small proportion of cases.[5] Overall, genetic factors seem to account for no more than perhaps 30–40% of all cases of neurodevelopmental disorders. Thus, non-genetic, environmental exposures are involved in causation, in some cases probably by interacting with genetically inherited predispositions.

Strong evidence exists that industrial chemicals widely disseminated in the environment are important contributors to what we have called the global, silent pandemic of neurodevelopmental toxicity.[6,7] The developing human brain is uniquely vulnerable to toxic chemical exposures, and major windows of developmental vulnerability occur in utero and during infancy and early childhood.[8] During these sensitive life stages, chemicals can cause permanent brain injury at low levels of exposure that would have little or no adverse effect in an adult.

In 2006, we did a systematic review of the published clinical and epidemiological studies into the neurotoxicity of industrial chemicals, with a focus on developmental neurotoxicity.[6] We identified five industrial chemicals that could be reliably classified as developmental neurotoxicants: lead, methylmercury, arsenic, polychlorinated biphenyls, and toluene. We also noted 201 chemicals that had been reported to cause injury to the nervous system in adults, mostly in connection with occupational exposures, poisoning incidents, or suicide attempts. Additionally, more than 1000 chemicals have been reported to be neurotoxic in animals in laboratory studies.

We noted that recognition of the risks of industrial chemicals to brain development has historically needed decades of research and scrutiny, as shown in the cases of lead and methylmercury.[9,10] In most cases, discovery began with clinical diagnosis of poisoning in workers and episodes of high-dose exposure. More sophisticated epidemiological studies typically began only much later. Results from such studies documented developmental neurotoxicity at much lower exposure levels than had previously been thought to be safe. Thus, recognition of widespread subclinical toxicity often did not occur until decades after the initial evidence of neurotoxicity. A recurring theme was that early warnings of subclinical neurotoxicity were often ignored or even dismissed.[11] David P Rall, former Director of the US National Institute of Environmental Health Sciences, once noted that "if thalidomide had caused a ten-point loss of intelligence quotient (IQ) instead of obvious birth defects of the limbs, it would probably still be on the market".[12] Many industrial chemicals marketed at present probably cause IQ deficits of far fewer than ten points and have therefore eluded detection so far, but their combined effects could have enormous consequences.

In our 2006 review,[6] we expressed concern that additional developmental neurotoxicants might lurk undiscovered among the 201 chemicals then known to be neurotoxic to adult human beings and among the many thousands of pesticides, solvents, and other industrial chemicals in widespread use that had never been tested for neurodevelopmental toxicity. Since our previous review, new data have emerged about the vulnerability of the developing brain and the neurotoxicity of industrial chemicals. Particularly important new evidence derives from prospective epidemiological birth cohort studies.

In this Review, we consider recent information about the developmental neurotoxicity of industrial chemicals

to update our previous report.[6] Additionally, we propose strategies to counter this pandemic and to prevent the spread of neurological disease and disability in children worldwide.

Unique vulnerability of the developing brain

The fetus is not well protected against industrial chemicals. The placenta does not block the passage of many environmental toxicants from the maternal to the fetal circulation,[13] and more than 200 foreign chemicals have been detected in umbilical cord blood.[14] Additionally, many environmental chemicals are transferred to the infant through human breastmilk.[13] During fetal life and early infancy, the blood–brain barrier provides only partial protection against the entry of chemicals into the CNS.[15]

Moreover, the developing human brain is exceptionally sensitive to injury caused by toxic chemicals,[6] and several developmental processes have been shown to be highly vulnerable to chemical toxicity. For example, in-vitro studies suggest that neural stem cells are very sensitive to neurotoxic substances such as methylmercury.[16] Some pesticides inhibit cholinesterase function in the developing brain,[17] thereby affecting the crucial regulatory role of acetylcholine before synapse formation.[18] Early-life epigenetic changes are also known to affect subsequent gene expression in the brain.[19] In summary, industrial chemicals known or suspected to be neurotoxic to adults are also likely to present risks to the developing brain.

Figure 1 shows the unique vulnerability of the brain during early life and indicates how developmental exposures to toxic chemicals are particularly likely to lead to functional deficits and disease later in life.

New findings about known hazards

Recent research on well-documented neurotoxicants has generated important new insights into the neurodevelopmental consequences of early exposures to these industrial chemicals.

Joint analyses that gathered data for lead-associated IQ deficits from seven international studies[20,21] support the conclusion that no safe level of exposure to lead exists.[22] Cognitive deficits in adults who had previously shown lead-associated developmental delays at school age suggest that the effects of lead neurotoxicity are probably permanent.[23] Brain imaging of young adults who had raised lead concentrations in their blood during childhood showed exposure-related decreases in brain volume.[24] Lead exposure in early childhood is associated with reduced school performance[25] and with delinquent behaviour later in life.[26,27]

Developmental neurotoxicity due to methylmercury occurs at much lower exposures than the concentrations that affect adult brain function.[28] Deficits at 7 years of age that were linked to low-level prenatal exposures to methylmercury were still detectable at the age of 14 years.[29] Some common genetic polymorphisms seem to increase the vulnerability of the developing brain to methylmercury toxicity.[30] Functional MRI scans of people exposed prenatally to excess amounts of methylmercury showed abnormally expanded activation of brain regions in response to sensory stimulation and motor tasks (figure 2).[31] Because some adverse effects might be counterbalanced by essential fatty acids from seafood, statistical adjustment for maternal diet during pregnancy results in stronger methylmercury effects.[32,33]

Prenatal and early postnatal exposures to inorganic arsenic from drinking water are associated with cognitive deficits that are apparent at school age.[34,35] Infants who survived the Morinaga milk arsenic poisoning incident had highly raised risks of neurological disease during adult life.[36]

The developmental neurotoxicity of polychlorinated biphenyls has been consolidated and strengthened by recent findings.[37] Although little new information has been published about the developmental neurotoxicity of toluene, much has been learned about the developmental neurotoxicity of another common solvent, ethanol, through research on fetal alcohol exposure. Maternal consumption of alcohol during pregnancy, even in very small quantities, has been linked to a range of neurobehavioural adverse effects in offspring, including reduced IQ, impaired executive function and social judgment, delinquent behaviour, seizures, other neurological signs, and sensory problems.[38]

Newly recognised developmental neurotoxicants

Prospective epidemiological birth cohort studies make it possible to measure maternal or fetal exposures in real time during pregnancy as these exposures actually occur, thus generating unbiased information about the degree and timing of prenatal exposures. Children in these prospective studies are followed longitudinally and assessed with age-appropriate tests to show delayed or deranged neurobehavioural development. These powerful epidemiological methods have enabled the discovery of additional developmental neurotoxicants.

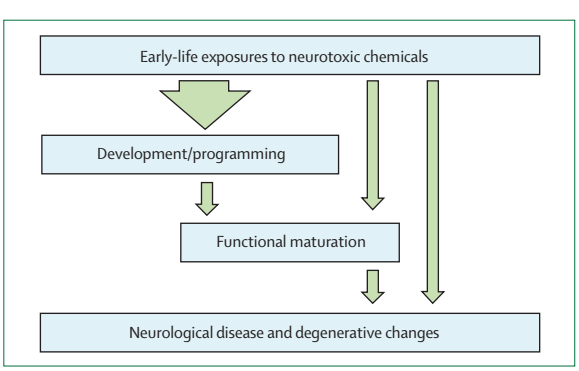


Figure 1: **Effect of neurotoxicants during early brain development**
Exposures in early life to neurotoxic chemicals can cause a wide range of adverse effects on brain development and maturation that can manifest as functional impairments or disease at any point in the human lifespan, from early infancy to very old age.

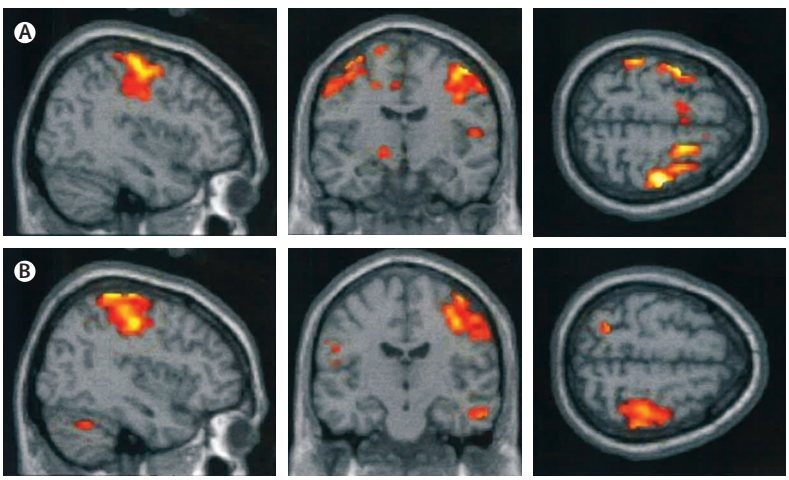


Figure 2: **Functional MRI scans show abnormal activation in the brain**
Average activation during finger tapping with the left hand in three adolescents with increased prenatal methylmercury exposure (A) and three control adolescents (B). The control participants activate the premotor and motor cortices on the right, whereas participants exposed to methylmercury activate these areas bilaterally.[31]

Cross-sectional data from Bangladesh show that exposure to manganese from drinking water is associated with reduced mathematics achievement scores in school children.[39] A study in Quebec, Canada, showed a strong correlation between manganese concentrations in hair and hyperactivity.[40] School-aged children living near manganese mining and processing facilities have shown associations between airborne manganese concentrations and diminished intellectual function[41] and with impaired motor skills and reduced olfactory function.[42] These results are supported by experimental findings in mice.[43]

A meta-analysis of 27 cross-sectional studies of children exposed to fluoride in drinking water, mainly from China, suggests an average IQ decrement of about seven points in children exposed to raised fluoride concentrations.[44] Confounding from other substances seemed unlikely in most of these studies. Further characterisation of the dose–response association would be desirable.

The occupational health literature[45] suggests that solvents can act as neurotoxicants, but the identification of individual responsible compounds is hampered by the complexity of exposures. In a French cohort study of 3000 children, investigators linked maternal occupational solvent exposure during pregnancy to deficits in behavioural assessment at 2 years of age.[46] The data showed dose-related increased risks for hyperactivity and aggressive behaviour. One in every five mothers in this cohort reported solvent exposures in common jobs, such as nurse or other hospital employee, chemist, cleaner, hairdresser, and beautician. In Massachusetts, USA, follow-up of a well-defined population with prenatal and early childhood exposure to the solvent tetrachloroethylene (also called perchlorethylene) in drinking water showed a tendency towards deficient neurological function and increased risk of psychiatric diagnoses.[47]

Acute pesticide poisoning occurs frequently in children worldwide, and subclinical pesticide toxicity is also widespread. Clinical data suggest that acute pesticide poisoning during childhood might lead to lasting neurobehavioural deficits.[48,49] Highly toxic and bio-accumulative pesticides are now banned in high-income nations, but are still used in many low-income and middle-income countries. In particular, the organochlorine compounds dichlorodiphenyltrichloroethane (DDT), its metabolite dichlorodiphenyldichloroethylene (DDE), and chlordecone (Kepone), tend to be highly persistent and remain widespread in the environment and in people's bodies in high-use regions. Recent studies have shown inverse correlations between serum concentrations of DDT or DDE (which indicate accumulated exposures), and neurodevelopmental performance.[50,51]

Organophosphate pesticides are eliminated from the human body much more rapidly than are organochlorines, and exposure assessment is therefore inherently less precise. Nonetheless, three prospective epidemiological birth cohort studies provide new evidence that prenatal exposure to organophosphate pesticides can cause developmental neurotoxicity. In these studies, prenatal organophosphate exposure was assessed by measurement of maternal urinary excretion of pesticide metabolites during pregnancy. Dose-related correlations were recorded between maternal exposures to chlorpyrifos or other organophosphates and small head circumference at birth—which is an indication of slowed brain growth in utero—and with neurobehavioural deficits that have persisted to at least 7 years of age.[52–54] In a subgroup study, MRI of the brain showed that prenatal chlorpyrifos exposure was associated with structural abnormalities that included thinning of the cerebral cortex.[55]

Herbicides and fungicides might also have neurotoxic potential.[56] Propoxur,[57] a carbamate pesticide, and permethrine,[58] a member of the pyrethroid class of pesticides, have recently been linked to neurodevelopmental deficits in children.

The group of compounds known as polybrominated diphenyl ethers (PBDEs) are widely used as flame retardants and are structurally very similar to the polychlorinated biphenyls. Experimental evidence now suggests that the PBDEs might also be neurotoxic.[59] Epidemiological studies in Europe and the USA have shown neurodevelopmental deficits in children with increased prenatal exposures to these compounds.[60–62] Thus, the PBDEs should be regarded as hazards to human neurobehavioural development, although attribution of relative toxic potentials to individual PBDE congeners is not yet possible.

Other suspected developmental neurotoxicants

A serious difficulty that complicates many epidemiological studies of neurodevelopmental toxicity in children is the problem of mixed exposures. Most populations are exposed to more than one neurotoxicant at a time, and yet

most studies have only a finite amount of power and precision in exposure assessment to discern the possible effects of even single neurotoxicants. A further problem in many epidemiological studies of non-persistent toxicants is that imprecise assessment of exposure tends to obscure associations that might actually be present.[63] Guidance from experimental neurotoxicity studies is therefore crucial. In the assessment of potential developmental neurotoxicants, we have used a strength of evidence approach similar to that used by the International Agency for Research on Cancer for assessing epidemiological and experimental studies.

