From:	Deming, Amy
To:	Water Utility Board
Subject:	FW: Fluoride Documents Tuesday Board Meeting
Date:	Thursday, August 20, 2020 3:56:23 PM
Attachments:	REFERENCES-FOR-UPDATED-NEUROTOXICITY-ONE-PAGER-3-10-20.pdf Till_Green_EvolvingScience.pdf Efficacy-Flyer-Print-FINAL-1.pdf World.pdf 2020_July_Best_practices_IQ_F_infant_Formula.pdf Neurotoxicity-One-pager-3-10-20.-pdf.pdf 2016-2020_Utilities_WI_discontinuedF.docx 2019_jamapediatrics_green_.pdf 2020_infant_formula.pdf EPA-trial-Hu-Declaration.pdf EPA-trial-Lanphear-declaration.pdf EPA-trial-Grandjean-Declaration.pdf EPA-trial-Thiessen-Declaration.pdf tsca-trial.closing.june2020.pdf neurath-ppt.w-notes.pdf

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From: Brenda Staudenmaier <thelovelybrenda@gmail.com>
Sent: Wednesday, August 19, 2020 12:31 PM
To: Deming, Amy <ADeming@madisonwater.org>; Water <water@cityofmadison.com>
Subject: Fluoride Documents Tuesday Board Meeting

Can we please include the following documents for the fluoride topic on Tuesday?

Thanks,
Brenda Staudenmaier
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WI Utilities Discontinued Fluoridation of Public Water Supplies Since 2016.
1. Potosi Waterworks
2. Fond Du Lac Waterworks
3. Coloma Waterworks
4. Blue Mounds Waterworks
5. South Wayne Waterworks
6. Luck Waterworks
7. Windsor Water utility North
8. Plymouth Utilities
9. Saukville Waterworks
10. Lake Delton Waterworks
11. St Croix Falls Waterworks
12. Mellen Water Utility
13. Bonduel Waterworks
14. Berlin Waterworks
15. Oconto Falls Waterworks
16. Rock Springs Waterworks
Source: WI DNR June 2020

JAMA Pediatrics | Original Investigation

Association Between Maternal Fluoride Exposure During Pregnancy and IQ Scores in Offspring in Canada

Rivka Green, MA; Bruce Lanphear, MD; Richard Hornung, PhD; David Flora, PhD; E. Angeles Martinez-Mier, DDS; Raichel Neufeld, BA; Pierre Ayotte, PhD; Gina Muckle, PhD; Christine Till, PhD

IMPORTANCE The potential neurotoxicity associated with exposure to fluoride, which has generated controversy about community water fluoridation, remains unclear.

OBJECTIVE To examine the association between fluoride exposure during pregnancy and IQ scores in a prospective birth cohort.

DESIGN, SETTING, AND PARTICIPANTS This prospective, multicenter birth cohort study used information from the Maternal-Infant Research on Environmental Chemicals cohort. Children were born between 2008 and 2012; 41% lived in communities supplied with fluoridated municipal water. The study sample included 601 mother-child pairs recruited from 6 major cities in Canada; children were between ages 3 and 4 years at testing. Data were analyzed between March 2017 and January 2019.

EXPOSURES Maternal urinary fluoride (MUF_{SG}), adjusted for specific gravity and averaged across 3 trimesters available for 512 pregnant women, as well as self-reported maternal daily fluoride intake from water and beverage consumption available for 400 pregnant women.

MAIN OUTCOMES AND MEASURES Children's IQ was assessed at ages 3 to 4 years using the Wechsler Primary and Preschool Scale of Intelligence-III. Multiple linear regression analyses were used to examine covariate-adjusted associations between each fluoride exposure measure and IQ score.

RESULTS Of 512 mother-child pairs, the mean (SD) age for enrollment for mothers was 32.3 (5.1) years, 463 (90%) were white, and 264 children (52%) were female. Data on MUF_{SG} concentrations, IQ scores, and complete covariates were available for 512 mother-child pairs; data on maternal fluoride intake and children's IQ were available for 400 of 601 mother-child pairs. Women living in areas with fluoridated tap water (n = 141) compared with nonfluoridated water (n = 228) had significantly higher mean (SD) MUF_{SG} concentrations (0.69 [0.42] mg/L vs 0.40 [0.27] mg/L; $P = .001$; to convert to millimoles per liter, multiply by 0.05263) and fluoride intake levels (0.93 [0.43] vs 0.30 [0.26] mg of fluoride per day; $P = .001$). Children had mean (SD) Full Scale IQ scores of 107.16 (13.26), range 52-143, with girls showing significantly higher mean (SD) scores than boys: 109.56 (11.96) vs 104.61 (14.09); $P = .001$. There was a significant interaction ($P = .02$) between child sex and MUF_{SG} (6.89; 95% CI, 0.96-12.82) indicating a differential association between boys and girls. A 1-mg/L increase in MUF_{SG} was associated with a 4.49-point lower IQ score (95% CI, −8.38 to −0.60) in boys, but there was no statistically significant association with IQ scores in girls ($B = 2.40$; 95% CI, −2.53 to 7.33). A 1-mg higher daily intake of fluoride among pregnant women was associated with a 3.66 lower IQ score (95% CI, −7.16 to −0.14) in boys and girls.

CONCLUSIONS AND RELEVANCE In this study, maternal exposure to higher levels of fluoride during pregnancy was associated with lower IQ scores in children aged 3 to 4 years. These findings indicate the possible need to reduce fluoride intake during pregnancy.

Editorial page 915 and Editor's Note page 948

Audio and Supplemental content

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For decades, community water fluoridation has been used to prevent tooth decay. Water fluoridation is supplied to about 66% of US residents, 38% of Canadian residents, and 3% of European residents.[1] In fluoridated communities, fluoride from water and beverages made with tap water makes up 60% to 80% of daily fluoride intake in adolescents and adults.[2]

Fluoride crosses the placenta,[3] and laboratory studies show that it accumulates in brain regions involved in learning and memory[4] and alters proteins and neurotransmitters in the central nervous system.[5] Higher fluoride exposure from drinking water has been associated with lower children's intelligence in a meta-analysis[6] of 27 epidemiologic studies and in studies[7,8] including biomarkers of fluoride exposure. However, most prior studies were cross-sectional and conducted in regions with higher water fluoride concentrations (0.88-31.6 mg/L; to convert to millimoles per liter, multiply by 0.05263) than levels considered optimal (ie, 0.7 mg/L) in North America.[9] Further, most studies did not measure exposure during fetal brain development. In a longitudinal birth cohort study involving 299 mother-child pairs in Mexico City, Mexico, a 1-mg/L increase in maternal urinary fluoride (MUF) concentration was associated with a 6-point (95% CI, −10.84 to −1.74) lower IQ score among school-aged children.[10] In this same cohort, MUF was also associated with more attention-deficit/hyperactivity disorder–like symptoms.[11] Urinary fluoride concentrations among pregnant women living in fluoridated communities in Canada are similar to concentrations among pregnant women living in Mexico City.[12] However, it is unclear whether fluoride exposure during pregnancy is associated with cognitive deficits in a population receiving optimally fluoridated water.

This study examined whether exposure to fluoride during pregnancy was associated with IQ scores in children in a Canadian birth cohort in which 40% of the sample was supplied with fluoridated municipal water.

Key Points

Question Is maternal fluoride exposure during pregnancy associated with childhood IQ in a Canadian cohort receiving optimally fluoridated water?

Findings In this prospective birth cohort study, fluoride exposure during pregnancy was associated with lower IQ scores in children aged 3 to 4 years.

Meaning Fluoride exposure during pregnancy may be associated with adverse effects on child intellectual development, indicating the possible need to reduce fluoride intake during pregnancy.

Methods

Study Cohort

Between 2008 and 2011, the Maternal-Infant Research on Environmental Chemicals (MIREC) program recruited 2001 pregnant women from 10 cities across Canada. Women who could communicate in English or French, were older than 18 years, and were within the first 14 weeks of pregnancy were recruited from prenatal clinics. Participants were not recruited if there was a known fetal abnormality, if they had any medical complications, or if there was illicit drug use during pregnancy. Additional details are in the cohort profile description.[13]

A subset of 610 children in the MIREC Study was evaluated for the developmental phase of the study at ages 3 to 4 years; these children were recruited from 6 of 10 cities included in the original cohort: Vancouver, Montreal, Kingston, Toronto, Hamilton, and Halifax. Owing to budgetary restraints, recruitment was restricted to the 6 cities with the most participants who fell into the age range required for the testing during the data collection period. Of the 610 children, 601 (98.5%) completed neurodevelopmental testing; 254 (42.3%) of these children lived in nonfluoridated regions and 180 (30%) lived in fluoridated regions; for 167 (27.7%) fluoridation status was unknown owing to missing water data or reported not drinking tap water (**Figure 1**).

This study was approved by the research ethics boards at Health Canada, York University, and Indiana University. All women signed informed consent forms for both mothers and children.

Maternal Urinary Fluoride Concentration

We used the mean concentrations of MUF measured in urine spot samples collected across each trimester of pregnancy at a mean (SD) of 11.57 (1.57), 19.11 (2.39), and 33.11 (1.50) weeks of gestation. Owing to the variability of urinary fluoride measurement and fluoride absorption during pregnancy,[14] we only included women who had all 3 urine samples. In our previous work, these samples were moderately correlated; intraclass correlation coefficient (ICC) ranged from 0.37 to 0.40.[12]

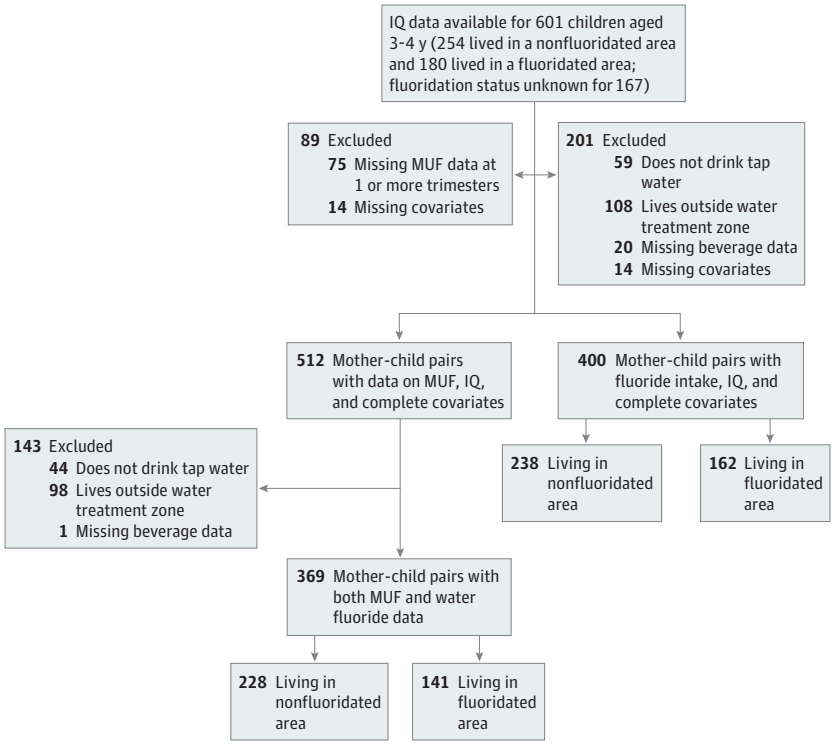
Urinary fluoride concentration was analyzed at the Indiana University School of Dentistry using a modification of the hexamethyldisiloxane (Sigma Chemical Co) microdiffusion procedure[15] and described in our previous work.[12] Fluoride concentration could be measured to 0.02 mg/L. We excluded 2 samples (0.002%) because the readings exceeded the highest concentration standard (5 mg/L) and there was less certainty of these being representative exposure values.

To account for variations in urine dilution at the time of measurement, we adjusted MUF concentrations for specific gravity (SG) using the following equation: $MUF_{SG} = MUF_i \times (SG_M\text{-}1)/(SG_i\text{-}1)$, where MUF_{SG} is the SG-adjusted fluoride concentration (in milligrams of fluoride per liter), MUF_i is the observed fluoride concentration, SG_i is the SG of the individual urine sample, and SG_M is the median SG for the cohort.[16] For comparison, we also adjusted MUF using the same creatinine adjustment method that was used in the 2017 Mexican cohort.[10]

Water Fluoride Concentration

Water treatment plants measured fluoride levels daily if fluoride was added to municipal drinking water and weekly or monthly if fluoride was not added to water.[12] We matched participants' postal codes with water treatment plant zones, allowing an estimation of water fluoride concentration for each woman by averaging water fluoride concentrations (in milligrams per liter) dur-

Figure 1. Flowchart of Inclusion Criteria



MUF indicates maternal urinary fluoride.

ing the duration of pregnancy. We only included women who reported drinking tap water during pregnancy.

Daily Fluoride Intake in Mothers

We obtained information on consumption of tap water and other water-based beverages (tea and coffee) from a self-report questionnaire completed by mothers during the first and third trimesters. This questionnaire was used in the original MREC cohort and has not been validated. Also, for this study, we developed methods to estimate and calculate fluoride intake that have not yet been validated. To estimate fluoride intake from tap water consumed per day (milligrams per day), we multiplied each woman's consumption of water and beverages by her water fluoride concentration (averaged across pregnancy) and multiplied by 0.2 (fluoride content for a 200-mL cup). Because black tea contains a high fluoride content (2.6 mg/L),[17,18] we also estimated the amount of fluoride consumed from black tea by multiplying each cup of black tea by 0.52 mg (mean fluoride content in a 200-mL cup of black tea made with deionized water) and added this to the fluoride intake variable. Green tea also contains varying levels of fluoride; therefore, we used the mean for the green teas listed by the US Department of Agriculture (1.935 mg/L).[18] We multiplied each cup of green tea by 0.387 mg (fluoride content in a 200-mL cup of green tea made with deionized water) and added this to the fluoride intake variable.

Primary Outcomes

We assessed children's intellectual abilities with the Wechsler Preschool and Primary Scale of Intelligence, Third Edition. Full Scale IQ (FSIQ), a measure of global intellectual functioning, was the primary outcome. We also assessed verbal IQ (VIQ), representing verbal reasoning and comprehension, and performance IQ (PIQ), representing nonverbal reasoning, spatial processing, and visual-motor skills.

Covariates

We selected covariates from a set of established factors associated with fluoride metabolism (eg, time of void and time since last void) and children's intellectual abilities (eg, child sex, maternal age, gestational age, and parity) (**Table 1**). Mother's race/ethnicity was coded as white or other, and maternal education was coded as either bachelor's degree or higher or trade school diploma or lower. The quality of a child's home environment was measured by the Home Observation for Measurement of the Environment (HOME)-Revised Edition[19] on a continuous scale. We also controlled for city and, in some models, included self-reported exposure to secondhand smoke (yes/no) as a covariate.

Statistical Analyses

In our primary analysis, we used linear regression analyses to estimate the associations between our 2 measures of fluoride exposure (MUF_{SG} and fluoride intake) and children's FSIQ scores. In addition to providing the coefficient corresponding to a 1-mg difference in fluoride exposure, we also estimated coefficients corresponding to a fluoride exposure difference spanning the 25th to 75th percentile range (which corresponds to a 0.33 mg/L and 0.62 mg F/d difference in MUF_{SG} and fluoride intake, respectively) as well as the 10th

Table 1. Demographic Characteristics and Exposure Outcomes for Mother-Child Pairs With MUF_{SG} (n = 512) and Fluoride Intake Data (n = 400) by Fluoridated and Nonfluoridated Status[a]

Variable[b]	No. (%)		
		Maternal-Child Pairs With Fluoride Intake, IQ, and Complete Covariate Data (n = 400)	
	MUF_{SG} Sample (n = 512)[c]	Nonfluoridated (n = 238)	Fluoridated (n = 162)
Mothers			
Age of mother at enrollment, mean (SD), y	32.33 (5.07)	32.61 (4.90)	32.52 (4.03)
Prepregnancy BMI, mean (SD)	25.19 (6.02)	25.19 (6.35)	24.33 (5.10)
Married or common law	497 (97)	225 (95)	159 (98)
Born in Canada	426 (83)	187 (79)	131 (81)
White	463 (90)	209 (88)	146 (90)
Maternal education			
Trade school diploma/high school	162 (32)	80 (34)	38 (24)
Bachelor's degree or higher	350 (68)	158 (66)	124 (76)
Employed at time of pregnancy	452 (88)	205 (86)	149 (92)
Net income household >$70 000 CAD	364 (71)	162 (68)	115 (71)
HOME total score, mean (SD)	47.32 (4.32)	47.28 (4.48)	48.14 (3.90)
Smoked in trimester 1	12 (2)	7 (3)	2 (1)
Secondhand smoke in the home	18 (4)	9 (4)	2 (1)
Alcohol consumption, alcoholic drink/mo			
None	425 (83)	192 (81)	136 (84)
<1	41 (8)	23 (10)	11 (7)
≥1	46 (9)	23 (10)	15 (9)
Parity (first birth)	233 (46)	119 (50)	71 (44)
Children			
Female	264 (52)	118 (50)	83 (51)
Age at testing, mean (SD), y	3.42 (0.32)	3.36 (0.31)	3.49 (0.29)
Gestation, mean (SD), wk	39.12 (1.57)	39.19 (1.47)	39.17 (1.81)
Birth weight, mean (SD), kg	3.47 (0.49)	3.48 (0.48)	3.47 (0.53)
FSIQ	107.16 (13.26)	108.07 (13.31)	108.21 (13.72)
Boys[d]	104.61 (14.09)	106.31 (13.60)	104.78 (14.71)
Girls[d]	109.56 (11.96)	109.86 (12.83)	111.47 (11.89)
Exposure variables			
MUF_{SG} concentration, mg/L[e]			
No.	512	228	141
Mean (SD)	0.51 (0.36)	0.40 (0.27)	0.69 (0.42)
Fluoride intake level per day, mg			
No.	369[a]	238	162
Mean (SD)	0.54 (0.44)	0.30 (0.26)	0.93 (0.43)
Water fluoride concentration, mg/L			
No.	369[a]	238	162
Mean (SD)	0.31 (0.23)	0.13 (0.06)	0.59 (0.08)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CAD, Canadian dollars; FSIQ, Full Scale IQ; HOME, Home Observation for Measurement of the Environment; MUF_{SG}, maternal urinary fluoride adjusted for specific gravity.