Phthalates and bisphenol A are added to many different types of plastics, cosmetics, and other consumer products. Since they are eliminated rapidly in urine, exposure assessment is complicated, and such imprecision might lead to underestimation of the true risk of neurotoxicity. The best-documented effects of early-life exposure to phthalates are the consequence of disruption of endocrine signalling.[64] Thus, prenatal exposures to phthalates have been linked to both neurodevelopmental deficits and to behavioural abnormalities characterised by shortened attention span and impaired social interactions.[65] The neurobehavioural toxicity of these compounds seems to affect mainly boys and could therefore relate to endocrine disruption in the developing brain.[66] In regard to bisphenol A, a prospective study showed that point estimates of exposure during gestation were linked to abnormalities in behaviour and executive function in children at 3 years of age.[67]

Exposure to air pollution can cause neurodevelopmental delays and disorders of behavioural functions.[68,69] Of the individual components of air pollution, carbon monoxide is a well-documented neurotoxicant, and indoor exposure to this substance has now been linked to deficient neurobehavioural performance in children.[70] Less clear is the reported contribution of nitrogen oxides to neurodevelopmental deficits,[71] since these compounds often co-occur with carbon monoxide as part of complex emissions. Tobacco smoke is a complex mixture of hundreds of chemical compounds and is now a well-documented cause of developmental neurotoxicity.[72] Infants exposed prenatally to polycyclic aromatic hydrocarbons from traffic exhausts at 5 years of age showed greater cognitive impairment and lower IQ than those exposed to lower levels of these compounds.[68]

Perfluorinated compounds, such as perfluorooctanoic acid and perfluorooctane sulphonate, are highly persistent in the environment and in the human body, and seem to be neurotoxic.[73] Emerging epidemiological evidence suggests that these compounds might indeed impede neurobehavioural development.[74]

Developmental neurotoxicity and clinical neurology

Exposures in early life to developmental neurotoxicants are now being linked to specific clinical syndromes in children. For example, an increased risk of attention-deficit hyperactivity disorder has been linked to prenatal exposures to manganese, organophosphates,[75] and phthalates.[76] Phthalates have also been linked to behaviours that resemble components of autism spectrum disorder.[77] Prenatal exposure to automotive air pollution in California, USA, has been linked to an increased risk for autism spectrum disorder.[78]

The persistent decrements in intelligence documented in children, adolescents, and young adults exposed in early life to neurotoxicants could presage the development of neurodegenerative disease later in life. Thus, accumulated exposure to lead is associated with cognitive decline in the elderly.[79] Manganese exposure may lead to parkinsonism, and experimental studies have reported Parkinson's disease as a result of developmental exposures to the insecticide rotenone, the herbicides paraquat and maneb, and the solvent trichloroethylene.[80] Any environmental exposure that increases the risk of neurodegenerative disorders in later life (figure 1) requires urgent investigation as the world's population continues to age.[81]

The expanding complement of neurotoxicants

In our 2006 review,[6] we expressed concern that additional developmental neurotoxicants might lie undiscovered in the 201 chemicals that were then known to be neurotoxic to human adults, in the roughly 1000 chemicals known to be neurotoxic in animal species, and in the many thousands of industrial chemicals and pesticides that have never been tested for neurotoxicity. Exposure to neurotoxic chemicals is not rare, since almost half of the 201 known human neurotoxicants are regarded as high production volume chemicals.

Our updated literature review shows that since 2006 the list of recognised human neurotoxicants has expanded by 12 chemicals, from 202 (including ethanol) to 214 (table 1 and appendix)—that is, by about two substances per year. Many of these chemicals are widely used and disseminated extensively in the global environment. Of the newly identified neurodevelopmental toxicants, pesticides constitute the largest group, as was already the case in

See Online for appendix

	Number known in 2006	Number known in 2013	Identified since 2006
Metals and inorganic compounds	25	26	Hydrogen phosphide[82]
Organic solvents	39*	40	Ethyl chloride[83]
Pesticides	92	101	Acetamiprid,[84] amitraz,[85] avermectin,[86] emamectin,[87] fipronil (Termidor),[88] glyphosate,[89] hexaconazole,[90] imidacloprid,[91] tetramethylenedisulfotetramine[92]
Other organic compounds	46	47	1,3-butadiene[93]
Total	202*	214	12 new substances

*Including ethanol.

Table 1: **Industrial chemicals known to be toxic to the human nervous system in 2006 and 2013, according to chemical group**

	Known in 2006	Newly identified
Metals and inorganic compounds	Arsenic and arsenic compounds, lead, and methylmercury	Fluoride and manganese
Organic solvents	(Ethanol) toluene	Tetrachloroethylene
Pesticides	None	Chlorpyrifos and DDT/DDE
Other organic compounds	Polychlorinated biphenyls	Brominated diphenyl ethers
Total	6*	6

DDT=dichlorodiphenyltrichloroethane. DDE=dichlorodiphenyldichloroethylene. *Including ethanol.

Table 2: **Industrial chemicals known to cause developmental neurotoxicity in human beings in 2006 and 2013, according to chemical group**

	Number of IQ points lost
Major medical and neurodevelopmental disorders	
Preterm birth	34 031 025
Autism spectrum disorders	7 109 899
Paediatric bipolar disorder	8 164 080
Attention-deficit hyperactivity disorder	16 799 400
Postnatal traumatic brain injury	5 827 300
Environmental chemical exposures	
Lead	22 947 450
Methylmercury	1 590 000*
Organophosphate pesticides	16 899 488
Other neurotoxicants	Unknown

IQ=intelligence quotient. Data from from Bellinger.[94] *From Grandjean and colleagues.[95]

Table 3: **Total losses of IQ points in US children 0–5 years of age associated with major risk factors, including developmental exposure to industrial chemicals that cause neurotoxicity**

2006. In the same 7-year period, the number of known developmental neurotoxicants has doubled from six to 12 (table 2). Although the pace of scientific discovery of new neurodevelopmental hazards is more rapid today than in the past, it is still slower than the identification of adult neurotoxicants.

The gap that exists between the number of substances known to be toxic to the adult brain and the smaller number known to be toxic to the much more vulnerable developing brain is unlikely to close in the near future. This discrepancy is attributable to the fact that toxicity to the adult brain is usually discovered as a result of acute poisoning incidents, typically with a clear and immediate association between causative exposure and adverse effects, as occurs for workplace exposures or suicide attempts. By contrast, the recognition of developmental neurotoxicity relies on two sets of evidence collected at two different points in time: exposure data (often obtained from the mother during pregnancy), and data for the child's postnatal neurobehavioural development (often obtained 5–10 years later). Because brain functions develop sequentially, the full effects of early neurotoxic damage might not become apparent until school age or beyond. The most reliable evidence of developmental neurotoxicity is obtained through prospective studies that include real-time recording of information about exposure in early life followed by serial clinical assessments of the child. Such research is inherently slow and is hampered by the difficulty of reliable assessment of exposures to individual toxicants in complex mixtures.

Consequences of developmental neurotoxicity

Developmental neurotoxicity causes brain damage that is too often untreatable and frequently permanent. The consequence of such brain damage is impaired CNS function that lasts a lifetime and might result in reduced intelligence, as expressed in terms of lost IQ points, or disruption in behaviour. A recent study compared the estimated total IQ losses from major paediatric causes and showed that the magnitude of losses attributable to lead, pesticides, and other neurotoxicants was in the same range as, or even greater than, the losses associated with medical events such as preterm birth, traumatic brain injury, brain tumours, and congenital heart disease (table 3).[94]

Loss of cognitive skills reduces children's academic and economic attainments and has substantial long-term economic effects on societies.[4] Thus, each loss of one IQ point has been estimated to decrease average lifetime earnings capacity by about €12 000 or US$18 000 in 2008 currencies.[96] The most recent estimates from the USA indicate that the annual costs of childhood lead poisoning are about US$50 billion and that the annual costs of methylmercury toxicity are roughly US$5 billion.[97] In the European Union, methylmercury exposure is estimated to cause a loss of about 600 000 IQ points every year, corresponding to an annual economic loss of close to €10 billion. In France alone, lead exposure is associated with IQ losses that correspond to annual costs that might exceed €20 billion.[98] Since IQ losses represent only one aspect of developmental neurotoxicity, the total costs are surely even higher.

Evidence from worldwide sources indicates that average national IQ scores are associated with gross domestic product (GDP)—a correlation that might be causal in both directions.[99] Thus, poverty can cause low IQ, but the opposite is also true. In view of the widespread exposures to lead, pesticides, and other neurotoxicants in developing countries, where chemical controls might be ineffective compared with those in more developed countries,[100,101] developmental exposures to industrial chemicals could contribute substantially to the recorded correlation between IQ and GDP. If this theory is true, developing countries could take decades to emerge from poverty. Consequently, pollution abatement might then be delayed, and a vicious circle can result.

The antisocial behaviour, criminal behaviour, violence, and substance abuse that seem to result from early-life exposures to some neurotoxic chemicals result in increased needs for special educational services, institutionalisation, and even incarceration. In the USA, the murder rate fell sharply 20 years after the removal of lead from petrol,[102] a finding consistent with the idea that

exposure to lead in early life is a powerful determinant of behaviour decades later. Although poorly quantified, such behavioural and social consequences of neurodevelopmental toxicity are potentially very costly.[76]

Prevention of developmental neurotoxicity caused by industrial chemicals is highly cost effective. A study that quantified the gains resulting from the phase-out of lead additives from petrol reported that in the USA alone, the introduction of lead-free petrol has generated an economic benefit of $200 billion in each annual birth cohort since 1980,[103] an aggregate benefit in the past 30 years of over $3 trillion. This success has since been repeated in more than 150 countries, resulting in vast additional savings. Every US$1 spent to reduce lead hazards is estimated to produce a benefit of US$17–220, which represents a cost-benefit ratio that is even better than that for vaccines.[4] Furthermore, the costs associated with the late-life consequences of developmental neurotoxicity are enormous, and the benefits from prevention of degenerative brain disorders could be very substantial.

New methods to identify developmental neurotoxicants

New toxicological methods now allow a rational strategy for the identification of developmental neurotoxicants based on a multidisciplinary approach.[104] A new guideline has been approved as a standardised approach for the identification of developmental neurotoxicants.[105] However, completion of such tests is expensive and requires the use of many laboratory animals, and reliance on mammals for chemicals testing purposes needs to be reduced.[106] US governmental agencies have established the National Center for Computational Toxicology and an initiative—the Tox 21 Program—to promote the evolution of toxicology from a mainly observational science to a predominantly predictive science.[107]

In-vitro methods have now reached a level of predictive validity that means they can be applied to neurotoxicity testing.[108] Some of these tests are based on neural stem cells. Although these cell systems do not have a blood–brain barrier and particular metabolising enzymes, these approaches are highly promising. As a further option, data for protein links and protein–protein interactions can now be used to explore potential neurotoxicity in silico,[109] thus showing that existing computational methods might predict potential toxic effects.[110]

In summary, use of the whole range of approaches along with clinical and epidemiological evidence, when available, should enable the integration of information for use in at least a tentative risk assessment. With these methods, we anticipate that the pace of scientific discovery in developmental neurotoxicology will accelerate further in the years ahead.

Conclusions and recommendations

The updated findings presented in this Review confirm and extend our 2006 conclusions.[6] During the 7 years since our previous report, the number of industrial chemicals recognised to be developmental neurotoxicants has doubled. Exposures to these industrial chemicals in the environment contribute to the pandemic of developmental neurotoxicity.

Two major obstacles impede efforts to control the global pandemic of developmental neurotoxicity. These barriers, which we noted in our previous review[6] and were recently underlined by the US National Research Council,[111] are: large gaps in the testing of chemicals for developmental neurotoxicity, which results in a paucity of systematic data to guide prevention; and the huge amount of proof needed for regulation. Thus, very few chemicals have been regulated as a result of developmental neurotoxicity.

The presumption that new chemicals and technologies are safe until proven otherwise is a fundamental problem.[111] Classic examples of new chemicals that were introduced because they conveyed certain benefits, but were later shown to cause great harm, include several neurotoxicants, asbestos, thalidomide, diethylstilboestrol, and the chlorofluorocarbons.[112] A recurring theme in each of these cases was that commercial introduction and wide dissemination of the chemicals preceded any systematic effort to assess potential toxicity. Particularly absent were advance efforts to study possible effects on children's health or the potential of exposures in early life to disrupt early development. Similar challenges have been confronted in other public health disasters, such as those caused by tobacco smoking, alcohol use, and refined foods. These problems have been recently termed industrial epidemics.[113]

To control the pandemic of developmental neurotoxicity, we propose a coordinated international strategy (panel). Mandatory and transparent assessment of evidence for neurotoxicity is the foundation of this strategy. Assessment of toxicity must be followed by governmental regulation and market intervention. Voluntary controls seem to be of little value.[11]

Panel: **Recommendations for an international clearinghouse on neurotoxicity**

The main purpose of this agency would be to promote optimum brain health, not just avoidance of neurological disease, by inspiring, facilitating, and coordinating research and public policies that aim to protect brain development during the most sensitive life stages. The main efforts would aim to:

- Screen industrial chemicals present in human exposures for neurotoxic effects so that hazardous substances can be identified for tighter control
- Stimulate and coordinate new research to understand how toxic chemicals interfere with brain development and how best to prevent long-term dysfunctions and deficits
- Function as a clearinghouse for research data and strategies by gathering and assessing documentation about brain toxicity and stimulating international collaboration on research and prevention
- Promote policy development aimed at protecting vulnerable populations against chemicals that are toxic to the brain without needing unrealistic amounts of scientific proof

The three pillars of our proposed strategy are: legally mandated testing of existing industrial chemicals and pesticides already in commerce, with prioritisation of those with the most widespread use, and incorporation of new assessment technologies; legally mandated premarket evaluation of new chemicals before they enter markets, with use of precautionary approaches for chemical testing that recognise the unique vulnerability of the developing brain; and the formation of a new clearinghouse for neurotoxicity as a parallel to the International Agency for Research on Cancer. This new agency will assess industrial chemicals for developmental neurotoxicity with a precautionary approach that emphasises prevention and does not require absolute proof of toxicity. It will facilitate and coordinate epidemiological and toxicological studies and will lead the urgently needed global programmes for prevention.