SI conversion factor: To convert fluoride to millimoles per liter, multiply by 0.05263.

[a] Owing to missing water treatment plant data and/or MUF data, the samples are distinct with some overlapping participants in both groups (n = 369).

[b] All of the listed variables were tested as potential covariates, as well as the following: paternal variables (age, education, employment status, smoking status, and race/ethnicity); maternal chronic condition during pregnancy and birth country; breastfeeding duration; and time of void and time since last void.

[c] Maternal urinary fluoride (averaged across all 3 trimesters) and corrected for specific gravity.

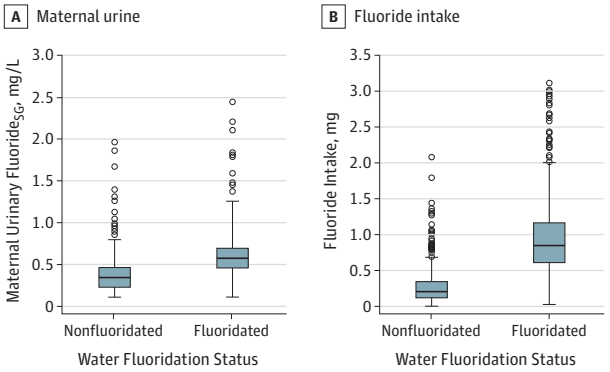
[d] The FSIQ score has a mean (SD) of 100 (15); US population norms used.

[e] Owing to missing water treatment plant data, the samples in the fluoridated and nonfluoridated regions do not add up to the MUF sample size.

to 90th percentile range (which corresponds to a 0.70 mg/L and 1.04 mg F/d difference in MUF_{SG} and fluoride intake, respectively).

We retained a covariate in the model if its *P* value was less than .20 or its inclusion changed the regression coefficient of the variable associated factor by more than 10% in any of the IQ models. Regression diagnostics confirmed that there were no collinearity issues in any of the IQ models with MUF_{SG} or fluoride intake (variance inflation factor <2 for all covariates). Residuals from each model had approximately normal distributions, and their Q-Q plots revealed no extreme outliers. Plots of residuals against fitted values did not suggest any assumption violations and there were no substantial influential observations as measured by Cook distance. Including quadratic or natural-log effects of MUF_{SG} or fluoride intake did not significantly improve the regression models. Thus, we present the more easily interpreted estimates from linear regression models. Additionally, we examined separate models with 2 linear splines to test whether the MUF_{SG} association significantly differed between lower and higher levels of MUF_{SG} based on 3 knots, which were set at 0.5 mg/L (mean MUF_{SG}), 0.8 mg/L (threshold seen in the Mexican birth cohort),[10] and 1 mg/L (op-

Figure 2. Distribution of Fluoride Levels in Maternal Urine and for Estimated Fluoride Intake by Fluoridation Status



To convert fluoride to millimoles per liter, multiply by 0.05263.

timal concentration in the United States until 2015).[20] For fluoride intake, knots were set at 0.4 mg (mean fluoride intake), 0.8 mg, and 1 mg (in accordance with MUF_{SG}). We also examined sex-specific associations in all models by testing the interactions between child sex and each fluoride measure.

In sensitivity analyses, we tested whether the associations between MUF_{SG} and IQ were confounded by maternal blood concentrations of lead,[21] mercury,[21] manganese,[21,22] perfluoro-octanoic acid,[23] or urinary arsenic.[24] We also conducted sensitivity analyses by removing IQ scores that were greater than or less than 2.5 standard deviations from the sample mean. Additionally, we examined whether using MUF adjusted for creatinine instead of SG affected the results.

In additional analyses, we examined the association between our 2 measures of fluoride exposure (MUF_{SG} and fluoride intake) with VIQ and PIQ. Additionally, we examined whether water fluoride concentration was associated with FSIQ, VIQ, and PIQ scores.

For all analyses, statistical significance tests with a type I error rate of 5% were used to test sex interactions, while 95% confidence intervals were used to estimate uncertainty. Analyses were conducted using R software (the R Foundation).[25] The *P* value level of significance was .05, and all tests were 2-sided.

Results

For the first measure of fluoride exposure, MUF_{SG}, 512 of 601 mother-child pairs (85.2%) who completed the neurodevelopmental visit had urinary fluoride levels measured at each trimester of the mother's pregnancy and complete covariate data (Figure 1); 89 (14.8%) were excluded for missing MUF_{SG} at 1 or more trimesters (n = 75) or missing 1 or more covariates included in the regression (n = 14) (Figure 1). Of the 512 mother-child pairs with MUF_{SG} data (and all covariates), 264 children were female (52%).

For the second measure of fluoride exposure, fluoride intake from maternal questionnaire, data were available for 400 of the original 601 mother-child pairs (66.6%): 201 women (33.4%) were excluded for reporting not drinking tap water (n = 59), living outside of the predefined water treatment plant zone (n = 108), missing beverage consumption data (n = 20), or missing covariate data (n = 14) (Figure 1).

Children had mean FSIQ scores in the average range (population normed) (mean [SD], 107.16 [13.26], range = 52-143), with girls (109.56 [11.96]) showing significantly higher scores than boys (104.61 [14.09]; *P* < .001) (Table 1). The demographic characteristics of the 512 mother-child pairs included in the primary analysis were not substantially different from the original MIREC cohort or subset of mother-child pairs without 3 urine samples (eTable 1 in the Supplement). Of the 400 mother-child pairs with fluoride intake data (and all covariates), 118 of 238 (50%) in the group living in a nonfluoridated region were female and 83 of 162 (51%) in the group living in a fluoridated region were female.

Fluoride Measurements

The median MUF_{SG} concentration was 0.41 mg/L (range, 0.06-2.44 mg/L). Mean MUF_{SG} concentration was significantly higher among women (n = 141) who lived in communities with fluoridated drinking water (0.69 [0.42] mg/L) compared with women (n=228) who lived in communities without fluoridated drinking water (0.40 [0.27] mg/L; *P* < .001) (Table 1; **Figure 2**).

The median estimated fluoride intake was 0.39 mg per day (range, 0.01-2.65 mg). As expected, the mean (SD) fluoride intake was significantly higher for women (162 [40.5%]) who lived in communities with fluoridated drinking water (mean [SD], 0.93 [0.43] mg) than women (238 [59.5%]) who lived in communities without fluoridated drinking water (0.30 [0.26] mg; *P* < .001) (Table 1; Figure 2). The MUF_{SG} was moderately correlated with fluoride intake (*r* = 0.49; *P* < .001) and water fluoride concentration (*r* = 0.37; *P* < .001).

Maternal Urinary Fluoride Concentrations and IQ

Before covariate adjustment, a significant interaction (*P* for interaction = .03) between MUF_{SG} and child sex (*B* = 7.24; 95% CI, 0.81-13.67) indicated that MUF_{SG} was associated with FSIQ in boys; an increase of 1 mg/L MUF_{SG} was associated with a 5.01 (95% CI, −9.06 to −0.97; *P* = .02) lower FSIQ score in boys. In contrast, MUF_{SG} was not significantly associated with FSIQ score in girls (*B* = 2.23; 95% CI, −2.77 to 7.23; *P* = .38) (**Table 2**).

Adjusting for covariates, a significant interaction (*P* for interaction = .02) between child sex and MUF_{SG} (*B* = 6.89; 95% CI, 0.96-12.82) indicated that an increase of 1 mg/L of MUF_{SG} was associated with a 4.49 (95% CI, −8.38 to −0.60; *P* = .02) lower FSIQ score for boys. An increase from the 10th to 90th percentile of MUF_{SG} was associated with a 3.14 IQ decrement among boys (Table 2; **Figure 3**). In contrast, MUF_{SG} was not significantly associated with FSIQ score in girls (*B* = 2.43; 95% CI, −2.51 to 7.36; *P* = .33).

Estimated Fluoride Intake and IQ

A 1-mg increase in fluoride intake was associated with a 3.66 (95% CI, −7.16 to −0.15; *P* = .04) lower FSIQ score among boys and girls (Table 2; Figure 3). The interaction between child sex and fluoride intake was not statistically significant (*B* = 1.17; 95% CI, −4.08 to 6.41; *P* for interaction = .66).

Table 2. Unadjusted and Adjusted Associations Estimated From Linear Regression Models of Fluoride Exposure Variables and FSIQ Scores

	Difference (95% CI)			
		Adjusted Estimates, Regression Coefficients Indicate Change in Outcome per[a]		
Variable	Unadjusted	1 mg	25th to 75th Percentiles	10th to 90th Percentiles
MUF_{SG}[b,c]	−2.60 (−5.80 to 0.60)	−1.95 (−5.19 to 1.28)	−0.64 (−1.69 to 0.42)	−1.36 (−3.58 to 0.90)
Boys	−5.01 (−9.06 to −0.97)	−4.49 (−8.38 to −0.60)	−1.48 (−2.76 to −0.19)	−3.14 (−5.86 to −0.42)
Girls	2.23 (−2.77 to 7.23)	2.40 (−2.53 to 7.33)	0.79 (−0.83 to 2.42)	1.68 (−1.77 to 5.13)
Fluoride intake[d,e]	−3.19 (−5.94 to −0.44)	−3.66 (−7.16 to −0.15)	−2.26 (−4.45 to −0.09)	−3.80 (−7.46 to −0.16)

Abbreviations: FSIQ, Full Scale IQ; HOME, Home Observation for Measurement of the Environment; MUF_{SG}, maternal urinary fluoride adjusted for specific gravity.

[a] Adjusted estimates pertain to predicted FSIQ difference for a value spanning the interquartile range (25th to 75th percentiles) and 80th central range (10th to 90th percentiles): (1) MUF_{SG}: 0.33 mg/L, 0.70 mg/L, respectively; (2) fluoride intake: 0.62 mg, 1.04 mg, respectively.

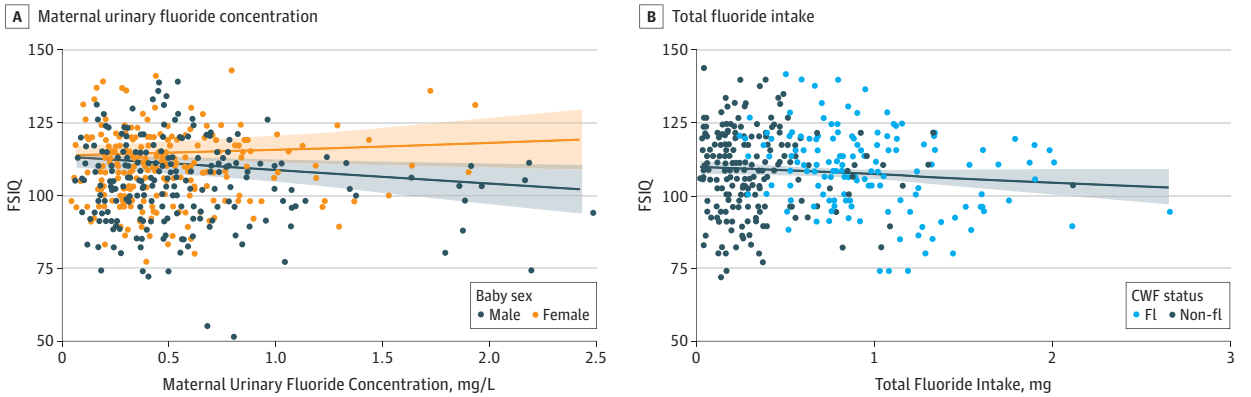
[b] n = 512.

[c] Adjusted for city, HOME score, maternal education, race/ethnicity, and including child sex interaction.

[d] n = 400.

[e] Adjusted for city, HOME score, maternal education, race/ethnicity, child sex, and prenatal secondhand smoke exposure.

Figure 3. Covariate Results of Multiple Linear Regression Models of Full Scale IQ (FSIQ) from Maternal Urinary Fluoride Concentration by Child Sex (n = 512) and Total Fluoride Intake Estimated from Daily Maternal Beverage Consumption (n = 400)



B, Community fluoridation status (CWF) is shown for each woman; black dots represent women living in nonfluoridated (non-Fl) communities and blue dots represent women living in fluoridated (Fl) communities.

Sensitivity Analyses

Adjusting for lead, mercury, manganese, perfluorooctanoic acid, or arsenic concentrations did not substantially change the overall estimates of MUF_{SG} for boys or girls (eTable 2 in the Supplement). Use of MUF adjusted for creatinine did not substantially alter the associations with FSIQ (eTable 2 in the Supplement). Including time of void and time since last void did not substantially change the regression coefficient of MUF_{SG} among boys or girls.

Estimates for determining the association between MUF_{SG} and PIQ showed a similar pattern with a statistically significant interaction between MUF_{SG} and child sex (P for interaction = .007). An increase of 1 mg/L MUF_{SG} was associated with a 4.63 (95% CI, −9.01 to −0.25; P = .04) lower PIQ score in boys, but the association was not statistically significant in girls (B = 4.51; 95% CI, −1.02 to 10.05; P = .11). An increase of 1 mg/L MUF_{SG} was not significantly associated with VIQ in boys (B = −2.85; 95% CI, −6.65 to 0.95; P = .14) or girls (B = 0.55; 95% CI, −4.28 to 5.37; P = .82); the interaction between MUF_{SG} and child sex was not statistically significant (P for interaction = .25) (eTable 3 in the Supplement).

Consistent with the findings on estimated maternal fluoride intake, increased water fluoride concentration (per 1 mg/L) was associated with a 5.29 (95% CI, −10.39 to −0.19) lower FSIQ score among boys and girls and a 13.79 (95% CI, −18.82 to −7.28) lower PIQ score (eTable 4 in the Supplement).

Discussion

Using a prospective Canadian birth cohort, we found that estimated maternal exposure to higher fluoride levels during pregnancy was associated with lower IQ scores in children. This association was supported by converging findings from 2 measures of fluoride exposure during pregnancy. A difference in MUF_{SG} spanning the interquartile range for the entire sample (ie, 0.33 mg/L), which is roughly the difference in MUF_{SG} concentration for pregnant women living in a fluoridated vs a nonfluoridated community, was associated with a 1.5-point IQ decrement among boys. An increment of 0.70 mg/L in MUF_{SG} concentration was associated with a 3-point IQ decrement in boys; about half of the women living in a fluoridated commu-

nity have a MUF_{SG} equal to or greater than 0.70 mg/L. These results did not change appreciably after controlling for other key exposures such as lead, arsenic, and mercury.

To our knowledge, this study is the first to estimate fluoride exposure in a large birth cohort receiving optimally fluoridated water. These findings are consistent with that of a Mexican birth cohort study that reported a 6.3 decrement in IQ in preschool-aged children compared with a 4.5 decrement for boys in our study for every 1 mg/L of MUF.[10] The findings of the current study are also concordant with ecologic studies that have shown an association between higher levels of fluoride exposure and lower intellectual abilities in children.[7,8,26] Collectively, these findings support that fluoride exposure during pregnancy may be associated with neurocognitive deficits.

In contrast with the Mexican study,[10] the association between higher MUF_{SG} concentrations and lower IQ scores was observed only in boys but not in girls. Studies of fetal and early childhood fluoride exposure and IQ have rarely examined differences by sex; of those that did, some reported no differences by sex.[10,27-29] Most rat studies have focused on fluoride exposure in male rats,[30] although 1 study[31] showed that male rats were more sensitive to neurocognitive effects of fetal exposure to fluoride. Testing whether boys are potentially more vulnerable to neurocognitive effects associated with fluoride exposure requires further investigation, especially considering that boys have a higher prevalence of neurodevelopmental disorders such as ADHD, learning disabilities, and intellectual disabilities.[32] Adverse effects of early exposure to fluoride may manifest differently for girls and boys, as shown with other neurotoxicants.[33-36]

The estimate of maternal fluoride intake during pregnancy in this study showed that an increase of 1 mg of fluoride was associated with a decrease of 3.7 IQ points across boys and girls. The finding observed for fluoride intake in both boys and girls may reflect postnatal exposure to fluoride, whereas MUF primarily captures prenatal exposure. Importantly, we excluded women who reported that they did not drink tap water and matched water fluoride measurements to time of pregnancy when estimating maternal fluoride intake. None of the fluoride concentrations measured in municipal drinking water were greater than the maximum acceptable concentration of 1.5 mg/L set by Health Canada; most (94.3%) were lower than the 0.7 mg/L level considered optimal.[37]

Water fluoridation was introduced in the 1950s to prevent dental caries before the widespread use of fluoridated dental products. Originally, the US Public Health Service set the optimal fluoride concentrations in water from 0.7 to 1.2 mg/L to achieve the maximum reduction in tooth decay and minimize the risk of enamel fluorosis.[38] Fluorosis, or mottling, is a symptom of excess fluoride intake from any source occurring during the period of tooth development. In 2012, 68% of adolescents had very mild to severe enamel fluorosis.[39] The higher prevalence of enamel fluorosis, especially in fluoridated areas,[40] triggered renewed concern about excessive ingestion of fluoride. In 2015, in response to fluoride overexposure and rising rates of enamel fluorosis,[39,41,42] the US Public Health Service recommended an optimal fluoride concentration of 0.7 mg/L, in line with the recommended level of fluoride added to drinking water in Canada to prevent caries. However, the beneficial effects of fluoride predominantly occur at the tooth surface after the teeth have erupted.[43] Therefore, there is no benefit of systemic exposure to fluoride during pregnancy for the prevention of caries in offspring.[44] The evidence showing an association between fluoride exposure and lower IQ scores raises a possible new concern about cumulative exposures to fluoride during pregnancy, even among pregnant women exposed to optimally fluoridated water.

Strengths and Limitations

Our study has several strengths and limitations. First, urinary fluoride has a short half-life (approximately 5 hours) and depends on behaviors that were not controlled in our study, such as consumption of fluoride-free bottled water or swallowing toothpaste prior to urine sampling. We minimized this limitation by using 3 serial urine samples and tested for time of urine sample collection and time since last void, but these variables did not alter our results. Second, although higher maternal ingestion of fluoride corresponds to higher fetal plasma fluoride levels,[45] even serial maternal urinary spot samples may not precisely represent fetal exposure throughout pregnancy. Third, while our analyses controlled for a comprehensive set of covariates, we did not have maternal IQ data. However, there is no evidence suggesting that fluoride exposure differs as a function of maternal IQ; our prior study did not observe a significant association between MUF levels and maternal education level.[12] Moreover, a greater proportion of women living in fluoridated communities (124 [76%]) had a university-level degree compared with women living in nonfluoridated communities (158 [66%]). Nonetheless, despite our comprehensive array of covariates included, this observational study design could not address the possibility of other unmeasured residual confounding. Fourth, fluoride intake did not measure actual fluoride concentration in tap water in the participant's home; Toronto, for example, has overlapping water treatment plants servicing the same household. Similarly, our fluoride intake estimate only considered fluoride from beverages; it did not include fluoride from other sources such as dental products or food. Furthermore, fluoride intake data were limited by self-report of mothers' recall of beverage consumption per day, which was sampled at 2 points of pregnancy, and we lacked information regarding specific tea brand.[17,18] In addition, our methods of estimating maternal fluoride intake have not been validated; however, we show construct validity with MUF. Fifth, this study did not include assessment of postnatal fluoride exposure or consumption. However, our future analyses will assess exposure to fluoride in the MIREC cohort in infancy and early childhood.

Conclusions

In this prospective birth cohort study from 6 cities in Canada, higher levels of fluoride exposure during pregnancy were associated with lower IQ scores in children measured at age 3 to 4 years. These findings were observed at fluoride levels typically found in white North American women. This indicates the possible need to reduce fluoride intake during pregnancy.

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Author Contributions: Ms Green and Dr Till had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Green, Lanphear, Martinez-Mier, Ayotte, Muckle, Till.
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Editor's Note

Decision to Publish Study on Maternal Fluoride Exposure During Pregnancy

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The decision to publish this article was not easy.[1] Given the nature of the findings and their potential implications, we subjected it to additional scrutiny for its methods and the presentation of its findings. The mission of the journal is to ensure that child health is optimized by bringing the best available evidence to the fore. Publishing it serves as testament to the fact that *JAMA Pediatrics* is committed to disseminating the best science based entirely on the rigor of the methods and the soundness of the hypotheses tested, regardless of how contentious the results may be. That said, scientific inquiry is an iterative process. It is rare that a single study provides definitive evidence. This study is neither the first, nor will it be the last, to test the association between prenatal fluoride exposure and cognitive development. We hope that purveyors and consumers of these findings are mindful of that as the implications of this study are debated in the public arena.

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Audio

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Fluoride exposure from infant formula and child IQ in a Canadian birth cohort

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ABSTRACT

Background: Infant consumption of formula reconstituted with fluoridated water can lead to excessive fluoride intake. We examined the association between fluoride exposure in infancy and intellectual ability in children who lived in fluoridated or non-fluoridated cities in Canada.

Methods: We examined 398 mother-child dyads in the Maternal-Infant Research on Environmental Chemicals cohort who reported drinking tap water. We estimated water fluoride concentration using municipal water reports. We used linear regression to analyze the association between fluoride exposure and IQ scores, measured by the Wechsler Primary and Preschool Scale of Intelligence-III at 3–4 years. We examined whether feeding status (breast-fed versus formula-fed) modified the impact of water fluoride and if fluoride exposure during fetal development attenuated this effect. A second model estimated the association between fluoride intake from formula and child IQ.

Results: Thirty-eight percent of mother-child dyads lived in fluoridated communities. An increase of 0.5 mg/L in water fluoride concentration (approximately equaling the difference between fluoridated and non-fluoridated regions) corresponded to a 9.3- and 6.2-point decrement in Performance IQ among formula-fed (95% CI: −13.77, −4.76) and breast-fed children (95% CI: −10.45, −1.94). The association between water fluoride concentration and Performance IQ remained significant after controlling for fetal fluoride exposure among formula-fed ($B = -7.93$, 95% CI: −12.84, −3.01) and breastfed children ($B = -6.30$, 95% CI: −10.92, −1.68). A 0.5 mg increase in fluoride intake from infant formula corresponded to an 8.8-point decrement in Performance IQ (95% CI: −14.18, −3.34) and this association remained significant after controlling for fetal fluoride exposure ($B = -7.62$, 95% CI: −13.64, −1.60).

Conclusions: Exposure to increasing levels of fluoride in tap water was associated with diminished non-verbal intellectual abilities; the effect was more pronounced among formula-fed children.

1. Introduction

Fluoride can occur naturally in water and, in some communities, is added to water supplies to reach the recommended concentration of 0.7 mg/L for the prevention of tooth decay (Health Canada, 2010). About 74% of Americans and 38% of Canadians on municipal water are supplied with fluoridated drinking water. Water fluoridation has been reported to reduce the prevalence of tooth decay by 26% to 44% (Iheozor-Ejiofor et al., 2015; National Health and Medical Research Council (NHMRC), 2017) in youth and by 26% (Iheozor-Ejiofor et al.,

Abbreviations: BF, breastfed; FF, formula fed; CI, confidence intervals; HOME, home observation for measurement of the environment; IQ, intelligence quotient; FSIQ, full scale IQ; PIQ, performance IQ; VIQ, verbal IQ; MIREC, maternal-infant research on environmental chemicals; MUF, maternal urinary fluoride; SD, standard deviation

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2015) to 27% (NHMRC, 2017) in adults. Infants who are fed formula reconstituted with fluoridated water have approximately three to four times greater exposure to fluoride than adults (National Research Council (NRC), 2006) on a per body-weight basis. Formula-fed infants residing in fluoridated areas have an approximate 70-fold higher fluoride intake than exclusively breastfed infants (Ekstrand, 1981; Zohoori et al., 2018; United States Environmental Protection Agency, 2010)

The prevalence of enamel fluorosis, a discoloration of enamel resulting from chronic, excessive ingestion of fluoride during tooth development (Brothwell and Limeback, 2003; Buzalaf et al., 2001), is higher among formula-fed infants than breastfed infants (Buzalaf et al., 2001; Do et al., 2012; Fv et al., 2012; Hong et al., 2006; Walton and Messer, 1981). While enamel fluorosis develops from excess fluoride exposure during the first four years of life, (Levy et al., 2010) the first 12 months are the most vulnerable period (Hong et al., 2006). The risk of fluorosis increases with higher levels of fluoride in the water supply for formula-fed infants (Hujoel et al., 2009).

Breastmilk contains extremely low concentrations of fluoride (0.005–0.01 mg/L) due to the limited transfer of fluoride in plasma into breastmilk (Dabeka et al., 1986; Ekstrand, 1981; Ekstrand and Hardell, 1984; Esala et al., 1982; Faraji et al., 2014; Zohoori et al., 2018). Exclusive breastfeeding for six months, which is recommended by current practice guidelines (Critch, 2013; Eidelman, 2012), is reported by 25% of mothers in the United States (Breastfeeding Report Card. United States, 2018) and Canada (Health Canada, 2001). Ninety percent of bottle-fed infants are fed powdered formula (Infant Feeding Practices Survey II) and 75% of mothers report using tap water to reconstitute formula (Van Winkle et al., 1995). Thus, reconstituted formula is the major source of nutrition for many infants in the United States and Canada.

Despite growing concerns about excessive exposure to fluoride during infancy and the vulnerability of the developing brain (Rice and Barone, 2000; Grandjean and Landrigan, 2006), no studies have tested the potential neurotoxicity of using optimally fluoridated drinking water to reconstitute formula during infancy (Harriehausen et al., 2019). Increased fluoride exposure during fetal brain development was associated with diminished IQ scores in two birth cohort studies (Bashash et al., 2017; Green et al., 2019; Valdez Jiménez et al., 2017), among a number of recent studies conducted in endemic fluorosis areas (Karimzade et al., 2014; Dong et al., 2018; Zhang et al., 2015), as well as a 2012 meta-analysis of 27 ecologic studies (Choi et al., 2012). Increased fluoride exposure has also been linked with ADHD-related behaviors in children (Malin and Till, 2015; Bashash et al., 2018; Riddell et al., 2019).

We investigated the association between water fluoride concentration and intellectual abilities of Canadian children who were formula-fed or breastfed. In addition, we tested whether postnatal effects of fluoride exposure on child IQ remained after controlling for fetal exposure.

2. Materials and methods

2.1. Study population

Between 2008 and 2011, the Maternal-Infant Research on Environmental Chemicals (MIREC) program recruited 2001 pregnant women from ten Canadian cities to participate in a longitudinal pregnancy cohort study. Women who could communicate in English or French, were > 17 years, and were < 14 weeks gestation were recruited from prenatal clinics. Participants were excluded if there was a known fetal abnormality, if they had any medical complications, or if there was known illicit drug use during pregnancy. Additional details are in the cohort profile description (Arbuckle et al., 2013).

Of the 610 children who were recruited to participate in the developmental follow-up phase of the study (MIREC-Child Development Plus), 601 completed all testing. Children were recruited from six of the cities in the original cohort (Vancouver, Toronto, Hamilton, Halifax, Kingston, Montreal); approximately half of the children lived in non-fluoridated cities and half lived in fluoridated cities.

This study received ethics approval from Health Canada and York University.

2.2. Infant feeding assessment

When children were between 30 and 48 months of age, mothers completed an infant feeding questionnaire asking, “How old was your baby when you ceased breastfeeding exclusively? At what age did you introduce other type of milk or food to your baby?”. Women who breastfed exclusively for six months or longer were included in the breastfeeding (BF) group; those who reported introducing formula within the first six months (never breastfed or partial breastfeeding) were included in the formula-feeding (FF) group.

To explore the possibility of recall or response bias of mothers completing the questionnaire, we compared information reported by mothers when their children were between 30 and 48 months of age (i.e. time when the questionnaire was completed for classifying the BF and FF groups) with information reported by a subset of women at an earlier visit when their children were between 6 and 8 months of age. Information about infant feeding was only available for 11% of the sample at the infant visit (note that responses could only be matched for women who had stopped breastfeeding at the time the questionnaire was completed at the infant visit). Among women who provided information at both occasions, the median difference for when breastfeeding was reported to be ceased was 0 months; responses were within 1.5 months of each other for two-thirds of this subsample.

We dichotomized feeding status at six months because the Canadian Pediatric Society and American Academy of Pediatrics both recommend exclusive breastfeeding for six months (Critch, 2013; Eidelman, 2012). Moreover, formula-fed infants who are younger than six-months derive most of their nutrition from formula, placing this group at highest risk of exceeding the recommended upper limit (0.7 mg/d) for fluoride (Harriehausen et al., 2019; Institutes of Medicine, 1997; National Research Council (NRC), 2006). Finally, fluoride intake differences become less evident when other dietary sources of fluoride are introduced at around six months (Zohoori et al., 2018).

2.3. Infant fluoride exposure

We estimated fluoride concentrations in drinking water by accessing daily or monthly reports provided by water treatment plants. Water reports were first linked with mothers’ postal codes and the daily or weekly amounts were averaged over the first six-months of the child’s life. We only included participants whose postal codes could be linked to a water treatment plant that provided water fluoride measurements. We also excluded participants who reported that their primary drinking source was from a well or ‘other’ (e.g. bottled water) (Table S1). Further details can be found in our previous report (Till et al., 2018).

To obtain a continuous fluoride exposure estimate collapsed across the BF and FF groups, we estimated fluoride intake from formula (in mg F/day) by multiplying water fluoride concentration by the amount of time that the infant was not exclusively breastfed in the first year using the following equation:

$$\textit{Fluoride intake from formula} = (\textit{water\_F mg/L}) * (1 - \#\textit{mo\_excl\_BF}/11.99) * 0.80\ \textit{L/day}$$

where *water_F mg/L* refers to the average water fluoride concentration and *1-#mo_excl_BF/11.99* represents the proportion over the 12-month period the infant was not exclusively breastfed. A value near one indicates that an infant was primarily formula-fed over the 12 months whereas a value near zero indicates an infant primarily breastfed. We

estimated fluoride intake based on an average of 0.80 L of water used to reconstitute powdered formula as suggested by an infant food diary completed for infants in a prior study (Carignan et al., 2015); the average milk intake at 3 months of age is 0.812 L per day, ranging from 0.523 to 1.124 L (Dewey et al., 1991). Because we did not know the type of formula used (i.e. soy- or milk-based), we did not add fluoride derived from formula to our fluoride intake estimate. Previous studies have indicated that fluoride from water used in formula is a greater source of fluoride than fluoride found in formula (Buzalaf et al., 2004).

2.4. Fetal fluoride exposure

We used maternal urinary fluoride (MUF) adjusted for specific gravity as a proxy of fetal fluoride exposure. MUF, which was derived by averaging three spot samples collected across all three trimesters of pregnancy, was considered our most reliable measure of exposure (Till et al., 2018). Urinary fluoride concentrations were analyzed at the Indiana University School of Dentistry using a modification (Martínez-Mier et al., 2011) of the hexamethyldisiloxane (Sigma Chemical Co., USA) micro-diffusion procedure previously described (Green et al., 2019).

2.5. Intelligence assessment

We assessed children's intellectual abilities between ages 3.0 and 4.0 years with the Wechsler Preschool and Primary Scale of Intelligence-III (Wechsler, 2002) using United States population-based normative data (*mean* = 100, *SD* = 15). Outcomes included Full Scale IQ (FSIQ), a measure of global intellectual functioning, Verbal IQ (VIQ), a measure of verbal reasoning, and Performance IQ (PIQ), a measure of non-verbal reasoning and visual-motor coordination skills.

2.6. Covariates

We adjusted for potential confounding by selecting covariates *a priori* that have been associated with fluoride, breastfeeding, and children's intellectual abilities. Final covariates included child's sex and age at testing, maternal education (dichotomized as either a bachelor's degree or higher versus trade school diploma or lower), maternal race (white or not), second-hand smoke in the home (yes, no), and quality of the child's home environment (measured at time of testing using the Home Observation for Measurement of the Environment (HOME) - Revised Edition (Caldwell and Bradley, 1984). For each analysis, a covariate was retained in the final model if its *p*-value was < 0.20 or its inclusion changed the regression coefficient of water fluoride concentration or fluoride intake from formula by more than 10% (Kleinbaum et al., 1982). City was not included as a covariate in Model 1 because it was strongly multi-collinear with water fluoride concentration (VIF > 20). City was also excluded from Model 2 because fluoride intake from formula is a function of water fluoride concentration and was therefore deemed redundant.

2.7. Statistical analyses

We used linear regression to model differences in child IQ by water fluoride concentration while controlling for covariates. In our first model, we examined whether feeding status (BF or FF) modified the impact of water fluoride. In our second model, we estimated the association between fluoride intake from formula and child IQ. We controlled potential confounders by including them simultaneously with predictors.

In secondary analyses, we controlled for MUF during pregnancy in both models to account for fetal exposure. We also tested for sex-specific effects because we previously found that MUF concentration was only associated with diminished FSIQ in males (Green et al., 2019).

Regression diagnostics indicated no assumption violations pertaining to linearity, normality, or homogeneity of variance. Specifically, QQ-plots of residuals were consistent with a normal distribution and plots of residuals against fitted values did not suggest any assumption violations. Two observations were investigated based on a plot of Cook's D that suggested they may be influential; these cases had extremely low IQ scores that were more than 2.5 standard deviations from the sample mean. In a sensitivity analyses, we re-estimated the models after removing these two observations. Finally, variance inflation factors indicated no concerns with excessive multicollinearity.

To aid interpretation, we divided all regression coefficients by 2 so that they represent the predicted IQ difference per 0.5 mg/L of fluoride in tap water or 0.5 mg fluoride from formula; 0.5 mg/L corresponds to the approximate difference between mean water fluoride level in fluoridated versus non-fluoridated regions in our sample.

3. Results

Of the 601 children who completed neurodevelopmental testing, 591 (99%) mother–child pairs completed the infant feeding questionnaire and IQ testing (BF: $n = 296$; FF: $n = 295$). Of these, 398 (67.3%) pairs reported drinking tap water, had water fluoride data and complete covariate data (BF: $n = 200$; FF: $n = 198$). The demographic characteristics of women included in the current analyses ($n = 398$) were not substantially different from the original MIREC cohort ($N = 1945$) or the subset without complete water fluoride and covariate data ($n = 203$) (Table S2, Mcknight-hanes et al., 1988).