These new approaches must reverse the dangerous presumption that new chemicals and technologies are safe until proven otherwise. They must also overcome the existing requirement to produce absolute proof of toxicity before action can be started to protect children against neurotoxic substances. Precautionary interpretation of data about developmental neurotoxicity should take into account the very large individual and societal costs that result from failure to act on available documentation to prevent disease in children.[114] Academic research has often favoured scepticism and required extensive replication before acceptance of a hypothesis,[114] thereby adding to the inertia in toxicology and environmental health research and the consequent disregard of many other potential neurotoxicants.[115] Additionally, the strength of evidence that is needed to constitute "proof" should be analysed in a societal perspective, so that the implications of ignoring a developmental neurotoxicant and of failing to act on the basis of available data are also taken into account.

Finally, we emphasise that the total number of neurotoxic substances now recognised almost certainly represents an underestimate of the true number of developmental neurotoxicants that have been released into the global environment. Our very great concern is that children worldwide are being exposed to unrecognised toxic chemicals that are silently eroding intelligence, disrupting behaviours, truncating future achievements, and damaging societies, perhaps most seriously in developing countries. A new framework of action is needed.

Search strategy and selection criteria

We identified studies published since 2006 on the neurotoxic effects of industrial chemicals in human beings by using the search terms "neurotoxicity syndromes"[MeSH], "neurotoxic", "neurologic", or "neuro*", combined with "exposure" and "poisoning" in PubMed, from 2006 to the end of 2012. For developmental neurotoxicity, the search terms were "prenatal exposure delayed effects"[MeSH], "maternal exposure" or "maternal fetal exchange", "developmental disabilities/chemically induced" and "neurotoxins", all of which were searched for with the limiters "All Child: 0–18 years, Human". We also used references cited in the publications retrieved.

Contributors

Both authors did the literature review, wrote and revised the report, and approved the final version.

Conflicts of interest

PG has provided paid expert testimony about mercury toxicology for the US Department of Justice. PJL has provided paid expert testimony in cases of childhood lead poisoning. We declare that we have no other conflicts of interest.

Acknowledgments

This work was supported by the National Institutes of Health, National Institute for Environmental Health Sciences (ES09584, ES09797, and ES11687). The funding source had no role in the literature review, interpretation of data, writing of this Review, or in the decision to submit for publication. The contents of this paper are solely the responsibility of the authors and do not represent the official views of the National Institutes of Health. We thank Mary S Wolff (Icahn School of Medicine at Mount Sinai, New York, NY, USA) and Linda S Birnbaum (US National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA) for their critical reading of the report.

References

1 Bloom B, Cohen RA, Freeman G. Summary health statistics for U.S. children: National Health Interview Survey, 2009. *Vital Health Stat* 2010; **10:** 1–82.

2 Landrigan PJ, Lambertini L, Birnbaum LS. A research strategy to discover the environmental causes of autism and neurodevelopmental disabilities. *Environ Health Perspect* 2012; **120:** a258–60.

3 Bellinger DC. Interpreting epidemiologic studies of developmental neurotoxicity: conceptual and analytic issues. *Neurotoxicol Teratol* 2009; **31:** 267–74.

4 Gould E. Childhood lead poisoning: conservative estimates of the social and economic benefits of lead hazard control. *Environ Health Perspect* 2009; **117:** 1162–67.

5 National Research Council. Scientific frontiers in developmental toxicology and risk assessment. Washington, DC: National Academies Press, 2000.

6 Grandjean P, Landrigan PJ. Developmental neurotoxicity of industrial chemicals. *Lancet* 2006; **368:** 2167–78.

7 Grandjean P. Only one chance. How environmental pollution impairs brain development – and how to protect the brains of the next generation. New York: Oxford University Press, 2013.

8 Rice D, Barone S Jr. Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. *Environ Health Perspect* 2000; **108** (suppl 3)**:** 511–33.

9 Needleman HL. The removal of lead from gasoline: historical and personal reflections. *Environ Res* 2000; **84:** 20–35.

10 Grandjean P, Satoh H, Murata K, Eto K. Adverse effects of methylmercury: environmental health research implications. *Environ Health Perspect* 2010; **118:** 1137–45.

11 Landrigan PJ, Goldman LR. Children's vulnerability to toxic chemicals: a challenge and opportunity to strengthen health and environmental policy. *Health Aff* 2011; **30:** 842–50.

12 Weiss B. Food additives and environmental chemicals as sources of childhood behavior disorders. *J Am Acad Child Psychiatry* 1982; **21:** 144–52.

13 Needham LL, Grandjean P, Heinzow B, et al. Partition of environmental chemicals between maternal and fetal blood and tissues. *Environ Sci Technol* 2011; **45:** 1121–26.

14 Environmental Working Group. Body burden—the pollution in newborns. Washington, DC: Environmental Working Group, 2005.

15 Zheng W, Aschner M, Ghersi-Egea JF. Brain barrier systems: a new frontier in metal neurotoxicological research. *Toxicol Appl Pharmacol* 2003; **192:** 1–11.

16 Bose R, Onishchenko N, Edoff K, Janson Lang AM, Ceccatelli S. Inherited effects of low-dose exposure to methylmercury in neural stem cells. *Toxicol Sci* 2012; **130:** 383–90.

17 Costa LG. Current issues in organophosphate toxicology. *Clin Chim Acta* 2006; **366:** 1–13.
18 Augusti-Tocco G, Biagioni S, Tata AM. Acetylcholine and regulation of gene expression in developing systems. *J Mol Neurosci* 2006; **30:** 45–48.
19 Roth TL. Epigenetics of neurobiology and behavior during development and adulthood. *Dev Psychobiol* 2012; **54:** 590–97.
20 Lanphear BP, Hornung R, Khoury J, et al. Low-level environmental lead exposure and children's intellectual function: an international pooled analysis. *Environ Health Perspect* 2005; **113:** 894–99.
21 Budtz-Jorgensen E, Bellinger D, Lanphear B, Grandjean P. An international pooled analysis for obtaining a benchmark dose for environmental lead exposure in children. *Risk Anal* 2013; **33:** 450–61.
22 Grandjean P. Even low-dose lead exposure is hazardous. *Lancet* 2010; **376:** 855–56.
23 Mazumdar M, Bellinger DC, Gregas M, Abanilla K, Bacic J, Needleman HL. Low-level environmental lead exposure in childhood and adult intellectual function: a follow-up study. *Environ Health* 2011; **10:** 24.
24 Cecil KM, Brubaker CJ, Adler CM, et al. Decreased brain volume in adults with childhood lead exposure. *PLoS Med* 2008; **5:** e112.
25 Zhang N, Baker HW, Tufts M, Raymond RE, Salihu H, Elliott MR. Early childhood lead exposure and academic achievement: evidence from Detroit public schools, 2008–2010. *Am J Public Health* 2013; **103:** e72–77.
26 Fergusson DM, Boden JM, Horwood LJ. Dentine lead levels in childhood and criminal behaviour in late adolescence and early adulthood. *J Epidemiol Community Health* 2008; **62:** 1045–50.
27 Wright JP, Dietrich KN, Ris MD, et al. Association of prenatal and childhood blood lead concentrations with criminal arrests in early adulthood. *PLoS Med* 2008; **5:** e101.
28 Oken E, Bellinger DC. Fish consumption, methylmercury and child neurodevelopment. *Curr Opin Pediatr* 2008; **20:** 178–83.
29 Debes F, Budtz-Jorgensen E, Weihe P, White RF, Grandjean P. Impact of prenatal methylmercury exposure on neurobehavioral function at age 14 years. *Neurotoxicol Teratol* 2006; **28:** 536–47.
30 Julvez J, Smith GD, Golding J, et al. Genetic predisposition to cognitive deficit at age 8 years associated with prenatal methylmercury exposure. *Epidemiology* 2013; **24:** 643–50.
31 White RF, Palumbo CL, Yurgelun-Todd DA, et al. Functional MRI approach to developmental methylmercury and polychlorinated biphenyl neurotoxicity. *Neurotoxicology* 2011; **32:** 975–80.
32 Budtz-Jorgensen E, Grandjean P, Weihe P. Separation of risks and benefits of seafood intake. *Environ Health Perspect* 2007; **115:** 323–27.
33 Strain JJ, Davidson PW, Bonham MP, et al. Associations of maternal long-chain polyunsaturated fatty acids, methyl mercury, and infant development in the Seychelles Child Development Nutrition Study. *Neurotoxicology* 2008; **29:** 776–82.
34 Wasserman GA, Liu X, Parvez F, et al. Water arsenic exposure and intellectual function in 6-year-old children in Araihazar, Bangladesh. *Environ Health Perspect* 2007; **115:** 285–89.
35 Hamadani JD, Tofail F, Nermell B, et al. Critical windows of exposure for arsenic-associated impairment of cognitive function in pre-school girls and boys: a population-based cohort study. *Int J Epidemiol* 2011; **40:** 1593–604.
36 Tanaka H, Tsukuma H, Oshima A. Long-term prospective study of 6104 survivors of arsenic poisoning during infancy due to contaminated milk powder in 1955. *J Epidemiol* 2010; **20:** 439–45.
37 Engel SM, Wolff MS. Causal inference considerations for endocrine disruptor research in children's health. *Annu Rev Public Health* 2013; **34**: 139–58.
38 Mattson SN, Crocker N, Nguyen TT. Fetal alcohol spectrum disorders: neuropsychological and behavioral features. *Neurospychol Rev* 2011; **21:** 81–101.
39 Khan K, Wasserman GA, Liu X, et al. Manganese exposure from drinking water and children's academic achievement. *Neurotoxicology* 2012; **33:** 91–97.
40 Bouchard M, Laforest F, Vandelac L, Bellinger D, Mergler D. Hair manganese and hyperactive behaviors: pilot study of school-age children exposed through tap water. *Environ Health Perspect* 2007; **115:** 122–27.
41 Riojas-Rodriguez H, Solis-Vivanco R, Schilmann A, et al. Intellectual function in Mexican children living in a mining area and environmentally exposed to manganese. *Environ Health Perspect* 2010; **118:** 1465–70.
42 Lucchini RG, Guazzetti S, Zoni S, et al. Tremor, olfactory and motor changes in Italian adolescents exposed to historical ferro-manganese emission. *Neurotoxicology* 2012; **33:** 687–96.
43 Moreno JA, Yeomans EC, Streifel KM, Brattin BL, Taylor RJ, Tjalkens RB. Age-dependent susceptibility to manganese-induced neurological dysfunction. *Toxicol Sci* 2009; **112:** 394–404.
44 Choi AL, Sun G, Zhang Y, Grandjean P. Developmental fluoride neurotoxicity: a systematic review and meta-analysis. *Environ Health Perspect* 2012; **120:** 1362–68.
45 Julvez J, Grandjean P. Neurodevelopmental toxicity risks due to occupational exposure to industrial chemicals during pregnancy. *Ind Health* 2009; **47:** 459–68.
46 Pele F, Muckle G, Costet N, et al. Occupational solvent exposure during pregnancy and child behaviour at age 2. *Occup Environ Med* 2013; **70:** 114–19.
47 Janulewicz PA, White RF, Martin BM, et al. Adult neuropsychological performance following prenatal and early postnatal exposure to tetrachloroethylene (PCE)-contaminated drinking water. *Neurotoxicol Teratol* 2012; **34:** 350–59.
48 Kofman O, Berger A, Massarwa A, Friedman A, Jaffar AA. Motor inhibition and learning impairments in school-aged children following exposure to organophosphate pesticides in infancy. *Pediatr Res* 2006; **60:** 88–92.
49 London L, Beseler C, Bouchard MF, et al. Neurobehavioral and neurodevelopmental effects of pesticide exposures. *Neurotoxicology* 2012; **33:** 887–96.
50 Torres-Sanchez L, Schnaas L, Rothenberg SJ, et al. Prenatal p,p'-DDE exposure and neurodevelopment among children 3.5–5 years of age. *Environ Health Perspect* 2013; **121:** 263–68.
51 Boucher O, Simard MN, Muckle G, et al. Exposure to an organochlorine pesticide (chlordecone) and development of 18-month-old infants. *Neurotoxicology* 2013; **35:** 162–68.
52 Rauh V, Arunajadai S, Horton M, et al. 7-year neurodevelopmental scores and prenatal exposure to chlorpyrifos, a common agricultural pesticide. *Environ Health Perspect* 2011; **119:** 1196–201.
53 Bouchard MF, Chevrier J, Harley KG, et al. Prenatal exposure to organophosphate pesticides and IQ in 7-year old children. *Environ Health Perspect* 2011; **119:** 1189–95.
54 Engel SM, Wetmur J, Chen J, et al. Prenatal exposure to organophosphates, paraoxonase 1, and cognitive development in childhood. *Environ Health Perspect* 2011; **119:** 1182–88.
55 Rauh VA, Perera FP, Horton MK, et al. Brain anomalies in children exposed prenatally to a common organophosphate pesticide. *Proc Natl Acad Sci USA* 2012; **109:** 7871–76.
56 Bjorling-Poulsen M, Andersen HR, Grandjean P. Potential developmental neurotoxicity of pesticides used in Europe. *Environ Health* 2008; **7:** 50.
57 Ostrea EM Jr, Reyes A, Villanueva-Uy E, et al. Fetal exposure to propoxur and abnormal child neurodevelopment at 2 years of age. *Neurotoxicology* 2012; **33:** 669–75.
58 Horton MK, Rundle A, Camann DE, Boyd Barr D, Rauh VA, Whyatt RM. Impact of prenatal exposure to piperonyl butoxide and permethrin on 36-month neurodevelopment. *Pediatrics* 2011; **127:** e699–706.
59 Dingemans MM, van den Berg M, Westerink RH. Neurotoxicity of brominated flame retardants: (in)direct effects of parent and hydroxylated polybrominated diphenyl ethers on the (developing) nervous system. *Environ Health Perspect* 2011; **119:** 900–07.
60 Roze E, Meijer L, Bakker A, Van Braeckel KN, Sauer PJ, Bos AF. Prenatal exposure to organohalogens, including brominated flame retardants, influences motor, cognitive, and behavioral performance at school age. *Environ Health Perspect* 2009; **117:** 1953–58.
61 Herbstman JB, Sjodin A, Kurzon M, et al. Prenatal exposure to PBDEs and neurodevelopment. *Environ Health Perspect* 2010; **118:** 712–19.
62 Eskenazi B, Chevrier J, Rauch SA, et al. In utero and childhood polybrominated diphenyl ether (PBDE) exposures and neurodevelopment in the CHAMACOS study. *Environ Health Perspect* 2013; **121:** 257–62.
63 Grandjean P, Budtz-Jorgensen E. An ignored risk factor in toxicology: the total imprecision of exposure assessment. *Pure Appl Chem* 2010; **82:** 383–91.