Among the BF group, more women who lived in a fluoridated region had a bachelor's degree or higher compared with those in a non-fluoridated region (86 vs. 74%, $p = .001$) (Table 1). Compared with the FF group, women in the BF group were more educated, more likely to be married or common law, and had higher HOME scores (all $ps < 0.05$). The BF group had significantly higher FSIQ and VIQ scores relative to the FF group (Table 1; Fig. S1). Children living in a fluoridated region had a significantly lower PIQ score, but higher VIQ score, relative to children living in a non-fluoridated region (Table 1; Fig. S1).

Water fluoride concentration was correlated with MUF (r = 0.37, $p < .001$) and estimated fluoride intake from formula (r = 0.79, $p < .001$); MUF was correlated with fluoride intake from formula (r = 0.55, $p < .001$).

3.1. Feeding status

The mean duration of exclusive breastfeeding was 4.98 months (*SD* = 3.48); 54 (13.6%) women reported never breastfeeding, 32 (8%) reported discontinuing breastfeeding after the first three months, and 200 (50.2%) reported continuing to breastfeed at six months or longer. Water fluoride concentration did not significantly differ between the BF ($M = 0.32$ mg/L) and FF groups ($M = 0.29$ mg/L; $p = .18$).

3.2. Model 1: IQ scores and water fluoride concentration by feeding status

A 0.5 mg/L increase in water fluoride concentration was associated with a decrease of 4.4 FSIQ points (95% CI: −8.34, −0.46, $p = .03$) in the FF group, but it was not significantly associated with FSIQ in the BF group ($B = -1.34$, 95% CI: −5.04, 2.38, $p = .48$) (Table 2; Fig. 1A); the interaction between water fluoride and feeding status was not statistically significant ($p = .26$). Controlling for fetal exposure by adding MUF to the model resulted in non-significant associations between water fluoride concentration and FSIQ in both the FF ($B = -3.58$, 95% CI: −7.83, 0.66, $p = .098$) and BF groups ($B = -1.69$, 95% CI: −5.66, 2.27, $p = .40$). Removing two cases with extreme IQ scores from the models resulted in non-significant associations between water fluoride concentration and FSIQ in both groups (Table S3).

Water fluoride concentration was significantly associated with lower PIQ in the FF ($B = -9.26$, 95% CI: −13.77, −4.76, $p < .001$) and the BF groups ($B = -6.19$, 95% CI: −10.45, −1.94, $p = .004$)

Table 1
Demographic characteristics and exposure outcomes for mother-child pairs by infant feeding status.

Characteristic	Breastfed ≥ 6 mo. (n = 200)		Formula-fed (n = 198)		
	Fluoridated (n = 83) Mean (SD)/%	Non-fluoridated (n = 117) Mean (SD)/%	Fluoridated (n = 68) Mean (SD)/%	Non-fluoridated (n = 130) Mean (SD)/%	*p* value comparing BF and FF groups
Maternal characteristics					
Years of age at delivery	32.54 (3.64)	32.86 (4.79)	32.91 (4.42)	32.39 (5.11)	.73
Net household income > $70 K	70.3	72.9	79.7	68	.88
Caucasian	88	93	88	84	.11
Maternal education					
Trade school diploma/high school	14	26*	28	42*	< .001
Bachelor's degree or higher	86	74*	72	58*	< .001
Employed at time of pregnancy	92	90	94	84*	.40
Married/common-law (at time of testing)	100	99	96	92	.001
Smoked in trimester 1	0	1.7	2.9	3.8	.17
Parity (first birth)	45	51	43	47	.61
Number of months exclusively breastfeeding	7.54 (2.95)	7.45 (2.46)	2.63 (2.08)	2.37 (2.13)	< .001
Child characteristics					
Years of age at IQ testing	3.48 (0.29)	3.34 (0.31)*	3.53 (0.28)	3.37 (0.3)*	.32
Female sex	51	53	54	47	.32
HOME total score	48.71 (3.42)	48.09 (3.86)	47.59 (4.33)	46.55 (4.76)	< .001
Second hand smoke in home	2.5	3.4	4.4	5.4	.43
Gestational age in weeks	39.22 (1.55)	39.17 (1.52)	38.68 (2.48)	39.15 (1.53)	.24
Birth weight (kg)	3.42 (0.50)	3.49 (0.46)	3.43 (0.62)	3.46 (0.52)	.75
Full Scale IQ	109.9 (12.4)	108.9 (13.6)	106.1 (15.8)	106.8 (13.5)	.03[a]
Verbal IQ[b]	115.1 (11.3)	110.4 (12.4)*	110.9 (14.9)	107.1 (13.3)	.00[a]
Performance IQ[b]	102.0 (15.2)	105.6 (15.8)	99.7 (15.1)	105.6 (13.4)*	.69
Exposure variables					
Water fluoride concentration (mg/L)	0.58 (0.08)	0.13 (0.06)*	0.59 (0.07)	0.13 (0.05)*	.18
% living in fluoridated region	41.5		34.3		14
Infant fluoride intake (mg F/day)	0.12 (0.07)	0.02 (0.02)*	0.34 (0.12)	0.08 (0.04)*	< .001
MUF concentration (mg/L)	0.70 (0.39)	0.42 (0.28)*	0.64 (0.37)	0.38 (0.27)*	.07

Abbreviations: HOME = Home Observation for Measurement of the Environment; MUF = Maternal urinary fluoride, adjusted for specific gravity; SD = standard deviation.

* $p < .05$ for comparing participants in the breastfed or formula-fed group living in a fluoridated versus non-fluoridated region.

[a] *p*-value reported for main effect of feeding status from 2 × 2 ANCOVA, adjusting for maternal education (binary), maternal race (binary), child's age at IQ testing (continuous), child's sex, HOME total score (continuous), second-hand smoke status in the child's house (yes, no), and water fluoridation status (fluoridated versus non-fluoridated).

[b] Main effect of fluoridation status, adjusting for maternal education (binary), maternal race (binary), child's age at IQ testing (continuous), child's sex, HOME total score (continuous), second-hand smoke status in the child's house (yes, no), and feeding status (BF vs. FF); VIQ: $p = .02$; PIQ: $p < .001$.

Table 2
Adjusted difference in IQ scores at 3–4 years of age per 0.5 mg/L water fluoride concentration and 0.5 mg infant fluoride intake from formula per day, with and without adjusting for maternal urinary fluoride (MUF).

Exposure variable	N	FSIQ B (95% CI)	N	PIQ B (95% CI)	N	VIQ B (95% CI)
Model 1						
Water Fl (mg/L)	398		393		397	
Formula-fed		−4.40 (−8.34, −0.46)*		−9.26 (−13.77, −4.76)*		0.89 (−2.87, 4.65)
Breastfed		−1.34 (−5.04, 2.38)		−6.19 (−10.45, −1.94)*		3.06 (−0.49, 6.61)
Water Fl (mg/L) adjusted for MUF[a]	350		345		349	
Formula-fed		−3.58 (−7.83, 0.66)		−7.93 (−12.84, −3.01)*		2.60 (−1.98, 7.16)
Breastfed		−1.69 (−5.66, 2.27)		−6.30 (−10.92, −1.68)*		4.20 (−0.06, 8.45)
Model 2						
Fluoride intake from formula	398	−2.69 (−7.38, 2.01)	393	−8.76 (−14.18, −3.34)*	397	3.08 (−1.40, 7.55)
Fluoride intake from formula adjusted for MUF[b]	350	−1.94 (−7.09, 3.21)	345	−7.62 (−13.64, −1.60)*	349	3.05 (−1.89, 7.98)

Abbreviations: Fl = fluoride; MUF = maternal urinary fluoride; Regression model adjusted for maternal education (binary), maternal race (binary), child's age at IQ testing (continuous), child's sex, HOME total score (continuous), and second-hand smoke status in the child's house (yes, no).

* $p < .05$.

[a] MUF was not significantly associated with FSIQ score ($B = -1.08$, 95% CI: −1.54, 0.47, $p = .29$), PIQ score ($B = -1.31$, 95% CI: −3.63, 1.03, $p = .27$), or VIQ score ($B = -0.34$, 95%CI: −2.21, 1.59, $p = .73$). Note: regression coefficients represent the predicted IQ difference per 0.5 mg/L MUF; effect for both sexes is reported. Variance inflation factor (VIF) for water Fl is 2.41 for FSIQ, 2.41 for PIQ, and 2.40 for VIQ when MUF is entered in the model.

[b] MUF is significantly associated with PIQ score ($B = -2.38$, 95% CI: −4.62, −0.27, $p = .04$), but not FSIQ score ($B = -1.50$, 95% CI: −3.41, 0.43, $p = .13$) or VIQ score ($B = -0.11$, 95% CI: −1.94, 1.74, $p = .91$); Note: regression coefficients represent the predicted IQ difference per 0.5 mg/L MUF; effect for both sexes is reported. Variance inflation factor (VIF) for infant fluoride intake is 1.10 for FSIQ, 1.12 for PIQ, and 1.10 for VIQ when MUF is entered in the model

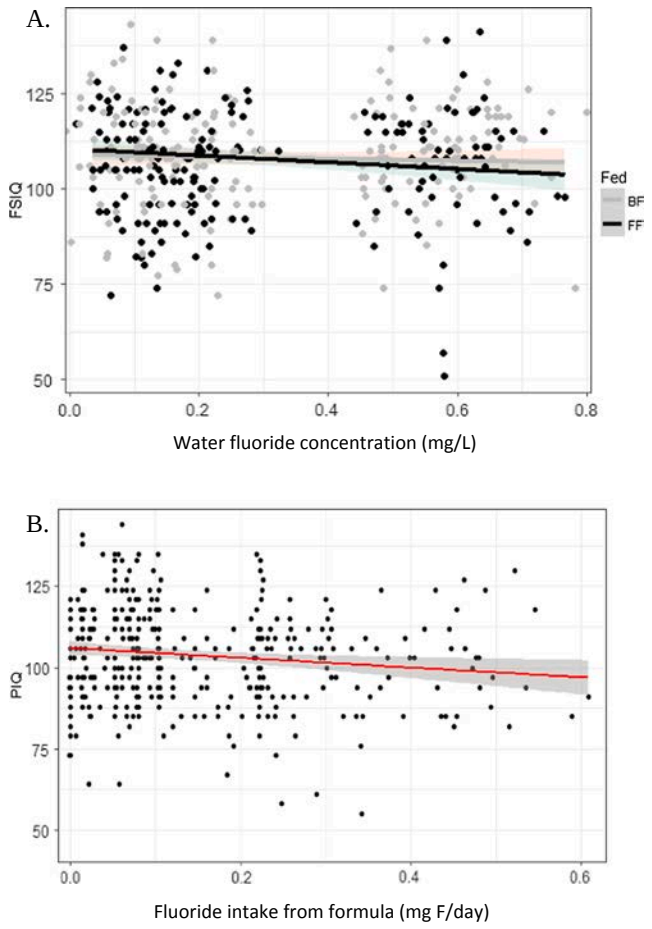

Fig. 1. A. Water fluoride concentration as a predictor of Full Scale IQ with an interaction by formula-fed (FF) vs. breastfed (BF) group. Black data points represent the FF group and grey data points represent the BF group. B. Fluoride intake from formula (mg F/day) as a predictor of Performance IQ score.

(Table 2); the interaction was not significant (p = .26). Controlling for MUF, water fluoride concentration remained significantly associated with PIQ in the FF (B = −7.93 95% CI: −12.84, −3.01, p = .002) and BF groups (B = −6.30, 95% CI: −10.92,-1.68, p = .008). Likewise, the associations between water fluoride concentration and PIQ remained significant for both groups after removing two cases with extreme IQ scores (Table S3).

In contrast, water fluoride concentration was not associated with VIQ in the FF (B = 0.89, 95% CI: −2.87, 4.65, p = .64) or BF group (B = 3.06, 95% CI: −0.49, 6.61, p = .09); these associations remained non-significant after controlling for MUF (Table 2) and removing two cases with extreme IQ scores (Table S3).

3.3. Model 2: IQ scores and fluoride intake from formula

Fluoride intake from formula was not significantly associated with FSIQ (B = −2.69, 95% CI: −7.38, 2.01, p = .26) or VIQ (B = 3.08, 95% CI: −1.40, 7.55, p = .18) (Table 2). In contrast, a 0.5 mg increase in fluoride intake predicted an 8.76-point decrement in PIQ score (95% CI: −14.18, −3.34, p = .002; Fig. 1B). Adding MUF to the PIQ model slightly attenuated the association between fluoride intake and PIQ (B = −7.62, 95% CI: −13.64, −1.60, p = .01) (Table 2). Removing two cases with extreme IQ scores did not appreciably alter the association between fluoride intake and PIQ score, with and without adjustment for MUF (Table S3).

4. Discussion

For each 0.5 mg/L increase in water fluoride concentration, we found a decrease of 4.4 FSIQ points among preschool children who were formula-fed in the first six months of life; 0.5 mg/L is the approximate difference in mean water fluoride level between fluoridated (0.59 mg/L) and non-fluoridated (0.13 mg/L) regions. In contrast, we did not find a significant association between water fluoride concentration and FSIQ among exclusively breastfed children. The association between water fluoride concentration and FSIQ must be interpreted with caution, however, because the association became non-significant when two outliers were removed. We observed an even stronger association between water fluoride and PIQ (non-verbal intelligence). A 0.5 mg/L increase in water fluoride level predicted a decrement in PIQ in both the formula-fed (9.3-points) and the breastfed groups (6.2-points). Adjusting for fetal exposure or removing two extreme scores did not appreciably alter these results.

We observed converging results using fluoride intake from formula, which is a continuous, time-weighted exposure estimate. For each 0.5 mg/day of fluoride intake, we found an 8.8-point decrement in PIQ; adjusting for fetal exposure using MUF attenuated the association only slightly (7.6-point decrement in PIQ). MUF was also negatively associated with PIQ (2.4-point decrement for each 0.5 mg/L increase in MUF). The fluoride intake estimate may reflect a more refined measure of exposure in infancy because it captures differences in both water fluoride level and the proportion of time each child was given formula over the first year of life. Yet, our binary classification of whether a child was exclusively breastfed for 6 months may better capture children who are most vulnerable to neurotoxic effects of fluoride because it subsets those exposed to fluoride during the early infancy period when the brain undergoes significant development (Huttenlocher and Dabholkar, 1997; Kostovic, 2006). Taken together, these findings suggest that using optimally fluoridated water (0.7 mg/L) to reconstitute infant formula may diminish the development of intellectual abilities in young children, particularly for non-verbal abilities. The findings also suggest that both prenatal and postnatal fluoride exposure affect the development of non-verbal intelligence to a greater extent than verbal intelligence. Prior studies examining prenatal exposure to fluoride and IQ showed a similar pattern (Bashash et al., 2017; Green et al., 2019).

Consistent with prior studies showing a positive effect of breastfeeding on cognition (Horta et al., 2015), children in the breastfed group had higher FSIQ and VIQ scores relative to the formula-fed group, regardless of fluoridation status (Table 1); higher education and income levels in the breastfed group likely accounts for part of this association (Walfisch et al., 2013). In contrast, the breastfed group did not differ significantly from the formula-fed group with respect to PIQ score. Children who lived in non-fluoridated regions showed higher PIQ scores than children who lived in fluoridated regions, though this difference was significant only for the formula-fed group, perhaps reflecting a higher vulnerability of nonverbal abilities to fluoride exposure in infancy.

Most studies of fluoride exposure from infant formula consumption have focused on risk for later development of dental enamel fluorosis (Brothwell and Limeback, 2003; Hong et al., 2006; Berg et al., 2011). Beyond fluorosis, the safety of fluoride exposure from infant formula has not been rigorously tested, despite warnings of overexposure (Diesendorf and Diesendorf, 1979). A recent study showed that up to 59% of infants younger than four months exceed the upper limit (0.1 mg/kg/day) (Institutes of Medicine, 1997) when optimally fluoridated water is used to reconstitute infant formula (Harriehausen et al., 2019); 33% and 14.3% of six- and nine-month old infants exceeded the upper limit threshold, respectively. Conversely, breastfed infants receive very low fluoride intake (generally less than 0.01 mg/L), even in communities with fluoridated water (Dabeka et al., 1986; Ekstrand, 1981; Fomon et al., 2000). Our estimate of fluoride intake (0.34 mg F/day) among formula-fed infants who live in a fluoridated region is an

underestimate of actual fluoride intake because we did not include fluoride from other sources, such as the fluoride found in the formula or foods; thus, the association between fluoride intake and IQ scores among formula-fed infants may be stronger than the association obtained in our analysis.

Our results, which showed that higher fluoride exposure in infancy was associated with diminished IQ scores in young children, are consistent with two longitudinal birth cohort studies. In one study involving 299 mother–child pairs living in Mexico City, there was a decrement of 3.2 IQ points in preschool aged children for every 0.5 mg/L of MUF level during pregnancy (Bashash et al., 2017). In the other study, which we conducted using the same Canadian cohort, we reported a decrement of 2.2 IQ points among preschool aged boys for every 0.5 mg/L of MUF level during pregnancy (Green et al., 2019). When MUF was included as a covariate in the current study, the association between MUF and FSIQ was not significant (see Table 2, note a). This discrepancy arises because (1) Green et al. (2019) did not include fluoride exposure in infancy as a covariate and (2) Green et al. (2019) estimated sex-specific MUF effects whereas the current study estimated an overall MUF effect.