64 Vandenberg LN, Colborn T, Hayes TB, et al. Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses. *Endocr Rev* 2012; **33:** 378–455.
65 Engel SM, Miodovnik A, Canfield RL, et al. Prenatal phthalate exposure is associated with childhood behavior and executive functioning. *Environ Health Perspect* 2010; **118:** 565–71.
66 Swan SH, Liu F, Hines M, et al. Prenatal phthalate exposure and reduced masculine play in boys. *Int J Androl* 2010; **33:** 259–69.
67 Braun JM, Kalkbrenner AE, Calafat AM, et al. Impact of early-life bisphenol A exposure on behavior and executive function in children. *Pediatrics* 2011; **128:** 873–82.
68 Perera FP, Li Z, Whyatt R, et al. Prenatal airborne polycyclic aromatic hydrocarbon exposure and child IQ at age 5 years. *Pediatrics* 2009; **124:** e195–202.
69 Calderon-Garciduenas L, Mora-Tiscareno A, Ontiveros E, et al. Air pollution, cognitive deficits and brain abnormalities: a pilot study with children and dogs. *Brain Cogn* 2008; **68:** 117–27.
70 Dix-Cooper L, Eskenazi B, Romero C, Balmes J, Smith KR. Neurodevelopmental performance among school age children in rural Guatemala is associated with prenatal and postnatal exposure to carbon monoxide, a marker for exposure to woodsmoke. *Neurotoxicology* 2012; **33:** 246–54.
71 Vrijheid M, Martinez D, Aguilera I, et al. Indoor air pollution from gas cooking and infant neurodevelopment. *Epidemiology* 2012; **23:** 23–32.
72 Hernandez-Martinez C, Arija Val V, Escribano Subias J, Canals Sans J. A longitudinal study on the effects of maternal smoking and secondhand smoke exposure during pregnancy on neonatal neurobehavior. *Early Hum Dev* 2012; **88:** 403–08.
73 Mariussen E. Neurotoxic effects of perfluoroalkylated compounds: mechanisms of action and environmental relevance. *Arch Toxicol* 2012; **86:** 1349–67.
74 Gump BB, Wu Q, Dumas AK, Kannan K. Perfluorochemical (PFC) exposure in children: associations with impaired response inhibition. *Environ Sci Technol* 2011; **45:** 8151–59.
75 Froehlich TE, Anixt JS, Loe IM, Chirdkiatgumchai V, Kuan L, Gilman RC. Update on environmental risk factors for attention-deficit/hyperactivity disorder. *Curr Psychiatry Rep* 2011; **13:** 333–44.
76 Carpenter DO, Nevin R. Environmental causes of violence. *Physiol Behav* 2010; **99:** 260–68.
77 Miodovnik A, Engel SM, Zhu C, et al. Endocrine disruptors and childhood social impairment. *Neurotoxicology* 2011; **32:** 261–67.
78 Volk HE, Lurmann F, Penfold B, Hertz-Picciotto I, McConnell R. Traffic-related air pollution, particulate matter, and autism. *JAMA Psychiatry* 2013; **70:** 71–77.
79 Bandeen-Roche K, Glass TA, Bolla KI, Todd AC, Schwartz BS. Cumulative lead dose and cognitive function in older adults. *Epidemiology* 2009; **20:** 831–39.
80 Lock EA, Zhang J, Checkoway H. Solvents and Parkinson disease: a systematic review of toxicological and epidemiological evidence. *Toxicol Appl Pharmacol* 2013; **266:** 345–55.
81 Landrigan PJ, Sonawane B, Butler RN, Trasande L, Callan R, Droller D. Early environmental origins of neurodegenerative disease in later life. *Environ Health Perspect* 2005; **113:** 1230–33.
82 Lauterbach M, Solak E, Kaes J, Wiechelt J, Von Mach MA, Weilemann LS. Epidemiology of hydrogen phosphide exposures in humans reported to the poison center in Mainz, Germany, 1983–2003. *Clin Toxicol* 2005; **43:** 575–81.
83 Demarest C, Torgovnick J, Sethi NK, Arsura E, Sethi PK. Acute reversible neurotoxicity associated with inhalation of ethyl chloride: a case report. *Clin Neurol Neurosurg* 2011; **113:** 909–10.
84 Imamura T, Yanagawa Y, Nishikawa K, Matsumoto N, Sakamoto T. Two cases of acute poisoning with acetamiprid in humans. *Clin Toxicol* 2010; **48:** 851–53.
85 Veale DJ, Wium CA, Muller GJ. Amitraz poisoning in South Africa: a two year survey (2008–2009). *Clin Toxicol* 2011; **49:** 40–44.
86 Sung YF, Huang CT, Fan CK, Lin CH, Lin SP. Avermectin intoxication with coma, myoclonus, and polyneuropathy. *Clin Toxicol* 2009; **47:** 686–88.
87 Yang CC. Acute human toxicity of macrocyclic lactones. *Curr Pharm Biotechnol* 2012; **13:** 999–1003.
88 Lee SJ, Mulay P, Diebolt-Brown B, et al. Acute illnesses associated with exposure to fipronil—surveillance data from 11 states in the United States, 2001–2007. *Clin Toxicol* 2010; **48:** 737–44.
89 Malhotra RC, Ghia DK, Cordato DJ, Beran RG. Glyphosate-surfactant herbicide-induced reversible encephalopathy. *J Clin Neurosci* 2010; **17:** 1472–73.
90 David D, Prabhakar A, Peter JV, Pichamuthu K. Human poisoning with hexastar: a hexaconazole-containing agrochemical fungicide. *Clin Toxicol* 2008; **46:** 692–93.
91 Shadnia S, Moghaddam HH. Fatal intoxication with imidacloprid insecticide. *Am J Emerg Med* 2008; **26:** 634.e1–4.
92 Deng X, Li G, Mei R, Sun S. Long term effects of tetramine poisoning: an observational study. *Clin Toxicol* 2012; **50:** 172–75.
93 Khalil M, Abudiab M, Ahmed AE. Clinical evaluation of 1,3-butadiene neurotoxicity in humans. *Toxicol Ind Health* 2007; **23:** 141–46.
94 Bellinger DC. A strategy for comparing the contributions of environmental chemicals and other risk factors to neurodevelopment of children. *Environ Health Perspect* 2012; **120:** 501–07.
95 Grandjean P, Pichery C, Bellanger M, Budtz-Jorgensen E. Calculation of mercury's effects on neurodevelopment. *Environ Health Perspect* 2012; **120:** A452.
96 Bellanger M, Pichery C, Aerts D, et al. Economic benefits of methylmercury exposure control in Europe: monetary value of neurotoxicity prevention. *Environ Health* 2013; **12:** 3.
97 Trasande L, Liu Y. Reducing the staggering costs of environmental disease in children, estimated at $76.6 billion in 2008. *Health Aff* 2011; **30:** 863–70.
98 Pichery C, Bellanger M, Zmirou-Navier D, Glorennec P, Hartemann P, Grandjean P. Childhood lead exposure in France: benefit estimation and partial cost-benefit analysis of lead hazard control. *Environ Health* 2011; **10:** 44.
99 Lynn R, Vanhanen T. IQ and the wealth of nations. Westport: Praeger, 2002.
100 Blacksmith Institute. The world's worst pollution problems: assessing health risks at hazardous waste sites. New York: Blacksmith Institute, 2012.
101 Trasande L, Massey RI, DiGangi J, Geiser K, Olanipekun AI, Gallagher L. How developing nations can protect children from hazardous chemical exposures while sustaining economic growth. *Health Aff* 2011; **30:** 2400–09.
102 Nevin R. Understanding international crime trends: the legacy of preschool lead exposure. *Environ Res* 2007; **104:** 315–36.
103 Schwartz J. Societal benefits of reducing lead exposure. *Environ Res* 1994; **66:** 105–24.
104 National Research Council. Toxicity testing in the 21st century: a vision and a strategy. Washington, DC: National Academies Press, 2007.
105 Makris SL, Raffaele K, Allen S, et al. A retrospective performance assessment of the developmental neurotoxicity study in support of OECD test guideline 426. *Environ Health Perspect* 2009; **117:** 17–25.
106 Rovida C, Longo F, Rabbit RR. How are reproductive toxicity and developmental toxicity addressed in REACH dossiers? *Altex* 2011; **28:** 273–94.
107 Collins FS, Gray GM, Bucher JR. Toxicology. Transforming environmental health protection. *Science* 2008; **319:** 906–07.
108 Crofton KM, Mundy WR, Lein PJ, et al. Developmental neurotoxicity testing: recommendations for developing alternative methods for the screening and prioritization of chemicals. *Altex* 2011; **28:** 9–15.
109 Audouze K, Grandjean P. Application of computational systems biology to explore environmental toxicity hazards. *Environ Health Perspect* 2011; **119:** 1754–59.
110 Willighagen EL, Jeliazkova N, Hardy B, Grafstrom RC, Spjuth O. Computational toxicology using the OpenTox application programming interface and Bioclipse. *BMC Res Notes* 2011; **4:** 487.
111 National Research Council. Science and decisions: advancing risk assessment. Washington, DC: National Academies Press, 2009.
112 Late lessons from early warnings: science, precaution, innovation. Copenhagen: European Environment Agency, 2013.
113 Moodie R, Stuckler D, Monteiro C, et al. Profits and pandemics: prevention of harmful effects of tobacco, alcohol, and ultra-processed food and drink industries. *Lancet* 2013; **381:** 670–79.
114 Grandjean P. Seven deadly sins of environmental epidemiology and the virtues of precaution. *Epidemiology* 2008; **19:** 158–62.
115 Grandjean P, Eriksen ML, Ellegaard O, Wallin JA. The Matthew effect in environmental science publication: a bibliometric analysis of chemical substances in journal articles. *Environ Health* 2011; **10:** 96.

From: Sprovieri, John Councillor [mailto:John.Sprovieri@brampton.ca]
Sent: August 22, 2018 1:48 PM
To: West, Helena
Cc: Sprovieri, John; John Sprovieri; Downey, Johanna; Palleschi, Michael; Kovac, John; Dale, Frank; Szwarc, David; Lockyer, Kathryn; O'Connor, Patrick
Subject: FW: Water Fluoridation Committee agenda

Hi Helena,
Can you place the attached information and information from Gilles Parent below on the September 27, 2018 Community Water Fluoridation Committee agenda.
Regards, John.

REFERRAL TO _____
RECOMMENDED
DIRECTION REQUIRED _____
RECEIPT RECOMMENDED ✓_____

A Section 508–conformant HTML version of this article is available at https://doi.org/10.1289/EHP655.