The beneficial effects of fluoride predominantly occur at the tooth surface, after teeth have erupted (Limeback, 1999). Fluoride contributes to the prevention of dental caries primarily when it is topically applied to teeth, such as brushing with fluoridated toothpaste (Featherstone, 2001; Limeback, 1999; NRC, 2006; Pizzo et al., 2007; Warren and Levy, 2003). Because fluoride is not essential for growth and development (Scientific Committee on Health and Environmental Risks (SCHER), 2011), there is no recommended intake level of fluoride during fetal development or in the first six months of life before teeth have erupted. Accordingly, the Canadian Pediatric Society recommends administering supplemental fluoride (i.e. systemic exposure) only when primary teeth begin to erupt (American Dental Association) (at approximately 6 months) and only if the child is susceptible to high caries activity and is not exposed to other fluoride-based interventions, such as toothbrushing or water fluoridation (Godel, 2002).

The American Dental Association (Berg et al., 2011; American Dental Association, 2018) advises parents to use optimally fluoridated drinking water to reconstitute concentrate infant formulas, while being cognizant of the potential risk of mild enamel fluorosis development. This recommendation is echoed by the Centers for Disease Control and Prevention (Community Water Fluoridation. Infant Formula) as well as the U.S. Department of Health and Human Services (2015). The Canadian Dental Association (2019) recommends using water with low fluoride concentration (or ready-to-feed formula) when the fluoride level in drinking water is above the optimal level. In addition to tap water, which is reportedly used by 93% of caregivers who feed formula to infants (Brothwell and Limeback, 2003), “nursery” water (which may contain up to 0.7 mg F/L) is marketed for reconstituting formula and sold in Canada and the United States. The availability of fluoridated nursery water gives the false impression that fluoride exposure during early infancy is beneficial prior to teeth eruption.

Formula-fed infants who reside in fluoridated areas have a 70-fold higher intake of fluoride than exclusively breastfed infants (Ekstrand, 1981; Zohoori et al., 2018; United States Environmental Protection Agency, 2010). Formula-fed infants also retain more fluoride than breastfed infants (Zohoori et al., 2018; Ekstrand and Hardell, 1984) because infants have a limited capacity to excrete fluoride before renal function reaches its full capacity at about two years of age (National Research Council (NRC), 2006; Zohoori et al., 2018). Fluoride absorption also depends on the presence of other nutrients (Health Canada, 2010); when fluoride intake is exclusively from reconstituted formula, the bioavailability of fluoride is 65%, whereas a varied diet reduces fluoride absorption in tissues and bone to about 47% (Ekstrand and Ehrnebo, 1979). These factors place formula-fed infants at an even higher risk of fluoride toxicity.

Our study has some limitations. First, infant formulas vary in fluoride content. Ready-to-use formulas typically have less fluoride than powdered formula (Dabeka and McKenzie, 1987; Fomon et al., 2000); information about formula type was only available for 100 of 198 (50.5%) participants in the formula group; of those, 75% reported using powdered formula, which is the most common type of formula used by the general population (Infant Feeding Practices Survey II; Fomon et al., 2000). Variability in fluoride content is also seen across different types of powdered formula (United States Environmental Protection Agency, 2010; Harriehausen et al., 2019; Mahvi et al., 2010). Additionally, soy-based formula reconstituted with distilled water has more fluoride (0.24–0.30 mg/L depending on whether it is ready-to-feed or concentrated) than milk-based powdered formulas (0.12–0.17 mg/L) (Harriehausen et al., 2019; Van Winkle et al., 1995). Although we lacked data on brand of formula, we have no reason to expect that use of powdered versus ready-to-feed or soy- versus milk-based formula would differ by fluoridation status. Moreover, our effects were primarily based on water fluoride content, which is the major source of fluoride (Buzalaf et al., 2001). Second, we did not have specific information on the type of water (bottled versus tap) used to reconstitute formula. However, mothers typically report using tap water for reconstituting formula (Van Winkle et al., 1995) and we only included children of women who reported drinking tap water in our analyses. Third, there is potential for non-differential misclassification of the feeding status variable because mothers may have been confused by the definition of exclusive breastfeeding on the questionnaire or the responses may have been affected by recall or response bias. As with any survey, women could be confused by the question, but given the demographic of the sample – highly educated, English speaking, and non-teenage mothers – confusion seems less likely. Fourth, our method of estimating infant fluoride intake has not been validated. Finally, children were tested between 3 and 4 years of age and we have no information regarding other possible sources of fluoride that occurred between post-weaning and the age of testing. Thus, other sources of fluoride (e.g. dental products) or more frequent brushing, might differ between participants who lived in fluoridated versus non-fluoridated communities or among those in the breastfeeding versus formula-feeding group. To control for these potential differences, we included maternal education in all models. In addition, the design of our study compares water fluoride level and IQ scores in the formula-fed children using the breast-fed children as a control.

In summary, fluoride intake among infants younger than 6 months may exceed the tolerable upper limits if they are fed exclusively with formula reconstitued with fluoridated tap water. After adjusting for fetal exposure, we found that fluoride exposure during infancy predicts diminished non-verbal intelligence in children. In the absence of any benefit from fluoride consumption in the first six months, it is prudent to limit fluoride exposure by using non-fluoridated water or water with lower fluoride content as a formula diluent.

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Contributors statement

Dr Till conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. Ms Green designed the study, curated the data, carried out the initial data analysis,

reviewed and revised the manuscript. Drs Flora and Hornung supervised data analysis, reviewed and revised the manuscript. Ms. Farmus assisted with data analysis, reviewed and revised the manuscript. Dr Martinez-Mier reviewed and revised the manuscript and supervised the analysis of maternal urinary fluoride. Mr Blazer collected the water fluoride data from water treatment plants and reviewed the manuscript. Drs Ayotte and Muckle assisted with initial data collection, and critically reviewed and revised the manuscript. Dr Lanphear conceptualized the study, and critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.105315.

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Ingestion of infant formula constituted from fluoridated water associated with IQ deficit

Till C, Green R, Flora D, Hornung R, Martinez-Mier EA, Blazer M, et al. Fluoride exposure from infant formula and child IQ in a Canadian birth cohort. *Environ Int* 2020;134:105315.

Question Among otherwise normal preschool children, what is the association between fluoridated water used to constitute formula as infants/toddlers and IQ?

Design Multicenter, prospective study drawn from participants in the Maternal-Infant Research on Environmental Chemicals (MIREC) program.

Setting 6 cities across Canada.

Participants 398 mother-child dyads, the children of which were 3-4 years old.

Intervention Wechsler Primary and Preschool Scale of Intelligence-III.

Outcomes IQ score.

Main Results 38% of the dyads lived in cities with fluoridated water. An increase of 0.5 mg/L in water fluoride concentration corresponded to a 9.3- and 6.2-point decrement in Performance IQ among both formula-fed (95% CI: −13.77 to −4.76) and breast-fed children (95% CI: −10.45 to −1.94), respectively.

Conclusions Ingestion of formula constituted from fluoridated water is associated with Performance IQ deficits.

Commentary This study by Till et al used data from the MIREC Study to demonstrate that fluoride intake from infant formula constituted from tap water is associated with lower performance IQ at age 3-4 years. Despite some limitations, eg, the use of estimated vs directly measured exposures to fluoride, the possibility of bias or confounding appears low. The results are consistent with increasing evidence suggesting that early life exposure to fluoride (prenatal and infancy) is associated with adverse neurobehavioral impacts. Evidence includes experimental studies in rodents as well as 3 recent longitudinal birth cohort studies (1 involving MIREC and 2 involving ourselves and colleagues) demonstrating significant associations between individual measures of prenatal fluoride exposure and lower performance on offspring measures of intelligence and behavior.[1-3] Overall, these studies inform the ongoing debate over the benefits vs risks associated with the fluoridation of water. Clearly, more research is needed. Meanwhile, since the beneficial effects of fluoride predominantly occur at the tooth surface after teeth have erupted, whereas fluoride is not essential for growth and development, a cautious step could be avoidance of fluoridated products and water by women during pregnancy and by infants during the first 6 months of life.

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Mandatory vaccine policies associated with increased vaccination rates and decreased measles incidence

Vaz OM, Ellingson MK, Weiss P, Jenness SM, Bardají A, Bednarczyk RA, et al. Mandatory Vaccination in Europe. *Pediatrics* 2020;145: pii e20190620.

Question Among children living in Europe, what is the association between mandatory vaccination and vaccine-preventable disease reduction?

Design Data analysis from the data banks of the European Centre for Disease Prevention and Control and the World Health Organization.

Setting 29 European countries.

Participants Children vaccinated.

Intervention Vaccination rates from 2006 to 2015 for measles, 2006 to 2016 for pertussis, and mandatory vaccination policies.

Outcomes Measles and pertussis vaccine coverage and the annual incidence of these diseases.

Main Results Mandatory vaccine policies were associated with higher vaccination prevalence, 3.71% (95% CI, 1.68 - 5.74) and 2.14% (95% CI, 0.13 to 4.15) for measles and pertussis, respectively. Some countries imposed a monetary penalty for non-compliance. Every €500 increase in the maximum penalty demonstrated an increase of 0.8% and 1.1% for measles pertussis vaccination prevalence, respectively ($P < .0001$ for both). Only countries without non-medical exemptions demonstrated an association with a lower measles rate compared with countries without a mandatory vaccine policy, adjusted incidence rate ratio, 0.14 (95% CI, 0.05 to 0.36). Pertussis rates were not statistically different.

Conclusions Mandatory vaccination policies were associated with higher vaccination rates and a decreased measles incidence.

Is Water Fluoridation Effective?

According to most major sources, estimates of fluoridation effectiveness amount to at most a reduction of only one-half cavity per child. Low end estimates find **no significant reduction at all**. Children aged 6-17 average 2.1 cavities in their permanent teeth[1]:

- Cochrane Collaboration[2] (2015): 26% (**0.5 cavity per child**)
- CDC[3] (2018): 25% (**0.5 cavity per child**)
- Iowa Fluoride Study[4] (2018): **No significant reduction**
- World Health Organization data[5] (2005): **No evidence of fluoridation's effectiveness**

There is already a consensus including CDC, Cochrane Collaboration, the Iowa Fluoride Study and others that fluoride's effectiveness in preventing cavities is mainly topical (not swallowed).

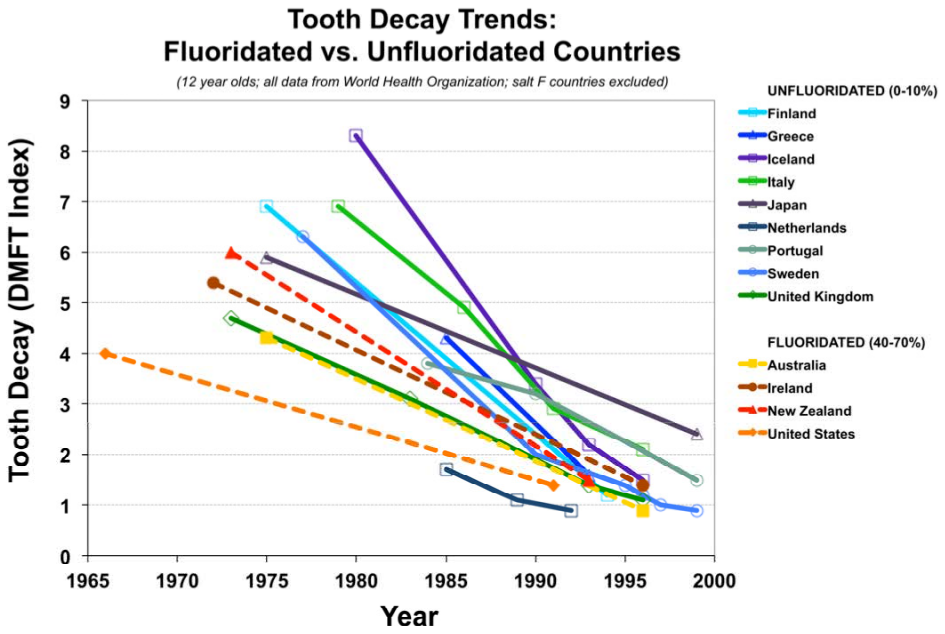
The Cochrane Collaboration is considered the gold standard of evaluating effectiveness. It said the cavity reduction referenced above was *"**based predominantly on old studies and may not be applicable today**."*

> *"Over 97% of the 155 studies were at a high risk of bias, which reduces the overall quality of the results… We did not identify any evidence… to determine the effectiveness of water fluoridation for preventing caries in adults… There is insufficient evidence to determine whether water fluoridation results in a change in disparities in caries levels across socio-economic status."*

The Iowa Fluoride Study (IFS), funded by the National Institutes of Health, is the most comprehensive, ongoing research project in the U.S., the only one measuring all sources of fluoride ingestion. The 2018 study from IFS referenced above found no significant correlation between ingested fluoride and cavity reduction, further validating a 2009 study[6] from IFS that stated:

> *" … achieving a caries-free status may have relatively little to do with fluoride **intake** (emphasis in the original) … recommending an 'optimal' fluoride intake is problematic."*

Finally, World Health Organization data show cavity rates in children (age 12) have dropped as much in nations that don't fluoridate (darker solid lines) as in nations that do (red/yellow dotted lines)**.** *(See graph)*



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U.S. FEDERAL COURT

ACTION NO. 17-CV-02162

FOOD AND WATER WATCH, *et al.* v. U.S. EPA

EXPERT DECLARATION OF PHILIPPE GRANDJEAN, MD, DMSc

PREPARED ON BEHALF OF PLAINTIFFS

20 May 2020

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I, Philippe Grandjean, MD, DMSc, declare that:

1. I am a physician and environmental epidemiologist and serve as both an Adjunct Professor at the Harvard T.H. Chan School of Public Health, and Professor and Chair of Environmental Medicine at the University of Southern Denmark.

2. I was asked by Plaintiffs' counsel to provide an evaluation of the neurological health risks associated with the exposure to fluoride in drinking water.

I. SUMMARY OF QUALIFICATIONS

3. A complete summary of my qualifications and publications can be found in my Curriculum Vitae, which has been marked as Plaintiffs' Exhibit 3 and attached herein.

4. Over the past 25 years, my research has focused on developmental exposures to environmental chemicals and the association with adverse health effects in children, as described in my book "Only One Chance" (2013) published by Oxford University Press.

5. My research has been entirely funded by public sources, mainly the National Institutes of Health (NIH). In 2003-2007, my study of children's vulnerability to environmental immunotoxicants was supported by the U.S. Environmental Protection Agency (EPA). My current funding as principal investigator includes grants from the Superfund Research Program at the National Institute of Environmental Health Sciences and the U.S. Agency for Toxic Substances and Disease Registry (ATSDR).

6. I have published about 500 scientific papers, of which most are research articles in international scientific journals with peer review. My h-index in the Web of Science data base is 70, and my work is cited in scientific journals well over a thousand times every year. Seven of my articles published in the last 10 years have earned the attribute "Highly Cited Paper," i.e., they received enough citations to place them in the top 1% of published papers in the field.

7. My study on the neurodevelopmental effects of prenatal mercury exposure in a birth cohort from Faroe Islands was relied upon by the EPA as the critical study for the Agency's derivation of a

Reference Dose for methylmercury (EPA 2001).

8. I have served as a technical advisor to the World Health Organization on environmental health issues, including five occasions where I was elected Rapporteur. I have also served on, sometimes chaired, or acted as rapporteur for, expert committees under the auspices of the EPA, ATSDR, Food & Drug Administration (FDA); NIH; White House Office of Science and Technology Policy; International Agency for Research on Cancer (IARC), European Commission, European Environmental Agency, European Food Safety Authority, and other organizations. I have also served for over 30 years as Consultant in Toxicology for the Danish Ministry of Health.

9. I am (Founding) Editor-in-Chief of the journal *Environmental Health* (since 2002), which ranks among the most frequently cited journals in the field. I also serve or have served on editorial boards of about a dozen journals within medicine, environmental science, and toxicology. As editor and as reviewer for other major journals, I frequently evaluate manuscripts on environmental epidemiology and toxicology.

10. I have received various awards and honors for my scientific work, including the John R. Goldsmith Award from the International Society for Environmental Epidemiology, which is given to investigators for "sustained and outstanding contributions to the knowledge and practice of environmental epidemiology."

11. I have been retained as an expert on the impact of environmental chemicals on human health by government bodies, including the U.S. Department of Justice (on behalf of the EPA) and the State of Minnesota.

12. I first began studying fluoride in 1980 at the suggestion of Dr. Irving J. Selikoff, who was my mentor at the Mt. Sinai School of Medicine during my two-year Senior Fulbright Scholarship. Upon returning to Denmark, I initiated a series of studies on a cohort of workers who had been occupationally exposed to fluoride. I have remained involved in fluoride research since that time and have published 16 peer-reviewed reports on fluoride exposure and toxicity in humans.

13. In 1984, I drafted the Environmental Criteria Document on fluoride for the World Health

Organization (WHO). Ten years later, I drafted the Criteria Document for an occupational exposure limit value for fluorine for the European Commission. In 2006, I served as a reviewer of the National Research Council's report *Fluoride in Drinking Water: A Scientific Review of EPA's Standards*.

14. During the past 10 years, my research work on fluoride has focused on its developmental effects on the brain. In 2012, I published a meta-analysis of the epidemiological studies on fluoride and IQ (Choi et al. 2012); in 2015, I published an epidemiological study of fluoride and IQ in China (Choi et al. 2015); and, in December of 2019, I published an updated review of fluoride neurotoxicity, which relied in part on the work that I have performed in this case (Grandjean 2019).