Prenatal Fluoride Exposure and Cognitive Outcomes in Children at 4 and 6–12 Years of Age in Mexico

Morteza Bashash,[1] Deena Thomas,[2] Howard Hu,[1] E. Angeles Martinez-Mier,[3] Brisa N. Sanchez,[2] Niladri Basu,[4] Karen E. Peterson,[2,5,6] Adrienne S. Ettinger,[2] Robert Wright,[7] Zhenzhen Zhang,[2] Yun Liu,[2] Lourdes Schnaas,[8] Adriana Mercado-García,[9] Martha María Téllez-Rojo,[9] and Mauricio Hernández-Avila[9]

[1]Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada
[2]University of Michigan School of Public Health, Ann Arbor, Michigan, USA
[3]Indiana University School of Dentistry, Indiana University-Purdue University Indianapolis, Indianapolis, Indiana, USA
[4]Faculty of Agricultural and Environmental Sciences, McGill University, Montreal, Quebec, Canada
[5]Center for Human Growth and Development, University of Michigan, Ann Arbor, Michigan, USA
[6]Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA
[7]Icahn School of Medicine at Mount Sinai, New York, New York, USA
[8]Instituto Nacional de Perinatología, Mexico City, Mexico
[9]Instituto Nacional de Salud Pública, Cuernavaca, Morelos, Mexico

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).

Please send correspondence to M. Bashash, Dalla Lana School of Public Health, 6th floor, 155 College St., Toronto, Ontario M5R3M7 Canada. Telephone: +1-416-978-6512. Email: m.bashash@utoronto.ca

Supplemental Material is available online (https://doi.org/10.1289/EHP655).

The authors declare they have no actual or potential competing financial interests.

Received 14 June 2016; Revised 8 May 2017; Accepted 9 May 2017; Published 19 September 2017.

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

STUDY SUBJECT INCLUSION FLOWCHART

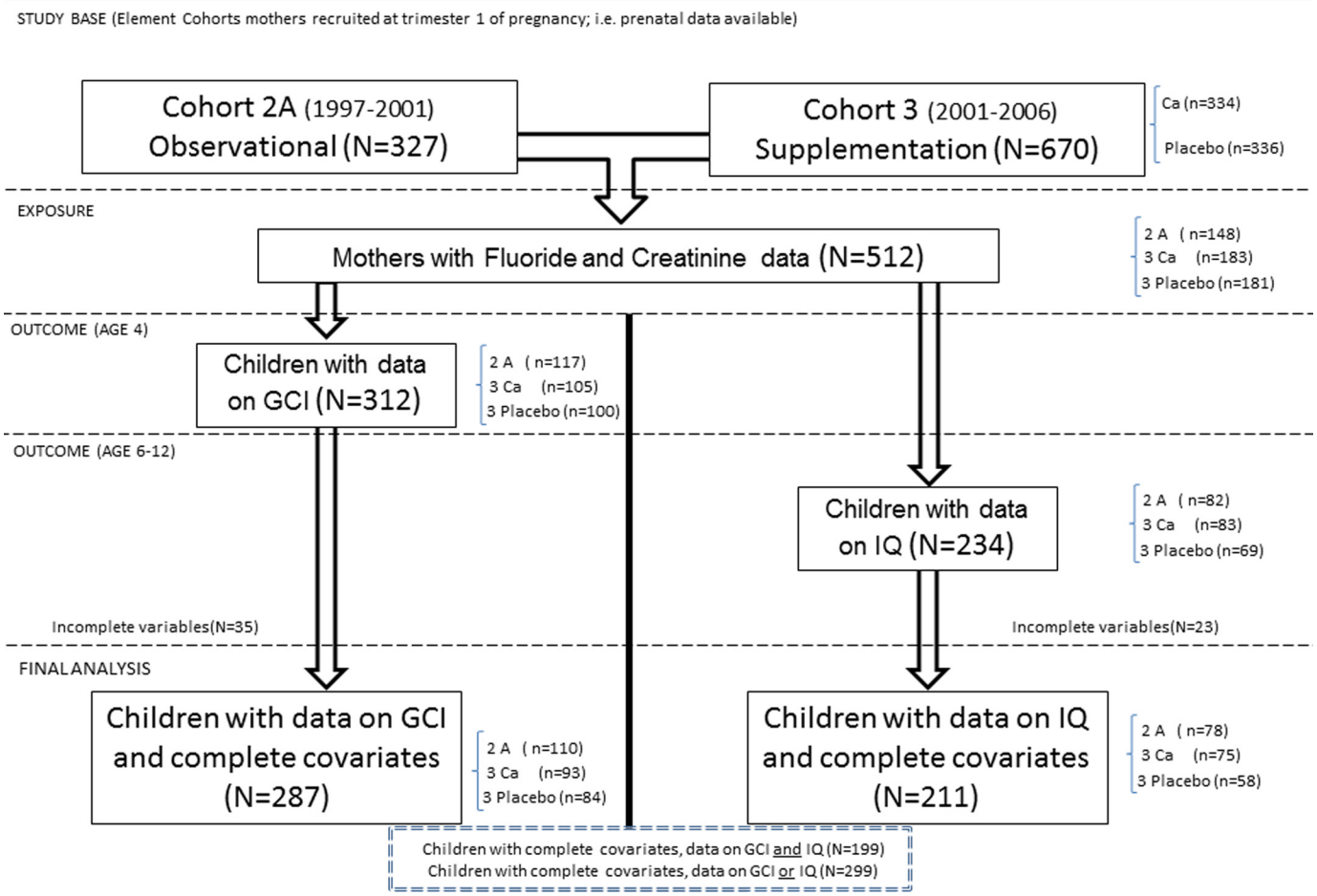


Figure 1. Flowchart describing source of mother–offspring subject pairs, fluoride and cognition study. Cohort 2A was designed as an observational birth cohort of lead toxicodynamics during pregnancy, with mothers recruited early during pregnancy from 1997 to 2001. Cohort 3 was designed as a randomized 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).

							Percentiles				
Analysis	Measurement	Cohort	*N*	Mean	SD	Min	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.

	GCI analysis		IQ analysis	
Characteristic	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

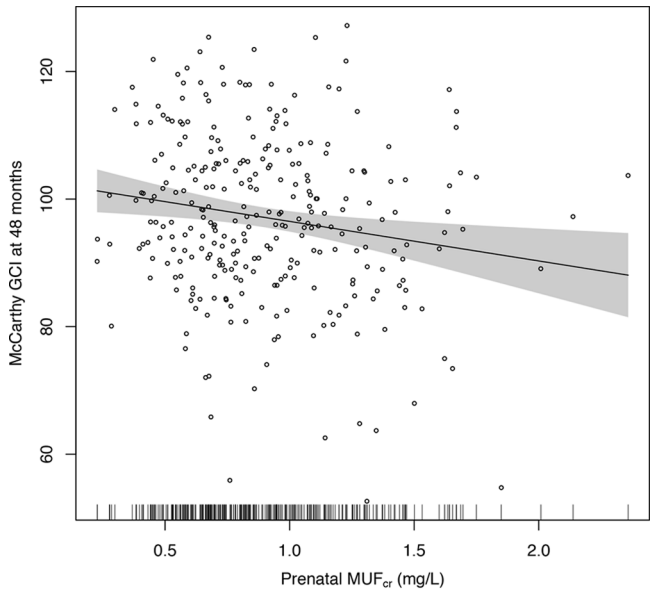


Figure 2. Adjusted association of maternal creatinine-adjusted urinary fluoride (MUF_{cr}) and General Cognitive Index (GCI) scores in children at age 4 y. Adjusted for gestational age, weight at birth, sex, parity (being the first child), age at outcome measurement, and maternal characteristics including 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

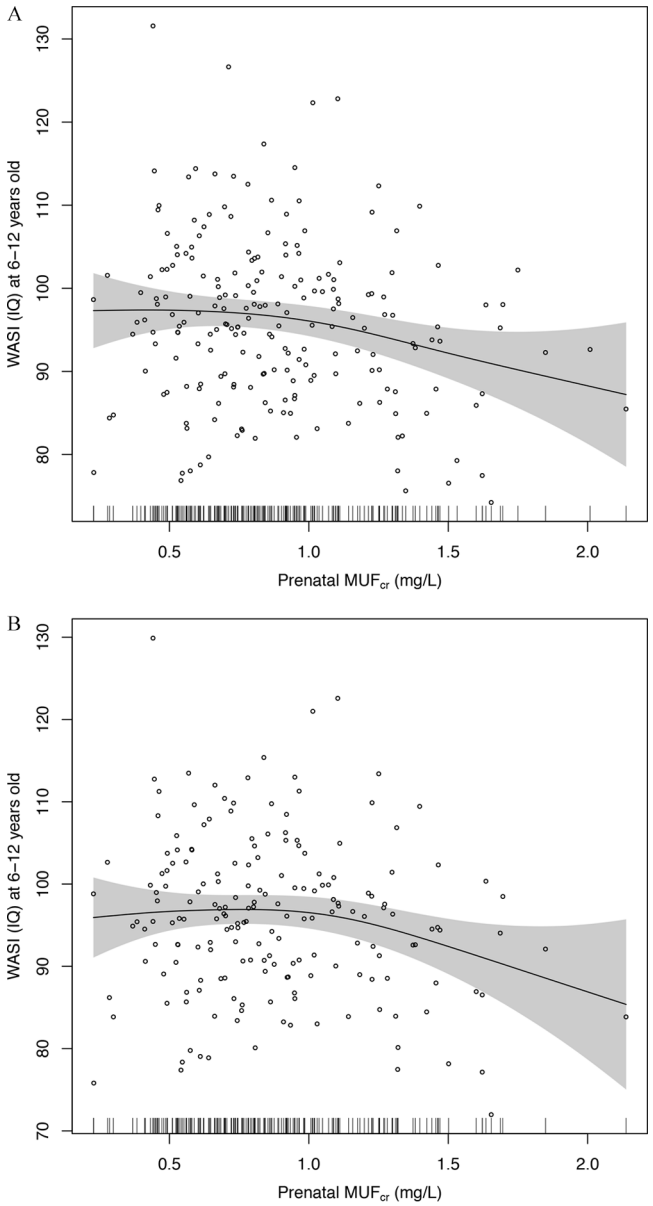


Figure 3. (A) Adjusted association of maternal creatinine-adjusted urinary fluoride (MUF_{cr}) and children's IQ at age 6–12 y. Adjusted for gestational age, weight at birth, sex, parity (being the first child), age at outcome measurement, and maternal characteristics including smoking history (ever 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.

References

Afeiche M, Peterson KE, Sánchez BN, Cantonwine D, Lamadrid-Figueroa H, Schnaas L, et al. 2011. Prenatal lead exposure and weight of 0- to 5-year-old children in Mexico City. Environ Health Perspect 119(10):1436–1441, PMID: 21715242, https://doi.org/10.1289/ehp.1003184.

Baez R, Petersen PE, Marthaler T. 2014. *Basic Methods for Assessment of Renal Fluoride Excretion in Community Prevention Programmes for Oral Health*. Geneva, Switzerland:World Health Organization.

Basu N, Tutino R, Zhang Z, Cantonwine DE, Goodrich JM, Somers EC, et al. 2014. Mercury levels in pregnant women, children, and seafood from Mexico City. Environ Res 135:63–69, PMID: 25262076, https://doi.org/10.1016/j.envres.2014.08.029.

Braun JM, Hoffman E, Schwartz J, Sanchez B, Schnaas L, Mercado-Garcia A, et al. 2012. Assessing windows of susceptibility to lead-induced cognitive deficits in Mexican children. Neurotoxicology 33(5):1040–1047, PMID: 22579785, https://doi.org/10.1016/j.neuro.2012.04.022.

Caldwell BM, Bradley RH. 2003. Administration Manual: HOME Observation for Measurement of the Environment. Little Rock, AK:University of Arkansas at Little Rock.

Choi AL, Sun G, Zhang Y, Grandjean P. 2012. Developmental fluoride neurotoxicity: a systematic review and meta-analysis. Environ Health Perspect 120(10):1362–1368, PMID: 22820538, https://doi.org/10.1289/ehp.1104912.

Choi AL, Zhang Y, Sun G, Bellinger DC, Wang K, Yang XJ, et al. 2015. Association of lifetime exposure to fluoride and cognitive functions in Chinese children: a pilot

study. Neurotoxicol Teratol 47:96–101, PMID: 25446012, https://doi.org/10.1016/j.ntt.2014.11.001.

Doull J, Boekelheide K, Farishian B, Isaacson R, Klotz J, Kumar J, et al. 2006. *Fluoride in Drinking Water: A Scientific Review of EPA's Standards*. Committee on Fluoride in Drinking Water, Board on Environmental Studies and Toxicology, Division on Earth and Life Studies, National Research Council of the National Academies. Washington, DC:National Academies Press.

Easley MW. 1995. Celebrating 50 years of fluoridation: a public health success story. Br Dent J 178(2):72–75, PMID: 7848761, https://doi.org/10.1038/sj.bdj.4808658.

Ettinger AS, Lamadrid-Figueroa H, Téllez-Rojo MM, Mercado-García A, Peterson KE, Schwartz J, et al. 2009. Effect of calcium supplementation on blood lead levels in pregnancy: a randomized placebo-controlled trial. Environ Health Perspect 117(1):26–31, PMID: 19165383, https://doi.org/10.1289/ehp.11868.

Gedalia I, Brzezinski A, Bercovici B. 1959. Urinary fluorine levels in women during pregnancy and after delivery. J Dent Res 38(3):548–551, PMID: 13654605, https://doi.org/10.1177/00220345590380031701.

Gomaa A, Hu H, Bellinger D, Schwartz J, Tsaih SW, Gonzalez-Cossio T, et al. 2002. Maternal bone lead as an independent risk factor for fetal neurotoxicity: a prospective study. Pediatrics 110(1):110–118, PMID: 12093955.

Grandjean P, Herz KT. 2011. Methylmercury and brain development: imprecision and underestimation of developmental neurotoxicity in humans. Mt Sinai J Med 78(1):107–118, PMID: 21259267, https://doi.org/10.1002/msj.20228.

Hu H, Téllez-Rojo MM, Bellinger D, Smith D, Ettinger AS, Lamadrid-Figueroa H, et al. 2006. Fetal lead exposure at each stage of pregnancy as a predictor of infant mental development. Environ Health Perspect 114(11):1730–1735, PMID: 17107860, https://doi.org/10.1289/ehp.9067.

Huang S, Hu H, Sánchez BN, Peterson KE, Ettinger AS, Lamadrid-Figueroa H, et al. 2016. Childhood blood lead levels and symptoms of attention deficit hyperactivity disorder (ADHD): a cross-sectional study of Mexican children. Environ Health Perspect 124(6):868–874, PMID: 26645203, https://doi.org/10.1289/ehp.1510067.

Jones S, Burt BA, Petersen PE, Lennon MA. 2005. The effective use of fluorides in public health. Bull World Health Organ 83:670–676.

Juárez-López M, Hernández-Guerrero JC, Jiménez-Farfán D, Molina-Frechero N, Murrieta-Pruneda F, Lopez-Jimenez G. 2007. Fluoride Urinary Excretion in Mexico City's Preschool Children [in Spanish]. Revista de investigacion clinica; organo del Hospital de Enfermedades de la Nutricion 60:241–247.

Julvez J, Ribas-Fito N, Torrent M, Forns M, Garcia-Esteban R, Sunyer J. 2007. Maternal smoking habits and cognitive development of children at age 4 years in a population-based birth cohort. Int J Epidemiol 36(4):825–832, PMID: 17550944, https://doi.org/10.1093/ije/dym107.

Kordas K, Ettinger AS, Bellinger DC, Schnaas L, Téllez Rojo MM, Hernández-Avila M, et al. 2011. A dopamine receptor (DRD2) but not dopamine transporter (DAT1) gene polymorphism is associated with neurocognitive development of Mexican preschool children with lead exposure. J Pediatr 159(4):638–643, PMID: 21592505, https://doi.org/10.1016/j.jpeds.2011.03.043.

Li XS, Zhi JL, Gao RO. 1995. Effect of fluoride exposure on intelligence in children. Fluoride 28(4):189–192.

Liu F, Ma J, Zhang H, Liu P, Liu YP, Xing B, et al. 2014. Fluoride exposure during development affects both cognition and emotion in mice. Physiol Behav 124:1–7, PMID: 24184405, https://doi.org/10.1016/j.physbeh.2013.10.027.

Marthaler T. 1999. *Monitoring of Renal Fluoride Excretion in Community Preventive Programmes on Oral Health*. Geneva, Switzerland:World Health Organization.

Martínez-Mier EA, Cury JA, Heilman JR, Katz BP, Levy SM, Li Y, et al. 2011. Development of gold standard ion-selective electrode-based methods for fluoride analysis. Caries Res 45(1):3–12, PMID: 21160184, https://doi.org/10.1159/000321657.

Martínez-Mier EA, Soto-Rojas AE, Buckley CM, Zero DT, Margineda J. 2005. Fluoride concentration of bottled water, tap water, and fluoridated salt from two communities in Mexico. Int Dent J 55(2):93–99, PMID: 15880964.

McCarthy D. 1991. *Manual for the McCarthy Scales of Children's Abilities. Spanish, User's Guide [in Spanish]*. Madrid, Spain:TEA Ediciones.

Mullenix PJ, Denbesten PK, Schunior A, Kernan WJ. 1995. Neurotoxicity of sodium fluoride in rats. Neurotoxicol Teratol 17(2):169–177, PMID: 7760776.

NTP (National Toxicology Program). 2016. Systematic Literature Review on the Effects of Fluoride on Learning and Memory in Animal Studies. NTP Research Report 1. Research Triangle Park, NC:NTP.

Opydo-Szymaczek J, Borysewicz-Lewicka M. 2005. Urinary fluoride levels for assessment of fluoride exposure of pregnant women in Poznan, Poland. Fluoride 38:312–317.

Puertas R, Lopez-Espinosa MJ, Cruz F, Ramos R, Freire C, Pérez-García M, et al. 2010. Prenatal exposure to mirex impairs neurodevelopment at age of 4 years. Neurotoxicology 31(1):154–160, PMID: 19818364, https://doi.org/10.1016/j.neuro.2009.09.009.

Renteria L, Li ST, Pliskin NH. 2008. Reliability and validity of the Spanish language Wechsler Adult Intelligence Scale (3rd Edition) in a sample of American, urban, Spanish-speaking Hispanics. Clin Neuropsychol 22(3):455–470, PMID: 17853132, https://doi.org/10.1080/13854040701336428.

Secretaría-de-Salud. 1995. Norma oficial Mexicana nom-040-ssa-1-1993. *Sal yodatada y sal fluorada* [in Spanish]. México:Diario Oficial de la Federación, 12–27.

Secretaría-de-Salud. 1996. Norma oficial Mexicana nom-127-ssa1-1994. Salud ambiental. Agua para uso y consumo humano. *Límites permisibles de calidad y tratamientos a que debe someterse el agua para su potabilización* [in Spanish]. México:Diario Oficial de la Federación, 41–46.

Shen YW, Taves DR. 1974. Fluoride concentrations in the human placenta and maternal and cord blood. Am J Obstet Gynecol 119(2):205–207, PMID: 4823388.

Thomas DB, Basu N, Martinez-Mier EA, Sánchez BN, Zhang Z, Liu Y, et al. 2016. Urinary and plasma fluoride levels in pregnant women from Mexico City. Environ Res 150:489–495, PMID: 27423051, https://doi.org/10.1016/j.envres.2016.06.046.

Usuda K, Kono K, Shimbo Y, Fujihara M, Fujimoto K, Kawano A, et al. 2007. Urinary fluoride reference values determined by a fluoride ion selective electrode. Biol Trace Elem Res 119(1):27–34, PMID: 17914216, https://doi.org/10.1007/s12011-007-0044-6.

Valdez Jiménez L, López Guzmán OD, Cervantes Flores M, Costilla-Salazar R, Calderón Hernández J, Alcaraz Contreras Y, et al. 2017. In utero exposure to fluoride and cognitive development delay in infants. Neurotoxicology 59:65–70, PMID: 28077305, https://doi.org/10.1016/j.neuro.2016.12.011.

Wang SX, Wang ZH, Cheng XT, Li J, Sang ZP, Zhang XD, et al. 2007. Arsenic and fluoride exposure in drinking water: children's IQ and growth in Shanyin county, Shanxi province, China. Environ Health Perspect 115(4):643–647, PMID: 17450237, PubMed Central PMCID: PMC1852689. https://doi.org/10.1289/ehp.9270.

Watanabe M, Kono K, Orita Y, Ydote T, Usuda K, Takahashi Y, et al. 1994. *Influence of dietary fluoride intake on urinary fluoride concentration and evaluation of corrected levels in spot urine*. In: *Proceedings of the XXth Conference of the International Society for Fluoride Research, Beijing, China*. Beijing, China: Ministry of Public Health of People's Republic of China, 246–247.

Wechsler D. 1999. *Wechsler Abbreviated Scale of Intelligence*. San Antonio, TX: Psychological Corporation.

Wechsler D, Jorge M, Velaco A. 1981. *WAIS-Español: Escala de Inteligencia para Adultos: El Manual Moderno [in Spanish]*. México, DF:El Manual Moderno, S.A.

Zohouri F, Swinbank C, Maguire A, Moynihan P. 2006. Is the fluoride/creatinine ratio of a spot urine sample indicative of 24-h urinary fluoride? Community Dent Oral Epidemiol 34(2):130–138, PMID: 16515677, https://doi.org/10.1111/j.1600-0528.2006.00269.x.

From: Kaur, Rupinder
Sent: August 28, 2018 9:23 AM
To: Sprovieri, John; Dundas, Peter F.; Polsinelli, Nancy; Roth, Julie; Szwarc, David; Dale, Frank; janette.smith@peelregion.c; aaa; Downey, Johanna; Kovac, John; Palleschi, Michael; West, Helena
Subject: RE: Water Fluoridation Committee Agenda

Good morning,

In addition to Councillor Sprovieri's previous email with the 5 attachments, he would also like to bring to your attention the disclaimer below:

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

Drinking water treatment chemicals — Health effects

Disclaimers[1]

NSF International (NSF), in performing its functions in accordance with its objectives, does not assume or undertake to discharge any responsibility of the manufacturer or any other party. The opinions and findings of NSF represent its professional judgment. NSF shall not be responsible to anyone for the use of or reliance upon this Standard by anyone. NSF shall not incur any obligations or liability for damages, including consequential damages, arising out of or in connection with the use, interpretation of, or reliance upon this Standard.

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.

Thanks,
Rupinder

Rupinder Kaur | Constituency Assistant, Wards 9 & 10 | City of Brampton
Supporting Councillor Gurpreet Dhillon & Regional Councillor John Sprovieri
2 Wellington Street West, 6th Floor | Brampton, ON | L6Y 4R2
T: 905-874-2635 | Rupinder.Kaur@brampton.ca

REFERRAL TO _____
RECOMMENDED
DIRECTION REQUIRED _____
RECEIPT RECOMMENDED ✓

HE-B1-1

Minister of Health

Ministre de la Santé

Ottawa, Canada K1A 0K9

APR 04 2012

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

Regional Municipality of Peel
Office of the Regional Chair
APR 17 2012
RECEIVED

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.

LEGISLATIVE SERVICES			
COPY TO:		FOR:	
Chair	✓	Committee	
CAO	✓		
Corporate Services		Council	
Public Works			
Employee and Business Services	May 22/12 R.G.		
Health Services	✓	For MOH	✓
Human Services			
Peel Living			

.../2

Canada

REFERRAL TO
RECOMMENDED
DIRECTION REQUIRED
RECEIPT RECOMMENDED ✓

Health Canada / Santé Canada

Access to Information and Privacy Division
7th Floor, Suite 700, Holland Cross, Tower B
1600 Scott Street
Address Locator: 3107A
Ottawa, Ontario K1A 0K9

May 26, 2014

Our file: A-2014-00168 / na

[redacted]

Dear [redacted]

This is in response to your request under the *Access to Information Act* (the *Act*) for: **Clarified Request Text:**
Reports, studies, toxicology and clinical tests relating to hydrofluosilicic acid in Canadian tap water

Original Request Text:
Documents pertaining specifically to hydrofluosilicic acid in Alberta and Canadian tap water:
- Studies from 1940 showing dental efficacy and human safety.
- Studies from 1950s showing dental efficacy and human safety.
- Any double blind study done by Canada or any province showing dental efficacy and human safety, of any date.
- Any double blind study done by anywhere in the world that was considered.
- Any toxicity study, of any date, done by Canada or the world that was considered.
- Evidence of any kind (not opinion) that shows statistical viability of water fluoridation in terms of efficacy, and margin of error calculations.
- Evidence of any kind (not opinion) that shows statistical viability of water fluoridation in terms of human safety over a life-time, and margin of error calculations.
- Evidence of any kind (not opinion) that shows statistical viability of water fluoridation in terms of human safety, and margin of error calculations, for infants, young children, elderly, or any adult with disability, diabetes, bone disease, autism, thyroid ailments, kidney disease, etc.
- Evidence of any kind of consideration of human rights and medical ethics, namely our human right to opt out of the forced water fluoridation program, and if that consideration exists, why the overriding of these well-established medical standards are breached.

After a thorough search for the requested information, no records were located which respond to your request.

If you have any questions or concerns about the processing of your request, please do not hesitate to contact Nancy Armstrong, the analyst responsible for this request, either by phone at (613) 960-4457, or by fax at (613) 941-4541, or by e-mail at nancy.armstrong@hc-sc.gc.ca with reference to the file number cited above.

Please be advised that you are entitled to complain to the Office of the Information Commissioner of Canada concerning the processing of your request within 60 days of the receipt of this notice. In the event you decide to avail yourself of this right, your notice of complaint should be addressed to:

Office of the Information Commissioner of Canada
30 Victoria Street
Gatineau, Québec K1A 1H3

Yours sincerely,

for Amanda Wilson
Coordinator, Access to Information and Privacy Division

...../2

Canadian Environmental Protection Act, 1999 (S.C. (Statutes of Canada) 1999, c. 33)

SCHEDULE 1

(Sections 56, 68, 71, 77, 79, 90, 91, 93 to 96 and 199)

List of Toxic Substances #40

For molecular formulae in this schedule, "n" = number of atoms.