15. In addition to my work on fluoride, I also have expertise in Benchmark Dose (BMD) analysis. My experience doing BMD analysis started about 20 years ago in connection with my research on the neurodevelopmental effects of methylmercury in the Faroe Islands that was selected as the critical study for risk assessment by the EPA. Based on this research, the EPA provided me with a contract to produce a BMD analysis of the data, which I carried out in collaboration with my biostatistician colleagues, Dr. Esben Budtz-Jorgensen and Professor Niels Keiding. The EPA relied on this BMD analysis to establish the safe level for methylmercury exposure in the U.S. (U.S. EPA 2001).

16. In 2009, I served on an expert panel that assisted the European Food Safety Authority (EFSA) in developing a guidance document on BMD analysis titled "Use of the Benchmark Dose (BMD) Approach in Risk Assessment."

17. In 2013, Dr. Budtz-Jorgensen and I extended our BMD methodology in collaboration with the International Pooled Lead Study Investigators, which was peer-reviewed and published in the journal *Risk Analysis* (Budtz-Jorgensen et al. 2013). As part of this analysis, we developed a BMD for lead and IQ by analyzing pooled data from multiple different cohort studies. The paper was co-authored by leading scholars on lead neurotoxicity, including Drs. David Bellinger and Bruce Lanphear.

18. More recently, Dr. Budtz-Jorgensen and I conducted an advanced BMD analysis on perfluorinated chemicals, which was published in 2018 in the peer-reviewed journal *PLOS One* (Budtz-Jorgensen and Grandjean 2018). In total, our achievements on BMD approaches and applications have

been published in seven articles so far in international biostatistical and biomedical journals.

19. In addition to my scientific training, I remain mindful, of the importance of translating the results of epidemiological studies in a way that can facilitate public participation in making informed decisions to protect their health, even prior to a "final proof" of causation being available; a final proof that, all too often, has come too late to protect the public from harm, as reviewed most recently in the monograph on *Late Lessons of Early Warnings*, published by the European Environment Agency (EEA Report No 1/2013), for which I served as an editor. As Dr. Selikoff once impressed upon me, "Never forget that the numbers in your tables are human destinies, although the tears have been wiped away."

II. SUMMARY OF OPINIONS

20. The weight of epidemiological evidence leaves no reasonable doubt that developmental neurotoxicity is a serious human health risk associated with elevated fluoride exposure, including those occurring at the levels added to drinking water in fluoridated areas. The IQ losses associated with community water fluoridation are substantial and of significant public health concern.

21. Application of the Benchmark Dose (BMD) methodology to the recent prospective birth cohort data shows that the level of fluoride added to water in fluoridation programs greatly exceeds the science-based limit needed to protect against developmental neurotoxicity.

22. The systematic review conducted by Dr. Ellen Chang, when corrected for its biases and errors in judgment, further supports my opinions on the neurotoxic risks posed by elevated fluoride exposure.

III. SUMMARY OF METHODOLOGY

A. Weight of the Evidence

23. I conducted a weight of the evidence assessment of available research on fluoride neurotoxicity, with an emphasis on the epidemiology. While I place the greatest weight on the strong epidemiological evidence, I also consider toxicokinetics, experimental toxicology data, and background

principles of brain development as part of my comprehensive analysis.

24. My review focuses on the evidence that carries the greatest weight which, as generally accepted, emphasizes the recent prospective cohort studies.

25. My methodology follows the general approach applied by the EPA, in the sense that I did a weight of the evidence analysis that focuses on the best available science (e.g., EPA 2017).

26. In light of my familiarity with the scientific literature on fluoride neurotoxicity, I did not conduct a formal systematic review on this occasion. Instead, my conclusions rely on a comprehensive and thorough review supplemented by a Benchmark Dose analysis of the recent prospective data.

27. I have read and considered the systematic review conducted by Dr. Ellen Chang, which mostly relies on the same evidence and which further confirms and supports my assessment of the literature. My opinions are thus fully informed by the insights offered by a formal systematic search of the literature.

B. Factors Considered When Assessing Epidemiological Literature

28. In evaluating the weight of the evidence, the question must be asked what each study could potentially reveal, given the design and choice of study parameters, including such factors as the precision of the exposure assessment. In the field of epidemiology, there is a well-known bias toward the null, e.g., from imprecise assessment of the exposure, of which epidemiologists (and readers of epidemiology reports) need to be careful, especially when human health is at stake (EPA 2005).

29. The following Table highlights common causes of bias toward the null in epidemiological studies, i.e., reasons that a study might not show the existence of a risk that indeed is present, though hidden due to the bias. While biases in the opposite direction also exist, they are usually of much less significance (Grandjean 2013).

Table 1. Causes of bias toward the null in epidemiology studies (Grandjean 2013a).

Inadequate statistical power in small studies
Lost cases and inadequate follow-up for long-term effects
Exposed or otherwise inappropriate comparison (control) group
Exposure misclassification
Insensitive or imprecise outcome measures
Failure to adjust for confounders with effects in the opposite direction
Disregarding vulnerable subgroups
5% probability level to minimize risk of false positives (Type I error)
20% probability level to minimize risk of false negatives (Type II error)
Pressure to avoid false alarm

30. Studies that do not show a statistical significance are sometimes called "negative," although this term is misleading. Joint analyses of several such studies may well show a significant difference or trend.

31. Observational studies will rarely if ever provide definitive proof of causation, and it is always possible for someone to raise doubts and uncertainties that require additional or improved data to resolve (Michaels 2008). It is important to recognize, however, that the presence of uncertainties often tends to cause underestimations of actual risks, not the opposite. This issue is of importance especially regarding substances that have not yet been studied in the detail desired or cannot be examined in randomized clinical trials. Many unfortunate past errors in regard to industrial chemicals have shown that initial assessments were often erroneous and led to an underestimation of the true risks (European Environment Agency 2001 & 2013).

32. In the context of developmental neurotoxicity, I place greatest weight on prospective studies of population-based birth cohorts followed over time (Grandjean et al. 2008; Grandjean & Landrigan 2014). Birth cohorts are crucial because it is not just the dose that can matter but also the timing of the dosing in regard to the developmental stage of the subjects (Grandjean et al. 2008; Grandjean et al. 2019). Follow-up studies of birth cohorts can thus reveal with greater certainty the

impacts of exposures incurred during early life stages.

C. Benchmark Dose Methodology

33. As part of my assessment in this case, I worked with my biostatistician colleague Dr. Budtz-Jørgensen on a BMD analysis of the prospective cohort data on fluoride and IQ using the same peer-reviewed method that we used for lead (Budtz-Jorgensen et al. 2013).

34. The statistical uncertainty in the BMD estimation is taken into account by calculating its lower one-sided 95% confidence limit, which is called the benchmark dose level (BMDL). The BMDL is then used as the point of departure for calculation of the exposure limit, by dividing the BMDL by an uncertainty factor (usually fixed at 10) to obtain a protective Reference Dose (RfD) or tolerable exposure (EFSA 2009; EPA 2012).

D. Materials Relied Upon

35. In my assessment, I relied upon my existing knowledge of the scientific literature (with citations to specific studies noted in my reports), my own meta-analysis of the epidemiological studies of fluoride and IQ (Choi et al. 2012), the more recent meta-analysis by Duan (2018), all available prospective studies, as well as the reviews by NRC (2006) and NTP (2016).

36. I also considered studies provided by counsel,[1] many of which I was already familiar with, and conducted supplemental searches on PubMed, including searches to see if there were any significant epidemiological studies published that I might have overlooked.

37. A complete list of the studies I relied upon is provided in my expert reports.

IV. GENERAL CONSIDERATIONS

A. Emergence of Brain Development as Vulnerable Target

38. Evidence has been accumulating over several decades that industrial chemicals can cause

[1] I understand that these studies were provided to EPA's experts as well, including Dr. Chang.

neurodevelopmental disorders that include learning disabilities, sensory deficits, developmental delays, and cerebral palsy (NRC 2000), and current evidence also relates to other neurodevelopmental deficits, such as attention deficit hyperactivity disorder (ADHD) (Bennett et al. 2016). Subclinical stages of these conditions also appear to be common, and the suspicion of a link between neurotoxic chemical exposures and widespread neurobehavioral damage has increased since it was first raised by research demonstrating that lead is particularly toxic to the developing brain across a wide range of exposures (Baghurst et al. 1987; Dietrich et al. 1987; Landrigan et al. 1975; Needleman et al. 1979).

39. The developing human brain is inherently much more susceptible to injury caused by toxic agents than the brain of an adult. This susceptibility reflects the fact that in the nine months of prenatal life the human brain must evolve from a strip of cells along the dorsal ectoderm into a complex organ comprised of billions of precisely located, highly interconnected and specialized cells. Optimal brain development requires that neurons move along precise pathways from their points of origin to their assigned locations, that they establish connections with other cells near and distant, and that they generate intercommunications in meaningful ways (Dobbing 1968; Rice and Barone 2000; Rodier 1995).

40. All of these processes must take place within a tightly controlled time frame, in which each developmental stage must be reached on schedule and in the correct sequence. Due to the extraordinary complexity of human brain development, windows of unique susceptibility to toxic interference occur that have no counterpart in the mature brain, or in any other organ. Because of the unique structure of the human brain and its advanced function, no other species shows similar degree of developmental vulnerability. Thus, if a developmental process in the brain is halted or inhibited, there is little potential for later repair, although plasticity will allow some compensation, and the consequences are therefore likely to be permanent (Dobbing 1968; Rice and Barone 2000).

41. To test chemicals for developmental neurotoxicity, standardized protocols have been developed using rodent models (OECD 2007). However, they may not necessarily be sufficiently sensitive, as rodent brains are far less complex than human brains, and intrauterine brain development is completed at a stage where the human fetal brain is still rapidly developing *in utero* for several more weeks with possible continued impact from maternal transfer of neurotoxicants (Bal-Price et al. 2018).

42. During fetal development, the placenta can offer some protection against unwanted chemical exposures, but it is not an effective barrier against most environmental neurotoxicants (Andersen et al. 2000), including fluoride (NRC 2006). In addition, the blood-brain barrier, which protects the adult brain from many toxic agents, is not completely formed until about 6 months after birth (Adinolfi 1985).

43. Postnatally, the human brain continues to develop, and the period of heightened vulnerability therefore extends over many months through infancy and into early childhood. While most neurons have been formed by the time of birth, growth of glial cells and myelinization of axons continue for several years and is not complete until late teenage years (Rice and Barone 2000; Rodier 1995).

44. The susceptibility of infants and children to industrial chemicals is further amplified by their relatively increased exposures in regard to body weight, their augmented absorption rates, and diminished ability to detoxify many exogenous compounds as compared to adults (Ginsberg et al. 2004; NRC 1993).

45. In 2005, when I evaluated the evidence of industrial chemicals regarding developmental neurotoxicity, only five substances (arsenic, lead, methylmercury, polychlorinated biphenyls, and toluene) fulfilled our criteria for causal relationship in humans (Grandjean and Landrigan 2006). Eight years later, when we reassessed the evidence, we added six more substances, including fluoride (Grandjean and Landrigan 2014), based on new evidence that had emerged.

46. Our 2014 assessment was focused on *hazard* (i.e., whether fluoride causes developmental neurotoxicity in humans), not on *risk* (i.e., the exposure level at which this hazard may occur). Substantial new evidence published since that time, particularly the prospective birth cohort studies, now permit an assessment of risk.

B. Toxicokinetics During the Fetal Period

47. In my assessment, I considered the toxicokinetics of fluoride, with a particular focus on the uptake, distribution and retention during the fetal period.

48. It is well accepted that fluoride crosses the placenta and reaches the fetus from the mother's blood stream (NRC 2006; WHO 2006).

49. The first documentation of placental transfer in humans was the observation in 1974 (Shen and Taves 1974) that fluoride concentrations in maternal and cord serum correlated well, with the cord blood showing slightly lower concentrations. These findings were replicated in 1986 (Ron et al. 1986), with results suggesting minor deviations depending on gestational age. A more recent study from an area with water-fluoride levels of 0.4-0.8 mg/L showed that cord serum contained about 80% of the concentrations occurring in maternal serum (Opydo-Szymaczek and Borysewicz-Lewicka 2007). Consistent with this, French researchers measured fetal blood concentrations of fluoride after the mothers were administered a small dose of sodium fluoride, and the elevations were statistically significantly higher (2.6 µmol/l) than in a control group (less than 1 µmol/l) (Forestier et al. 1990).

50. A recent study from scientists at the University of California San Francisco (UCSF) further confirms the placental transfer of fluoride (Uyghurturk et al. 2020). In this study, fluoride concentrations were measured in the urine, blood, and amniotic fluid among pregnant women in fluoridated and non-fluoridated areas of Northern California. Each additional 0.1 mg/L of fluoride in water was associated with a significant increase in the fluoride levels in the amniotic fluid ($p < 0.001$), thus confirming the

transplacental passage of fluoride.

51. As would be expected, given the undeveloped nature of the blood-brain barrier during the fetal period, laboratory studies of animals exposed to prenatal fluoride have found significant elevations of fluoride in the brain (McPherson et al. 2018; Mullenix et al. 1995). Similarly, in aborted human fetuses, fluoride concentrations in the brain have been shown to be higher in geographic areas with endemic fluorosis as compared to controls at lower exposures (Du et al. 2008; He et al. 2008).

C. Toxicological Findings

52. Neurotoxicity is a documented hazard of fluoride exposure in laboratory animals (NRC 2006), which supports the plausibility of fluoride causing neurotoxic effects in humans.

53. One of the first U.S. reports on experimental fluoride neurotoxicity emerged when a new method was developed for computerized surveillance of rat behavior. Fluoride was selected for a test of the new methodology and showed clear neurotoxicity (Mullenix et al. 1995). The authors noted that the behavioral effects they observed in the rats are indicative of fluoride's potential ability to cause IQ deficits in humans. This assessment, which was made prior to the publication of any studies of fluoride and IQ in western journals, proved prescient.

54. Since the Mullenix study was published in 1995, many additional animal studies have documented neurochemical and anatomic changes in the brains of fluoride-treated animals. By 2006, the NRC concluded that there was enough neurochemical and anatomic data to conclude that fluoride interferes with brain functions by both direct and indirect means.

55. Among prominent adverse outcome pathways, the NRC concluded that fluoride is an endocrine disrupter that can affect thyroid function at intake levels as low as 0.01 to 0.03 mg/kg/day in individuals with iodine deficiency (NRC 2006).[2] Thyroid toxicity supports the plausibility of fluoride

[2] Large epidemiological studies published since the NRC report suggest that thyroid dysfunction is a relevant risk at elevated fluoride exposures in fluoridated communities, especially in

neurotoxicity because availability of thyroid hormone is crucial for optimal brain development (Rovet 2014).

56. At the time of the NRC's review, there was little data yet available on fluoride's impact on behavior and cognition in animals, but considerable data has since been published. In 2016, the National Toxicology Program (NTP) conducted a systematic review of these behavioral/cognitive studies (NTP 2016). Although NTP did not consider any of the neurochemical/anatomical effects, it still concluded that the evidence is "suggestive of an effect on learning and memory" (NTP 2016, p. vii). The NTP characterized its confidence in the evidence as "moderate" for adult studies, and "low" for the few available developmental studies.

57. Additional animal research on learning/memory has been published subsequent to the NTP review, and most of it has reported adverse effects. As is often the case, the animal studies on learning/memory have limitations or discrepancies but given the general consistency in their findings they continue to be *at least* "suggestive" of fluoride being a neurocognitive hazard.

V. EPIDEMIOLOGICAL STUDIES (CROSS-SECTIONAL)

A. Neurotoxicity from Occupational Fluoride Exposure

58. The neurotoxicity of chemicals is often first discovered from workplace exposures (Grandjean and Landrigan 2006), which are later followed by case reports that involve children or pregnant women from the general population (Grandjean 2013). The same is true of fluoride.

59. Although largely overlooked or ignored, Roholm first reported evidence of nervous system effects in his seminal study of cryolite workers in Copenhagen (Roholm 1937): "The marked frequency of nervous disorders after employment has ceased might indicate that cryolite has a particularly harmful effect on the central nervous system" (p. 178). The nervous system effects reported by Roholm included tiredness, sleepiness, indisposition, headaches, and giddiness (p. 138).

adults with iodine deficiency (Malin et al. 2018; Peckham et al. 2015).

60. My own mortality study of the cryolite workers studied by Roholm showed an excess of violent deaths (Grandjean et al. 1985), but information on the causes of death did not allow any conclusions on deaths from nervous system disease.

61. One of the challenges with occupational studies of fluoride-exposed workers is that the fluoride exposure usually occurs as part of a mixture. In the 1940s, scientists at the Manhattan Project recorded CNS effects in workers exposed to uranium hexafluoride gas (UF_6). They observed a "rather marked central nervous system effect with mental confusion, drowsiness and lassitude as the conspicuous features" and attributed it to the fluoride rather than uranium (Ferry 1944; Mullenix 2005).

62. Consistent with the observations of the Manhattan Project scientists, published case reports have highlighted difficulties with concentration and memory accompanied by general malaise and fatigue following occupational fluoride exposures (Spittle 1994).

63. More recently, skeletal fluorosis in workers was found to be associated with gradually progressive effects on the normal function and metabolism of the brain and other aspects of the nervous system (Duan et al. 1995), and application of neuropsychological tests (i.e., WHO's Neurobehavioural Core Test Battery) have reported significant associations between workplace fluoride exposures and cognitive problems (Guo et al. 2008; Yazdi et al. 2011).

64. The available evidence from occupationally exposed workers supports the neurotoxicity of fluoride but does not allow any detailed consideration of its dependence on dose, timing, and duration.