1 Chlorobiphenyls that have the molecular formula $C_{12}H_{(10-n)}Cl_n$ in which "n" is greater than 2

2 Dodecachloropentacyclo [5.3.0.$0^{2,6}$.$0^{3,9}$.$0^{4,8}$] decane (Mirex)

3 Polybrominated Biphenyls that have the molecular formula $C_{12}H_{(10-n)}Br_n$ in which "n" is greater than 2

4 Chlorofluorocarbon: totally halogenated chlorofluorocarbons that have the molecular formula $C_nCl_xF_{(2n+2-x)}$

5 Polychlorinated Terphenyls that have a molecular formula $C_{18}H_{(14-n)}Cl_n$ in which "n" is greater than 2

6 Asbestos

7 Lead

8 Mercury and its compounds

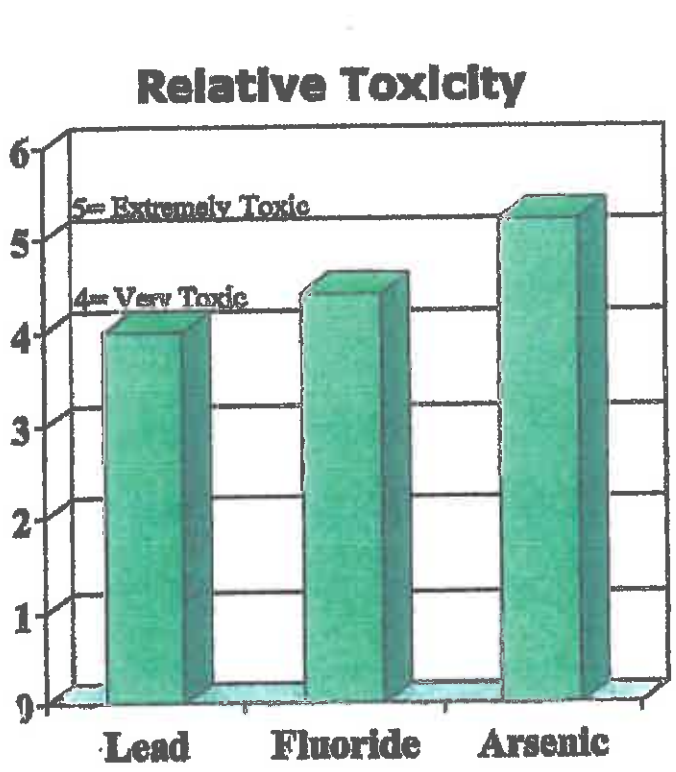
40 Inorganic fluorides

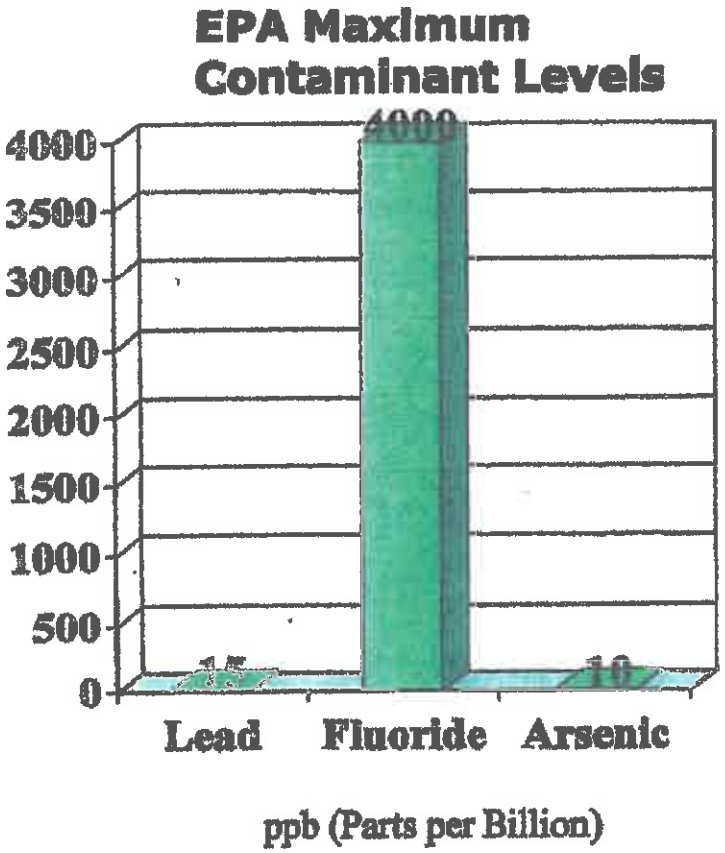
41 Refractory ceramic fibre

42 Oxidic, sulphidic and soluble inorganic nickel compounds

43 Polycyclic aromatic hydrocarbons

How Toxic is Fluoride compared to Lead & Arsenic.





Source: Clinical Toxicology of Commercial Products LD50 data - 1984

Clinical Toxicology of Commercial Products

Robert E. Gosselin (Author): was retired Doctor from Dartmouth Medical School in Hanover, N.H., where he was the founding chairman of the Department of Pharmacology and Toxicology.

Roger P. Smith (Author): PhD Emeritus Professor of Pharmacology & Toxicology

Harold C. Hodge (Author): was a well-known toxicologist who published close to 300 papers and 5 books with a PhD

Jeannet Braddock (Author): PhD

Building a Database of Developmental Neurotoxicants: Evidence from Human and Animal Studies

W. Mundy[1], *S. Padilla*[1], *T. Shafer*[1], *M. Gilbert*[1], J. Breier[1,2], J. Cowden[1], *K. Crofton*[1], *D. Herr*[1], *K. Jensen*[1], *K. Raffaele*[3], N. Radio[4], and K. Schumacher[5].
[1]Neurotoxicology Div. U.S. EPA, RTP, NC 27711; [2]Curriculum in Toxicology, Univ. of N.C. at Chapel Hill, Chapel Hill, NC, 27514; [3] NCEA/ORD, U.S. EPA, Washington, DC, 20460; [4]Cellumen, Inc., Pittsburgh, PA. 15238; [5]U.S. EPA, Region 7, Kansas City, KS, 66101.

Introduction

EPA's program for the screening and prioritization of chemicals for developmental neurotoxicity makes it essential to assemble a list of chemicals that are toxic to the developing mammalian nervous system. Listed chemicals will be used to evaluate the sensitivity, reliability, and predictive power of alternative developmental neurotoxicity assays. To establish this list, a literature review was conducted for over 400 compounds that have been suggested to be developmental neurotoxicants, neurotoxicants, or developmental toxicants. Compounds were assigned one of three groups based on the strength of the evidence for developmental neurotoxicity:

(1) no evidence: either there were no reports that met our criteria for evidence, or there were reports which showed no developmental neurotoxicity;
(2) minimal evidence: one report only or multiple reports from only one laboratory; or
(3) substantial evidence: reports from more than one laboratory.

The chemicals in the latter group will be especially useful for vetting protocols that have been proposed as screens for developmental neurotoxicity.

This presentation has been reviewed by the National Health and Environmental Effects Research Laboratory and approved. Approval does not signify that the contents reflect the views of the Agency.

Approach

Collect lists of putative DNT chemicals (n≈400)

Each chemical was assigned to one of three categories:

1. **No available evidence existed: exclude from manuscript.**
2. **Minimal evidence existed: put in table in manuscript.**
3. **Substantial evidence existed: write a descriptive paragraph for manuscript.**

*Registration Eligibility Decision Documents (available online or via Freedom of Information Act)

Evidence: Criteria for Assessment and Endpoints

a) We included only mammalian studies.
 -no *in vitro* studies were included.
b) We included only studies with the pure chemical (or reasonably so).
 -no mixture studies were included.
 -no human studies were included wherein there was exposure to more than one compound.
 -no formulations were included.
c) We included only studies where the exposure took place during pregnancy or during the period before weaning.
d) We included only studies in which the administered dose was below 5 grams/kg.
e) Where knowledge was available, we considered only studies where the administered dose would not be lethal to the offspring.
f) We did not include any case reports.
g) In studies where the chemical was administered during gestation, to the extent possible, we looked for a litter-based statistical design.
h) If only acute pharmacological effects were reported (either during dosing or shortly thereafter), we did not include that study.

Endpoints assessed included, but were not limited to:

- ☒ Head Circumference
- ☒ Brain Weight
- ☒ Exencephaly
- ☒ Brain Morphology
- ☒ Motor Activity
- ☒ Learning and Memory
- ☒ Grip Strength
- ☒ Negative Geotaxis
- ☒ Startle Response
- ☒ Righting Reflex
- ☒ Neurochemical Levels
- ☒ Receptor Affinity/Number

Chemicals with Minimal Evidence of Developmental Neurotoxicity (n≈100)

1,1,1-Trichloroethane
Abamectin
Acephate
Acetamiprid
ActinomycinD
Amiodarone (MCH 3808)
Antemisole
Atorvastatin
Atrazine
Azinphos methyl
BAS 510 (Boscalid)
BAS 670H
Bifenthrin
Bismuth Nitrophenate
Brominated veg oil
Busulfan
Carbofuran
Carbon disulfide
Chlordane
Chlordimeform
Chlorfenapyr
Chloride, sodium
CI-943 (Antipsychotic)
Clodinafop-propargyl
Clothianidin
Coumaphos
Cyfluthrin
Cyhalothrin
Cymoxanil
Danazol
DDT
Dextromoramide
Diaminotoluene (2,5-)
Dichloromethane (methylene chloride)
Dichlorvos (DDVP)
Dicrotophos
Difluoromethylornithine
Dimethoate
Dinoseb
Diphenhydramine
Disulfoton
Emamectin
Endosulphan
Endrin
EPTC (S-Ethyl dipropylthiocarbamate)
Ergotamine
Ethoxyethanol (2-)
Ethylene dibromide
Ethylene oxide
Etofenprox
Fenamiphos
Fenitrothion
Fenvalerate
FK 33-824 (Synthetic enkephalin)
Flufenacet (thiafluamide)
Formaldehyde
Glufosinate ammonium
Glyphosate trimesium
Hexachloroplatinate (IV)
Imidacloprid
Ivermectin
Lamotrigine
Levo-alpha-acetylmethadol
Lidocaine
Malathion
Mancozeb
Maytansine
Methamidophos
Methyl Ethyl Ketone
MNDA
Molinate
Naled
n-Hexane
Nickel carbonyl
Perchlorate
Phorate (BAS 228 I)
Picrotoxin
Primidone
Profenofos
Prothioconazole
Selenium compounds
Simvastatin
Spirodiclofen
Sucrose
Terbufos
tert-Butylhydroquinone, 2-
Tetrachlorodiphene
Tetracycline
Thiamethoxam
Tribufos (DEF)
Triethylene glycol dimethyl ether
Triamethadione
Triphenyl phosphate
VM-26 (Teniposide)
VP-16-213 (Etoposide)

Chemicals with Substantial Evidence of Developmental Neurotoxicity (n≈100)

2-Ethoxyethyl Acetate
Azobenzole-5-methyl
Acrylamide
Aldicarb
Allethrin
Aluminum (cl or lactate)
Amino-nicotinamide(6-)
Aminopterin
Amphetamine(d-)
Arsenic
Aspartame
Azacytidine(5-)
Benomyl
Benzene
Bioallethrin
Bis(tri-n-butyltin)oxide
Bisphenol A
Bromodeoxyuridine(5-)
Butylated Hydroxy Anisol
Butylated hydroxytoluene
Cadmium
Caffeine
Carbamazepine
Carbaryl
Carbon monoxide
Chlordecone
Chlordiazepoxide
Chlorine dioxide
Chlorpromazine
Chlorpyrifos
Cocaine
Colcemid
Colchicine
Cypermethrin
Dexamethasone
Diamorphine hydrochloride
Diazepam
Cytosine Arabinoside
DEET
Deltamethrin
Diazinon
Dieldrin
Diethylstilbestrol
Diphenylhydantoin
Epidermal Growth Factor
Ethanol
Ethylene thiourea
Flourouracil(5-)
Fluoxetine
Fluoride
Griseofulvin
Haloperidol
Halothane
Heptachlor
Hexachlorobenzene
Hexachlorophene
Hydroxyurea
Iminodipropionitrile (IDPN)
Ketamine
Lead
Lindane
LSD
Maneb
Medroxyprogesterone
Mepivacaine
Methadone
Methanol
Methimazole
Methylparathion
Monosodium Glutamate
MPTP
Naloxone
Naltrexone
Nicotine
Methoxyethanol, 2-
Methylazoxymethanol
Methylmercury
Ozone
Paraquat
Parathion (ethyl)
PBDEs
PCBs (generic)
Penicillamine
Permethrin
Phenylacetate
Phenylalanine (d,l)
Phthalate, di-(2-ethylhexyl)
Propylthiouracil
Retinoids/Vit.A/Isotretinoin
Salicylate
Tebuconazole
Tellurium (salts)
Terbutaline
Thalidomide
THC
Toluene
Triamcinolone
Tributyltin chloride
Trichlorfon
Trichloroethylene
Triethyllead
Triethyltin
Trimethyltin
Trypan blue
Urethane
Valproate
Vincristine

Sample Paragraph

DEXAMETHASONE
CAS Number: 50-02-2

Formula:

Dexamethasone is synthetic member of the glucocorticoid class of steroid hormones. It is used to treat inflammation and autoimmune conditions (e.g., rheumatoid arthritis), and to counteract side-effects of chemotherapy in cancer patients. Synthetic glucocorticoids, including dexamethasone, are also administered to women at risk for preterm labor to advance fetal maturation and reduce neonatal morbidity and mortality.

Numerous studies in animals have shown neurodevelopmental effects of perinatal dexamethasone treatment in rodents. Doses of 0.2 – 3 mg/kg (which encompasses the therapeutic range in humans) given to the pregnant dam during gestation or to the offspring postnatally alter neurogenesis and differentiation (Bohn, 1984; Carlos et al., 1992), decrease brain size and brain weight (DeKosky et al., 1982; Carlos et al., 1992; Ferguson and Holson, 1999), and alter locomotor activity and learning and memory behavior (DeKosky et al., 1982; Vicedomini et al., 1986; Ferguson et al., 2001; Kreider et al., 2005a). Relatively low doses (0.05 – 0.2 mg/kg) have also been shown to result in long-lasting changes in neurotransmitter systems and intracellular signaling (Kreider et al., 2005b; Kreider et al., 2006; Slotkin et al., 2006). Effects of dexamethasone, including decreased brain weight and hippocampal damage, have also been observed in nonhuman primates (reviewed in Coe and Lubach, 2005).

Human developmental neurotoxicity is associated with perinatal exposure to dexamethasone. Prenatal dexamethasone is routinely administered to mothers at risk for preterm delivery to reduce mortality and the incidence of respiratory distress syndrome and intraventricular hemorrage in premature infants. Postnatal dexamethasone treatment in preterm infants is also used to reduce the risk and severity of chronic lung disease. A preponderance of epidemiologic and clinical evidence, however, indicates that both pre- and post-natal exposure to dexamethasone can result in an increased risk for cerebral palsy, decreased brain size, and long-term effects on cognition and behavior (reviewed in Baud, 2004; Purdy, 2004; Purdy and Wiley, 2004; Sloboda et al., 2005).

Building a Database of Developmental Neurotoxicants: Evidence from Human and Animal Studies

W. Mundy[1], *S. Padilla*[1], *T. Shafer*[1], *M. Gilbert*[1], J. Breier[1,2], J. Cowden[1], *K. Crofton*[1], *D. Herr*[1], *K. Jensen*[1], *K. Raffaele*[3], N. Radio[4], and K. Schumacher[5].
[1]Neurotoxicology Div. U.S. EPA, RTP, NC 27711; [2]Curriculum in Toxicology, Univ. of N.C. at Chapel Hill, Chapel Hill, NC, 27514; [3] NCEA/ORD, U.S. EPA, Washington, DC, 20460; [4]Cellumen, Inc., Pittsburgh, PA. 15238; [5]U.S. EPA, Region 7, Kansas City, KS, 66101.

Chemicals with Substantial Evidence of Developmental Neurotoxicity (n≈100)

2-Ethoxyethyl Acetate
Acibenzolar-*S*-methyl
Acrylamide
Aldicarb
Allethrin
Aluminum (cl or lactate)
Amino-nicotinamide(6-)
Aminopterin
Amphetamine(*d*-)
Arsenic
Aspartame
Azacytidine(5-)
Benomyl
Benzene
Bioallethrin
Bis(tri-n-butyltin)oxide
Bisphenol A
Bromodeoxyuridine(5-)
Butylated Hydroxy Anisol
Butylated hydroxytoluene
Cadmium
Caffeine
Carbamazepine
Carbaryl
Carbon monoxide
Chlordecone
Chlordiazepoxide
Chlorine dioxide
Chlorpromazine
Chlorpyrifos
Cocaine
Colcemid
Colchicine
Cypermethrin
Dexamethasone
Diamorphine hydrochloride
Diazepam
Cytosine Arabinoside
DEET
Deltamethrin
Diazinon
Dieldrin
Diethylstilbestrol
Diphenylhydantoin
Epidermal Growth Factor
Ethanol
Ethylene thiourea
Flourouracil(5-)
Fluazinam
Fluoride
Griseofulvin
Haloperiodol
Halothane
Heptachlor
Hexachlorobenzene
Hexachlorophene
Hydroxyurea
Imminodiproprionitrile (IDPN)
Ketamine
Lead
Lindane
LSD
Maneb
Medroxyprogesterone
Mepivacaine
Methadone
Methanol
Methimazole
Methylparathion
Monosodium Glutamate
MPTP
Naloxone
Naltrexone
Nicotine
Methoxyethanol, 2-
Methylazoxymethanol
Methylmercury
Ozone
Paraquat
Parathion (ethyl)
PBDEs
PCBs (generic)
Penicillamine
Permethrin
Phenylacetate
Phenylalanine (d,l)
Phthalate, di-(2-ethylhexyl)
Propylthiouracil
Retinoids/vit.A/isotretinoin
Salicylate
Tebuconazole
Tellurium (salts)
Terbutaline
Thalidomide
THC
Toluene
Triamcinolone
Tributyltin chloride
Trichlorfon
Trichloroethylene
Triethyllead
Triethyltin
Trimethyltin
Trypan blue
Urethane
Valproate
Vincristine

From: Christine Massey
Sent: September 25, 2018 3:49 PM
To: Frank; Kovac, John; Palleschi, Michael; Downey, Johanna; Sprovieri, John
Cc: Crombie, Bonnie; Jeffrey, Linda Mayor; Thompson, Allan; Health Minister Jaczek Ontario; Premier of Ontario | Première ministre de l'Ontario; ZZG-RegionalClerk; Lockyer, Kathryn; West, Helena; mayor_tory@toronto.ca
Subject: problems in staff report on water fluoridation, Region of Peel: June 26th, 2018

Dear CWFC Members,

(Please include this communication in the agenda for the September 27, 2018 meeting of the CWFC.)

I am a professional biostatistician who has been working in the field of cancer research over roughly the past decade, having earned my Master's degree at the Dalla Lana School of Public Health, University of Toronto.

I wish to bring to your attention some troubling problems with the June 26, 2018 report from Commissioner of Health Services Nancy Polsinelli and Medical Officer Dr. Jessica Hopkins entitled *Community Water Fluoridation – Staff Responses to Statements and Questions,* which includes misleading statements regarding a matter of public safety.

Below is just a sample of the problems I have noticed; I wish I had time to elaborate much more fully for you.

Re: statement #7 (see page 25):

The CDC states that fluoride is mainly effective in reducing cavities when applied topically.

Commissioner Polsinelli and Dr. Hopkins responded:

Staff were unable to locate a statement by the CDC related to Statement 7 provided by the Committee

The following statements published by the CDC can be located in minutes via a simple internet search:

CDC, October 22, 1999:

Biologic Mechanism

> *Fluoride's caries-preventive properties initially were attributed to changes in enamel during tooth development because of the association between fluoride and cosmetic changes in enamel and a belief that fluoride incorporated into enamel during tooth development would result in a more acid-resistant mineral. However, laboratory and*

REFERRAL TO _____
RECOMMENDED
DIRECTION REQUIRED _____
RECEIPT RECOMMENDED ✓ _____

epidemiologic research suggests that fluoride prevents dental caries predominately after eruption of the tooth into the mouth, and its actions primarily are topical for both adults and children

https://www.cdc.gov/mmwr/preview/mmwrhtml/mm4841a1.htm

CDC, August 17, 2001:

The laboratory and epidemiologic research that has led to the better understanding of how fluoride prevents dental caries indicates that fluoride's predominant effect is posteruptive and topical and that the effect depends on fluoride being in the right amount in the right place at the right time.

https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5014a1.htm

Re: statement #8 (see page 25):

Dr. Cooney admitted that water fluoridation prevents less than ½ cavity per person per lifetime

Commissioner Polsinelli and Dr. Hopkins responded:

Staff were unable to locate an official statement or transcript to verify this statement.

The audio recording of Dr. Cooney's verbal admission can be located in seconds via a simple internet search:
http://cof-cof.ca/2012/01/does-water-fluoridation-really-save-dental-treatment-dollars/

Re: statement #9 (see page 26):

The W.H.O. reports that cavity rates in unfluoridated counties are similar to fluoridated countries.

Commissioner Polsinelli and Dr. Hopkins responded:

WHO country-level data does not allow for direct comparison of cavity rates comparing countries. There are several methodological challenges due to confounders...

I consider this response simply absurd. Commissioner Polsinelli and Dr. Hopkins were not asked to carry out a carefully controlled study with the WHO data and no one suggested that the requested comparison would take the place of a carefully controlled study. Commissioner Polsinelli and Dr. Hopkins were merely asked to confirm whether the rates are similar, and there is nothing to prevent them from doing this.

Further, Public Health Staff point to studies that control for no confounders (such as the bizarre Calgary study that was so grossly misrepresented by the media and its lead author, and subsequently shredded in a critique published in *Community Dentistry and Oral Epidemiology*), when it suits their purposes.

Re: statement #16 (see page 30):

Toxicology studies are required on Fluoridation products to obtain NSF Standard 60 certification.

Commissioner Polsinelli and Dr. Hopkins responded:

NSF Standard 60 certification requires that toxicological studies are done for water treatment additives with the following caveat under Section A.3.2: Data requirements for published risk assessments – Substance regulated by USEPA or Health Canada of NSF/ANSI 60,

"where Health Canada has finalized a Maximum Acceptable Concentration, no additional toxicological evaluation shall be required prior to performance of the risk estimation."

As mentioned previously, complete dissociation of HFSA is achieved when added to water. As a result, drinking water is a source of fluoride, not a source of HFSA. Health Canada conducted a comprehensive health risk assessment of fluoride in drinking water, including the examination of chronic toxicological studies on fluoride, to establish a MAC concentration of 1.5 mg/L.

Quite aside from the problems around Health Canada's MAC for fluoride, this MAC pertains only to fluoride. It does not pertain to, and certainly does not ensure the safety of, a cocktail of regulated water contaminants such as the fluoridation product HFSA, dissociated or not, or synergistic effects between constituents of the product and tap water. There is no MAC for fluoridation products.

Further, as has been pointed out to Regional Council repeatedly over the years, Staff has never provided experimental proof of the claimed total dissociation of HFSA in public drinking water.

In 2001, senior EPA research staff acknowledged that their "*longstanding confidence in the "virtually total" dissociation of SiFs (silicofluorides) may have been misplaced*" (see http://fluoridealert.org/studies/westendorf-foreword/.) The 2006 experiment referenced by Staff as providing experimental proof of the total dissociation of HFSA in tap water (Finney et al) was carried out using Nanopure water (devoid of impurities, unlike tap water) and likely a higher grade of HFSA than is added to tap water.

Re: statement #19 (see page 32):

Harmful chemicals that make up fluoridation products [HFSA] accumulate in our bodies.

Commissioner Polsinelli and Dr. Hopkins did not address statement #19. They were asked to verify whether or not the constituents of fluoridation products (fluoride, arsenic, lead, etc.) accumulate in our bodies. Instead they obfuscated with distracting claims of dissociation, commentary on MACs and comparisons with other communities.

Further, regarding MACs, see below a screenshot from Health Canada's Guidelines for Canadian Drinking Water Quality.

Arsenic: "*classified as human carcinogen*"; "*MAC based on treatment achievability*", not safety; "*levels should be kept as low as reasonably achievable*". Also note that the province's MAC for arsenic is 2.5 times higher than Health Canada's suggested MAC.

The province's MAC for lead is the same as Health Canada's suggested MAC, which is over 25 years old; Health Canada's guideline states that "*exposure to lead should nevertheless be kept to a minimum*".)

Type[1]	Parameter (approval, reaffirmation)	MAC (mg/L)	Other value (mg/L)	Common sources of parameter in water	Health considerations	Comments
I	Antimony (1997)	0.006		Naturally occurring (erosion); soil runoff; industrial effluents; leaching from plumbing materials and solder	**Health basis of MAC:** Microscopic changes in organs and tissues (thymus, kidney, liver, spleen, thyroid)	MAC takes into consideration analytical achievability; plumbing should be thoroughly flushed before water is used for consumption.
I	Arsenic (2006)	0.010 ALARA		Naturally occurring (erosion and weathering of soils, minerals, ores); releases from mining; industrial effluent	**Health basis of MAC:** Cancer (lung, bladder, liver, skin) (classified as human carcinogen) **Other:** Skin, vascular and neurological effects (numbness and tingling of extremities) tingling of extremities)	MAC based on treatment achievability; elevated levels associated with certain groundwaters; levels should be kept as low as reasonably achievable.
I	Lead (1992)	0.010		Leaching from plumbing (pipes, solder, brass fittings and lead service lines)	**Health basis of MAC:** Biochemical and neurobehavioural effects (intellectual development, behaviour) in infants and young children (under 6	Because the MAC is based on chronic effects, it is intended to apply to average concentrations in water consumed for extended periods. Exposure to lead should

-
- The World Health Organization states that "*There is no known level of lead exposure that is considered safe*" http://www.who.int/mediacentre/factsheets/fs379/en/
-
- The EPA's MCLGs for both arsenic and lead are zero. *"Definitions: Maximum Contaminant Level Goal (MCLG)—The level of a contaminant in drinking water below which there is no known or expected risk to health. MCLGs allow for a margin of safety and are non-enforceable public health goals."* https://www.epa.gov/ground-water-and-drinking-water/table-regulated-drinking-water-contaminants#one

I find Commissioner Polsinelli and Dr. Hopkins' June 26th report especially disturbing in light of the grossly misleading and fraudulent statement on dental fluorosis published in the *Oral Health in Peel 2017: A Taste of Risk Factors and Oral Health Outcomes* report written by Julie Stratton, Manager, Population Health Assessment, Dr. Faahim Rashid, Dental Consultant and Paul Sharma, Director, Chronic Disease and Injury Prevention (see page 61: https://www.peelregion.ca/health/resources/pdf/2017-oral-health-report.pdf).

Highlights from the *Oral Health in Peel 2017* report were provided to Council by Commissioner Polsinelli and the Region's former Medical Officer Dr. Eileen de Villa (see page 47 of Council's meeting agenda for February 9, 2017: https://www.peelregion.ca/council/agendas/2017/2017-02-09-rc-agenda.pdf). That report is still in circulation and posted on the Regions' website despite it's glaring problems, which I pointed out in an official complaint to the Region in February 2017, never having been addressed.

Best wishes,
Christine Massey, M. Sc.
Spokesperson, Fluoride Free Peel
http://fluoridefreepeel.ca/