B. Neurotoxicity in Endemic Fluorosis Areas

65. Fluoride toxicity has received particular attention in China, where widespread dental fluorosis indicates pervasive high exposures (Wang et al. 2012). Areas with high prevalences of dental (and skeletal) fluorosis are known as "endemic fluorosis" areas.

66. Although microbiologically safe, water supplies from wells, small springs or mountain

sources have created pockets of increased fluoride exposures near or within areas of low exposures, thus representing optimal settings for epidemiological research because only the fluoride exposure would likely differ between nearby neighborhoods. In addition, rural families in China move much less frequently than U.S. families, thus facilitating assessment of impacts from long-term exposures. Chinese researchers took advantage of this fact and published their findings, though mainly in Chinese journals, and according to the standards of science at the time. The early research dates to the 1980s but has not been widely cited, in part because of limited access to Chinese journals, in part because the notion of adverse effects from fluoride intake has often been considered unwelcome.

67. Most of the studies on fluoride neurotoxicity from China, and other countries (i.e., India, Iran, and Mexico), have focused on IQ measures as the endpoint of concern, with the clear majority of these studies reporting inverse associations (i.e., higher levels of fluoride exposure are associated with lower IQ).

68. Many of the studies from China have significant limitations, including lack of information on covariates, missing information on study details, assessment of exposures on a community basis, and use of cross-sectional study designs. The reports have also tended to be relatively brief and simple in design. These deficiencies, which in some cases are rather severe, limit the conclusions that can be drawn, but are unlikely to explain the almost uniformly consistent inverse associations that have been reported.

69. While most of the endemic fluorosis studies have rather simple designs and may have failed to control for confounding factors of possible importance, they also have important strengths, including: 1) Stable populations with stable water-fluoride concentrations; many of the studies specifically limited the populations to those who had lived in the community their entire life. 2) Unlike in the U.S., children in rural China have very little exposure to fluoridated dental products (Zhu et al.

2003), thus making water a more important and reliable metric of fluoride exposure. 3) The studies in endemic fluorosis areas that have controlled for or excluded key confounding factors (arsenic exposure, iodine deficiency, parental education) were still capable of identifying clear associations between elevated fluoride exposure and cognitive deficits (Choi et al. 2012).

70. I will discuss the Chinese research on IQ in fluoride-exposed communities in more detail, but I begin first with studies that have examined other neurotoxicity endpoints, including neuropathological outcomes in aborted fetuses, neurobehavioral effects during infancy, and cognitive deficits and other neurological problems in adults.

1. Neurotoxic Endpoints in Fetuses and Neonates

71. In brain tissue obtained from aborted fetuses in endemic fluorosis areas, electron microscopy showed retarded cell growth in the cerebral cortex, with substantial cytology changes (He et al. 2008). A similar study used stereology to examine nerve cell numbers and volumes in fetal brain tissue and found lower densities (Du et al. 2008). A third study focused on neurotransmitters and receptors and found deviations that suggested neural dysplasia (Yu et al. 2008). Another study of aborted fetal brain tissue showed similar neurotransmitter results (Dong et al. 1993). These studies are consistent with prenatal fluoride exposure causing anatomic and biochemical changes in the fetal brain, as concluded by the NRC. A limiting factor, however, is that the elevated fluoride exposure in these studies came primarily from coal burning, which may have contributed other contaminants besides fluoride that were not assessed.

72. The impact of elevated fluoride in drinking water on neurological behavior in 91 neonates was assessed by Li et al. (2008). The study found that neonates born in an endemic fluorosis area (water-fluoride concentrations of 1.7 - 6.0 mg/L) scored more poorly on the standard Neonatal Behavioral Assessment, and that visual and auditory responses were also deficient, as compared to controls from

areas with less than 1 mg/L (Li et al. 2008). These findings are again consistent with the notion that fluoride can affect the brain during the prenatal period, although neonatal neurological assessments can be somewhat imprecise and may be only weakly predictive of subsequent brain development.

73. In a separate study, infants from an endemic area were examined at ages 3, 6, 9 and 12 months and scored significantly lower in mental and psychomotor development indices than those of the control group (Chang et al. 2017). The exposed group also showed lower birth weight, and it is unclear whether this difference can lead to confounding or if a lower birth weight is a concomitant effect of the fluoride exposure. As with the fetal neuropathology studies, the source of fluoride exposure in this study was coal, not water, which limits the conclusions that can be drawn due to the potential for confounding.

2. Neurotoxic Endpoints in Adults

74. Studies in China using cross-sectional designs have also found cognitive problems and neurological symptoms in adults with skeletal fluorosis living in endemic fluorosis areas. Using neuropsychological tests, including the Wechsler scale, 49 adult fluorosis patients (it is not clear whether the patients were from a coal- or waterborne fluorosis area) were compared with controls and showed deficits in language fluency, recognition, similarities, associative learning, and working memory (Shao et al. 2003). Likewise, cognitive impairment in elderly subjects was clearly elevated in a waterborne fluorosis area, although within-group assessment of urine-fluoride concentrations failed to show a clear gradient of effect (Li et al. 2016). Excess occurrence of neurological symptoms has also been recorded in both adults and children from waterborne fluorosis areas, with headaches being the primary manifestation (Sharma et al. 2009).

3. Childhood IQ

75. As noted above, most of the epidemiological studies on fluoride neurotoxicity have focused on IQ scores in childhood. In 2012, my colleagues and I published a meta-analysis of the

available 27 studies, most of which were published in China[3] (Choi et al. 2012). Because these published studies were conducted independently, we used meta-analysis—a quantitative, formal, statistical technique—to systematically review and assess these published research studies to derive conclusions about the neurotoxicity of fluoride. The outcome of the meta-analysis includes a more precise estimate of the association than any individual study that contributes to the pooled analysis. The variability or heterogeneity in study results was also examined. We did not attempt to generate any dose-response relationship, and the fluoride concentrations were used only for definitions of high and low (reference) groups in each study.

76. Among the 27 studies we reviewed, two involved populations exposed to fluoride from coal burning (Guo et al. 1991; Li et al. 2010); the rest of the studies involved exposure to fluoride through drinking water containing fluoride from soil minerals. The Combined Raven's Test – The Rural Edition in China (CRT-RC) was used to measure the children's intelligence in 16 studies. Other intelligence measures included the Wechsler Intelligence scale (3 studies), Binet IQ test (2 studies), Raven's test (2 studies), Japan IQ test (2 studies), Chinese comparative intelligence test (1 study), and the mental work capacity index (1 study). As each of the intelligence tests used is designed to measure general intelligence, we used data from all eligible studies to estimate the possible effects of fluoride exposure on the children's intelligence. We conducted a sensitivity analysis restricted to studies that used similar tests to measure the outcome (specifically, the CRT-RC, Wechsler Intelligence test, Binet IQ test, or Raven's test), and an analysis restricted to studies that used the CRT-RC. We also performed an analysis that excluded studies with possible concerns about co-exposures, such as iodine status and arsenic exposure, or with non-drinking water fluoride exposure from coal burning, without finding appreciable differences, as described below.

[3] Two of the 27 studies included in the analysis were conducted in Iran (Poureslami et al. 2011; Seraj et al. 2006), otherwise the study cohorts were populations from China.

77. The levels of fluoride exposure in the studies we examined, while higher than those associated with fluoridation programs (0.7 mg/L), are not as high as some have claimed. A surprising number of commentators, including the EPA, have only mentioned the *highest* concentration examined in the studies (11.5 mg/L) (Allukian et al. 2018; EPA 2018), although this high concentration occurred in only one of the 27 studies. The majority of studies that reported the water-fluoride level in the exposed group had between 1.5 and 4 mg/L, which is elevated, but only modestly.[4] Similarly, Duan's more recent meta-analysis of waterborne fluoride exposures reported that 18 of 27 studies addressed water-fluoride concentrations below 4 mg/L, and IQ reductions were observed at elevated concentrations of 1 to 2 mg/L (Duan et al. 2018 Table 2).

78. Among the 27 studies, all but one showed random-effect standardized mean difference (SMD) estimates that indicated an inverse association, ranging from -0.95 to -0.10 (one study showed a slight, non-significant effect in the opposite direction). The overall random-effects SMD estimate (and the 95% confidence interval, CI) were -0.45 (-0.56, -0.34). Given that the standard deviation (SD) for the IQ scale is 15, an SMD of -0.45 corresponds to a loss of **6.75 IQ points**.[5] I shall return to this result later. Among the restricted sets of intelligence tests, the SMD for the model with only CRT-RC tests and drinking-water exposure was lower than that for all studies combined, but the difference was not significant, and heterogeneity remained at a similar magnitude in the restricted analyses.

79. Several studies (Hong et al. 2001; Lin et al. 1991; Wang et al. 2001; Wang et al. 2007; Xiang et al. 2003; Zhao et al. 1996) reported other risk factors, such as iodine status, and exposure to arsenic or lead, both neurotoxicants, and our sensitivity analyses showed similar associations between

[4] The fluoride levels in the control groups in the studies often approximated the concentrations (~0.7 mg/L) used in fluoridation programs. Some ill-informed commentators have mistakenly interpreted this to mean that these control levels are thereby safe. This is false. The control groups are not being compared to *lower* or zero fluoride groups, and, as such, provide no information about the safety, or lack thereof, of the control values.

[5] The effect size we found is consistent with the prior meta-analysis of Tang (2008), who reported a mean difference of 5.03 IQ points between the high- and low-fluoride areas.

high fluoride exposure and the outcomes even after exclusion of these studies. Although large tracts of China have superficial fluoride-rich minerals, there is little, if any, likelihood of contamination by other neurotoxicants that would be consistently associated with fluoride concentrations in drinking water and thereby systemically confound the results. For example, follow-up testing documented lower levels of blood-lead concentrations and waterborne arsenic in the high-fluoride community than the control (Xiang et al. 2003; Xiang et al. 2003; Xiang et al. 2013). In some instances, therefore, potential co-exposure to other neurotoxicants may cause reverse confounding (i.e., may attenuate the real relationship between fluoride and IQ), as we have documented for methylmercury exposure from seafood (Choi et al. 2008).

80. Additional IQ studies in endemic fluorosis areas have been published since our 2012 review. As with the previous studies, these newer studies continue to replicate the consistent inverse association between fluoride exposure and IQ, although many—but not all—suffer from similar limitations. Two of the studies reported linear relationships between urinary fluoride excretion and IQ (one study also included plasma-fluoride) among children living in areas with mean water-fluoride contents of 1.4 mg/L and 1.5-2.5 mg/L (Cui et al. 2018; Zhang and Cheng 2015).[6] Another study published since our meta-analysis is the one I conducted with colleagues in China, which I will now discuss.

81. To ascertain the validity of the Chinese reports on fluoride neurotoxicity, we carried out a pilot study in Sichuan using methods commonly applied in neurobehavioral epidemiology (Choi et al. 2015). The children examined had lived in their respective communities since conception. Although we examined only 51 children, our results are consistent with elevated fluoride exposure being a cause of cognitive deficits. Interestingly, negative associations were found for cognitive function tests regarding

[6] These results are consistent with the findings of Ding et al. (2011), who reported a dose-response relationship between urine-fluoride concentrations (range = 0.24-2.84 mg/L) and reduced IQ in a population without any severe dental fluorosis (Ding et al. 2011).

all three measures of fluoride exposure. One was the known water-fluoride concentration at the residence where the child was born and had grown up, another was the child's morning urine-fluoride after having ingested fluoride-free water the night before (neither measure reached formal statistical significance as a predictor of cognitive deficits). The strongest and statistically significant association was seen with the degree of dental fluorosis that served as a marker of early-life fluoride exposure. While the milder forms of dental fluorosis have been considered a cosmetic effect (Aoba and Fejerskov 2002; WHO 2006), our study suggested that fluorosis can serve as a useful marker of early fluoride exposure in studies of neurodevelopmental toxicity.[7]

C. Studies of Fluoride and ADHD in North America

82. Four epidemiological studies have investigated the relationship between fluoride and ADHD behaviors in North America, the most important of which is the prospective cohort study by Bashash (2018). Two of the other three studies examined ADHD-related outcomes in the Canadian Health Measures Survey (CHMS) (Barberio et al. 2017; Riddell et al. 2019).[8]

83. In 2017, Barberio et al. examined two cycles of the CHMS to investigate the relationship between randomly measured urine-fluoride levels (in 3-to-12-year-old children) and parental reports or self-reported learning disabilities. When the two cycles of the CHMS were combined (both including at least 1,100 subjects), unadjusted urine-fluoride was significantly correlated with an increased incidence of learning disabilities. However, this effect lost its statistical significance after controlling for urine dilution by creatinine and specific gravity. The authors concluded that there was no robust association

[7] A prior study that was co-authored by my colleague David Bellinger failed to observe a relationship between dental fluorosis and behavior, as determined from parental questionnaires (Morgan et al. 1998). Due to several weaknesses, the conclusions were cautious and, in the authors' wording, "cannot lay this issue to rest." The relationship between dental fluorosis and neurobehavioral deficits is an issue that thus requires further study, including the possibility that the relationship is only apparent for fluorosis of certain teeth that share windows of susceptibility that overlap the windows of susceptibility for developmental neurotoxicity.

[8] The third study (Malin and Till 2015) was an ecological study that found an association between ADHD and water fluoridation in the U.S. This association was not robust, however, as it lost its significance after adjustment for altitude, although this adjustment is questionable.

between fluoride exposure and reported learning disability among Canadian children at the ages studied.

84. A more sophisticated study using the same CHMS data has now been completed and shows a significant association between fluoridated water and ADHD diagnoses/symptoms (Riddell et al. 2019). The latter study controlled for more potential covariates than Barberio and focused on an older subset of children (6 to 17 years old). Riddell's focus on an older group of children is an improvement because 90% of children with ADHD are diagnosed after age 6 (Riddell et al. 2019). Riddell also focused specifically on ADHD symptoms and diagnoses, rather than the broader category of "learning disabilities." The Riddell team also analyzed fluoride in water as well as in urine and conducted regression analyses to test the association with specific ADHD parameters: i.e., ADHD diagnosis and the hyperactivity/inattention score on the Strengths and Difficulties Questionnaire (SDQ).

85. After adjustment for covariates, including lead exposure, Riddell and colleagues found that fluoridation of the home water supply significantly increased the risk of an ADHD diagnosis. An increase in water-fluoride by 1 mg/L was associated with a (statistically significant) 6-fold higher odds of an ADHD diagnosis in the 710 children known to rely on community water, although this association was not replicated using urine concentrations that may have been more variable. Similar tendencies were seen for the SDQ scores of hyperactivity/inattention, especially among the older youth (not covered by the Barberio study).

86. With its individual exposure data, more specific ADHD outcomes in adolescents, and large effect size, the Riddell study, along with Bashash et al. (2018) that I will discuss below, provide additional weight to the evidence of fluoride being a neurotoxicant at current levels of exposure in fluoridated areas.

VI. EPIDEMIOLOGICAL STUDIES (PROSPECTIVE)

A. Prospective Cohort Studies with Individual Assessment of Prenatal Exposure

87. 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 subsequent clinical assessments of the child. (Grandjean & Landrigan 2014; Grandjean 2008). In our meta-analysis we recommended that prospective studies be conducted to formally evaluate dose-response relations based on individual-level measures over time, including more precise prenatal measurements (Choi et al. 2012). Five such studies have now been conducted, and they have each found significant adverse associations between prenatal fluoride exposure and neurodevelopmental harm (Bashash 2017; Bashash 2018; Green 2019; Valdez-Jiminez 2017), with an additional study finding an association between fluoride exposure during early infancy and IQ loss (Till 2020). The quality of these studies, coupled with the consistency of their findings, also in regard to the cross-sectional studies, add *substantial* weight to the evidence for developmental neurotoxicity from fluoride exposure.

88. I understand that Dr. Hu and Dr. Lanphear will be discussing the ELEMENT and MIREC cohort studies in detail, so I will forego doing so here. As I explained in my initial expert report, these are high-quality studies given their prospective birth cohort design, individual measurements of fluoride exposure, and extensive control for potential confounders.

89. In addition to the ELEMENT and MIREC studies, a prospective birth cohort study has also been published from a separate area of Mexico where there are elevated levels of fluoride in drinking water (Valdez Jiminez 2017). In this study, maternal urine-fluoride (corrected for specific gravity) was examined for its association with scores on the Bayley Scales among 65 children evaluated at age 3-15 months. The mothers in the study had average urine-fluoride concentrations at each of the three trimesters of pregnancy of 1.9, 2.0, and 2.7 mg/L. These fluoride exposure indicators during the first and second trimesters were associated with large and significant reductions in the Bayley Mental Development Index (MDI) (cognitive) score after adjusting for covariates, including gestational age.

While this study is not as robust as the ELEMENT and MIREC studies due to the limited size, its findings are consistent with and reinforce their findings, and add further weight to the neurotoxicity assessment given its prospective cohort design.

B. Prospective Cohort Studies without Prenatal Exposure Assessment

90. Two additional prospective studies have been previously published on fluoride and neurodevelopment (Shannon et al. 1986; Broadbent et al. 2015), both from New Zealand. They have substantial limitations that make them much less informative than the North American studies, including a failure to obtain individual measurements of fluoride exposure, and a failure to ascertain prenatal fluoride exposure.

91. The first of the New Zealand studies was published in 1986 by Shannon. It found no association between childhood behavior (as scored by mothers and teachers) and the duration of time the child had lived in a fluoridated area during the first 7 years of life. The authors, however, made no attempt to ascertain prenatal and early postnatal exposures. Postnatal exposures were measured by simply tallying the number of years a child resided in a fluoridated area, with no distinctions made for the *timing* of postnatal exposure. Under this exposure metric, a child who lived her first year of life in a fluoridated area (a period of increased vulnerability) would be treated the same as a child who lived her seventh year of life in a fluoridated area.

92. A second prospective study from New Zealand was based on a birth cohort established from births in 1972-1973 (Broadbent et al. 2015). The 1,037 children were recruited at age 3 years, and IQ tests were administered at ages 7, 9, 11 and 13 years, and again at age 38. Urine samples were again not available for analysis, and the authors had no individual data on water intake. Instead, the authors compared individuals who had lived for an undefined period of time in a fluoridated area during their first five years of life, with individuals who had not lived in a fluoridated area during their first five

years. No significant differences in IQ were noted using this exposure metric, and this finding was independent of potential confounding variables, including sex, socioeconomic status, breastfeeding, and birth weight.[9]

93. The Broadbent study also made no attempt to ascertain prenatal exposures, including maternal tea consumption, which is an important limitation given the high rate of tea consumption in New Zealand. Tea contains elevated levels of fluoride, and tea consumption can be a major source of fluoride intake among adults (Waugh 2017). During the time that the children in this study were born (1972-1973), New Zealanders consumed as much as 2.6 kg of tea per capita per year (corresponding to 3-4 teabags per day), as compared to the consumption of 0.5 kg in Canada in the approximate time the MIREC cohort was recruited (Grigg 2002). The failure of both New Zealand studies to consider maternal tea consumption may have introduced substantial imprecision into the exposure classification.

94. An additional concern is that the 10% of cohort subjects who had not lived in fluoridated areas very likely received fluoride supplements, which would eliminate much of the (postnatal) difference in exposure between the fluoridated and non-fluoridated areas. In a letter published subsequent to the study, the authors estimated that the average difference in exposure between children in fluoridated vs. non-fluoridated areas was only 0.3 mg/day (Broadbent et al. 2016).

95. Based on the absence of individual measurements of exposure; failure to control for the timing of exposure, including prenatal exposures; and the relatively small difference in postnatal exposures in the Broadbent study, the New Zealand studies provide virtually no information about the neurotoxic impact of early-life fluoride exposures. They carry little weight in my assessment.

VII. SYSTEMATIC REVIEW

96. Although I decided not to conduct a formal systematic review for my weight-of-the-

[9] Despite the fact that lead exposure in this cohort was later reported to cause IQ deficits (Reuben et al. 2017), the authors of the fluoride study chose not to control for exposure to lead or other chemicals that can affect neurodevelopment.

evidence analysis, I had the opportunity to consider and analyze the review conducted by Dr. Ellen Chang of Exponent. As I described in my expert rebuttal report, Dr. Chang's systematic review provides no credible grounds for questioning my assessment of the literature; in fact, it further supports it.

A. Dr. Chang's Systematic Review Confirms that I Considered All Significant Data

97. Dr. Chang stated that her systematic review identified numerous studies that I did not address, with the apparent implication that these studies are somehow at odds with my opinion (p. 8). What Dr. Chang failed to reveal, however, is that the great majority of these studies reported significant associations between fluoride exposure and neurotoxic outcomes, further confirming my own assessment.

98. Of the 31 studies that Dr. Chang has identified and which I did not specifically address, 27 found associations of elevated fluoride exposure with adverse effects.[10] These studies, which provide further *support* for my opinions, were not cited in my report because most are repetitions of the cross-sectional study design in endemic fluorosis areas that I have already discussed at length; some are only available in abstract form;[11] some are secondary analyses of primary studies that I already addressed;[12] and one was not available to me at the time of submitting my report (Till et al. 2020). As explained in my report, I do not consider it necessary to address and discuss each and every paper that reports on fluoride effects, especially when peer-reviewed systematic reviews are available, including our own (Choi et al. 2012). I consider it more informative to examine the various *types* of studies, including toxicokinetics (e.g., distribution of fluoride throughout the body, including transfer through the placenta and blood-brain barrier); toxicological findings from animals; and different endpoints relevant to

[10] Aravind (2016); Asawa (2014), Calderon (2000), Das (2016), Khan (2015), Kundu (2015), Liu (2000); Lu (2019), Manju (2017), Mustafa (2018), Nagarajappa (2013); Qin (1990), Razdan (2017), Rocha-Amador (2007), Rocha-Amador (2008), Rocha-Amador (2009), Saxena (2012), Shivaprakash (2011), Singh (2013), Sudhir (2009), Thomas (2018), Till (2019), Trivedi (2007), Wang (2005), Xiang (2015), and Yu (2018).

[11] Calderon (2000); Thomas (2018).

[12] Xiang (2015); Wang (2012).

neurotoxicity (e.g., cognitive tests, thyroid function, histological assessments of fetal brain).

99. Conversely, many of the studies that I addressed in my report[13] were not considered by Dr. Chang for unexplained or spurious reasons. Dr. Chang's review, for example, never addressed or considered fluoride's (i) passage through the placenta, (ii) uptake into fetal brain, and (iii) neurochemical and anatomical effects, and she spuriously dismisses the evidence of neurotoxicity in adults as irrelevant to developmental effects in humans (p. 31). In several important ways, therefore, Dr. Chang's review is not as systematic as my own.

100. Dr. Chang's systematic search of the literature identified four papers that reported no significant associations with neurodevelopmental effects and that I did not rely on, but upon inspection, they have no material effect on the conclusions that can be drawn, as I will now discuss.

101. One study highlighted by Dr. Chang is a publication by Spittle and colleagues (Spittle 1998) that Dr. Chang refers to repeatedly throughout her review. Although noted in a lengthy table at the end, Dr. Chang fails to acknowledge in the body of her review that this report is in the form of an abstract and relates to a previous (full) publication (Shannon et al. 1986) that I addressed in my report (and above). I did not cite the Spittle abstract in my report, just as I did not cite abstracts of studies reporting harm.[14] It is standard practice for systematic reviews to omit abstracts, as practiced in systematic reviews conducted by the authoritative Cochrane group (Iheozor-Ejiofor et al. 2015). Dr. Chang provides no justification for including abstracts in her review, such as the one by Spittle (Spittle 1998). Dr. Chang's prominent references to the Spittle abstract is particularly surprising given that it does not describe *any* confounder adjustment,[15] and uses an ecological metric for exposure (group water

[13] *E.g.*, Dong (1993); Duan (1995); Ekstrand (1981); Li (2016); Spittle (1994); Guo (2001); Malin (2018); Opydo-Szymaczek (2005, 2007); Peckham (2015); Ron (1986); Salgarello (2016); Shao (2003); Shen & Taves (1974); Yazdi (2011); Yu (2008).

[14] Calderon (2000); Thomas (2018).

[15] On p. 132 of her Table, Dr. Chang "assume[s]" that the Spittle analysis controlled for the same confounders as the Shannon analysis. I understand that neither Dr. Chang, nor anyone else in her

F level) – features which Dr. Chang has used to dismiss many papers that support the neurotoxicity of fluoride.

102. The other three "no-effect" studies that Dr. Chang cites and that I did not address are similarly unavailing. Two are cross-sectional studies from China which fail to show statistically significant associations between fluoride exposure and IQ,[16] and one is an ecological analysis (Perrott 2018) of the Malin & Till (2015) study on ADHD which I addressed but placed little weight on. As I explained in my report, there are many reasons why an ecological/cross-sectional study can fail to detect an effect even when one is present. The failure of these three studies to find statistically significant effects does nothing to contradict the robust literature that I rely upon, including the prospective birth cohort studies that I placed the greatest weight on. Even Dr. Chang appears to recognize this, as she does not include any of these three studies in her causal analysis, and correctly notes that the analysis by Perrott (Perrott 2018) is a "relatively low quality" ecological study (p. 66).

103. In summary, despite asserting that my review failed to consider "numerous" papers, Dr. Chang's own review confirms that I addressed and considered the most relevant epidemiological studies on cognitive outcomes. Dr. Chang's literature search also confirms that the majority of studies that I did not specifically address are consistent with and further support the association between fluoride and cognitive impairment, in accordance with my conclusions.

B. Dr. Chang's Review Fails to Identify Any Systematic Biases that Explain Fluoride's Consistent Association with Neurodevelopmental Harm

104. Dr. Chang's systematic assessment of study quality provides a lengthy discussion of real or perceived methodological limitations in the available studies. Importantly, however, Dr. Chang failed to identify a likely explanation for how these limitations can explain the consistent adverse associations

office has contacted Dr. Spittle to confirm this statement (Personal email communication with Bruce Spittle, August 13, 2019). According to Dr. Spittle, the abstract provided all important methodological details.

[16] He (2010); Kang (2011).

between fluoride and IQ across both cross-sectional and prospective studies. For example, Dr. Chang referred to "high potential for selection bias" but did not consider how unlikely it is that dozens of studies should all suffer from some particular exposure misclassification or selectivity that would all cause bias *away* from the null, e.g., selection bias that would result in participation of intellectually disabled children only in the high-fluoride group, or residual confounding resulting in bias only away from the null in the many different study settings.

105. Dr. Chang claimed that "methodological uncertainties remain about the assessment of fluoride exposure and neurodevelopmental outcomes; and the reported findings are plausibly explained by confounding, bias, and chance" (p. 9). However, she did not provide any convincing evidence that such issues could have resulted in erroneous conclusions, especially in the high-quality prospective studies.

106. Throughout her analysis, Dr. Chang failed to grapple with the fact that random (i.e., non-differential) error is unlikely to cause a bias away from the null, as is well-known in epidemiology, as I have also discussed in past publications (Grandjean and Budtz-Jorgensen 2007, 2010). Dr. Chang thus did not articulate a plausible basis for why the limitations she claimed to have identified can *systematically* bias the results across the many study settings, including the North American birth cohorts.

107. Dr. Chang described cross-sectional studies as if they are all equal and as if the exposure parameter always represents a current and short-lasting exposure only. In so doing, Dr. Chang failed to acknowledge in her causal analysis that exposure measures in many studies represent long-term community conditions, in some studies also likely covering prenatal exposures, a critical detail.

108. Dr. Chang referred to exaggerated associations that can result from lack of blinding (p. 59), but failed to acknowledge that at least 11 of the studies reporting adverse neurocognitive effects

have clearly been blinded, including the recent birth cohort studies, where the exposure was determined *after* the cognitive tests had been completed. Thus, while lack of blinding can create observation bias, it cannot explain the inverse association between fluoride and IQ because similar associations have been consistently found in studies known to be blinded. Despite producing a 56-page table to address "key characteristics" of the studies, Dr. Chang failed to mention this methodological strength in her summary of the studies (pp. 90-146).

109. Dr. Chang repeatedly highlighted the risk of publication bias, e.g., in the biomedical journal *Fluoride*, which is not indexed by PubMed. However, she does not mention the bias *against* publication, i.e., a bias that acts in the opposite direction. The examples that I mentioned in my report illustrate that such bias exists.[17] Further, Dr. Chang speculated that Chinese-language studies that did not find adverse effects may not have been translated into English (p. 37). Instead of speculating about this, Dr. Chang's systematic review could have included a search of online databases of Chinese-language research (e.g., CNKI) but, for unexplained reasons, did not do so.[18]

110. In summary, although Dr. Chang's systematic assessment of study quality correctly identified limitations in a number of studies, she failed to credibly explain how these limitations can plausibly explain the significant inverse associations that have consistently been found across many study settings and designs.[19] Although I recognize the issues that Dr. Chang has raised and have fully

[17] The desire to use fluoride in caries prevention programs has sometimes made it difficult for researchers, including myself, to present findings of potential toxic effects. In addition to my own personal experiences, published case reports suggest that some studies reporting adverse results have been suppressed, and, in at least one instance, a respected scientist at the Forsythe Dental Institute lost her job after publishing evidence of neurotoxicity.

[18] A search of PubMed for "CNKI database" shows that many systematic reviews include CNKI as one of the databases to retrieve studies, and the Institute of Medicine recommendations for systematic review (which Chang relies on) calls for searching for foreign language studies when appropriate (IOM 2011, p. 8). CNKI is publicly available online at: http://oversea.cnki.net/kns55/default.aspx.

[19] Unable to explain why so many studies have found significant associations between fluoride and IQ, Dr. Chang claims that "most published scientific research findings are anticipated to be false" (p. 38, citing Ioannidis (2005)). Although the original report by John Ioannidis (Ioannidis 2005)

considered them in my assessment, it remains extremely unlikely, if not impossible, that the overwhelming evidence of fluoride neurotoxicity is a mirage caused by bias, as Dr. Chang apparently believes. A far more likely and plausible explanation for the consistent findings in the epidemiological studies is that fluoride is a developmental neurotoxicant that reduces IQ and that this association is strong enough to be apparent also in studies with less-than-ideal designs.

C. Bradford Hill Aspects Support, Rather than Detract from, the Causal Nature of Fluoride's Association with Neurodevelopmental Harm

111. Dr. Chang used the Bradford Hill aspects to evaluate the causal relationship between fluoride and neurotoxicity. As I explained in my rebuttal report, her causal analysis is superficial and pays lip service only to Sir Austin's wise advice. An appropriate and systematic assessment of the Bradford Hill guidelines supports, rather than refutes, the causal relationship between elevated fluoride exposure and IQ loss. I will summarize here:

112. *Strength*: Dr. Chang dismissed the strength of the association between fluoride and IQ on the grounds that a loss of 3 to 5 IQ points is relatively small in comparison with normal, expected variation (p. 69). Under this arbitrarily high standard, other well-known neurotoxicants (e.g., lead, methylmercury, arsenic) would fail Dr. Chang's strength criterion. By failing to consider the strength of association of other well-known neurotoxicants, Dr. Chang subjectively analyzed the data on fluoride in a meaningless vacuum. Had Dr. Chang considered the strength of association for other neurotoxicants, she would have found that the effect size for fluoride actually is actually large, not small (i.e., it rivals the effects of lead), which *supports*, rather than detracts, from a causal relationship.

113. *Consistency*: One of the most compelling aspects about the epidemiological research on

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did provide some stunning examples of how clinical medicine could be misled by single reports, it would be reckless and counterproductive if we were to ignore all published reports, as Dr. Chang seems to prefer. This nihilistic view was also not the intent of the author. In a more recent paper in the same journal, Dr. Ioannidis highlighted the need for balanced review of scientific evidence in the interest of inspiring responsible policy decisions (Ioannidis 2018).

fluoride is how consistent it has been in finding significant associations with IQ (Choi et al. 2012). Dr. Chang obscured this by highlighting non-informative studies that made no attempt to measure or investigate prenatal or early postnatal fluoride exposures (Barberio et al. 2017; Broadbent et al. 2015; Morgan et al. 1998; Shannon et al. 1986; Spittle 1998) as being on the same level as, and contradicting, the highly significant findings from the prospective ELEMENT (Bashash et al. 2017) and MIREC (Green et al. 2019) prospective birth cohort studies (pp. 70-71). A particularly poor judgment by Dr. Chang was to place the Spittle abstract on the same level as the ELEMENT and MIREC studies despite the fact that Spittle's abstract does not describe *any* confounder adjustment. Dr. Chang cited the "mixed" nature of the findings as a basis to conclude that the consistency factor has not been met, while failing to acknowledge the inappropriate apples-to-oranges nature of comparing the prospective ELEMENT/MIREC studies to much, much weaker studies.

114. In her assessment of consistency, Dr. Chang failed to mention the fact that every single prospective birth cohort study with prenatal exposure measurements has found a significant adverse effect of prenatal fluoride on neurodevelopment (Bashash et al. 2017; Bashash et al. 2018; Green et al. 2019; Valdez Jimenez et al. 2017). Dr. Chang also gave short shrift to the consistent association between fluoride exposure and reduced IQ reported in the numerous cross-sectional studies (Choi et al. 2012; Duan et al. 2018; Tang et al. 2008). This latter shortcoming may be a result of Dr. Chang's critical misunderstanding of our meta-analysis (Choi et al. 2012), which I will now address.

115. Dr. Chang claimed that our meta-analysis found an average loss of 0.45 IQ points in the high-fluoride areas and characterizes this as a 10-fold difference with the Tang meta-analysis (Tang et al. 2008). This, however, is not what we reported (see paragraph 78). Because different intelligence scales had been used in the studies considered, we expressed the outcome as a random-effect standardized weighted mean difference estimate, as we clearly explained (Choi et al. 2012). In order to

translate this measure to a difference on the same IQ scale, the joint result must be multiplied by the standard deviation of the IQ scale, i.e., 15. An SMD of -0.45 thus corresponds to a loss of 6.75 IQ points. Contrary to Dr. Chang's mischaracterization, therefore, the results of our meta-analysis are consistent with the Tang meta-analysis, a fact that we actually mention in our published paper (Choi et al. 2012).

116. Dr. Chang's assessment of consistency also entirely ignored the findings from occupational studies, as well as the neuropathology data from examinations of fetal brains in endemic fluorosis areas. As I explained in my report, each of these types of studies is consistent with, and provide support for, fluoride being a neurotoxic agent.

117. *Specificity*: As Kenneth Rothman (2012) and others (Neutra 2018) have emphasized, and as Dr. Chang recognized, lack of specificity between an exposure and an outcome (e.g., asbestos and mesothelioma) does not weigh against or in favor of a causal conclusion.

118. *Temporality*: Dr. Chang's assessment of temporality mirrored her assessment of consistency in that she cited the two New Zealand studies as contradicting the findings from the ELEMENT and MIREC cohorts. Once again, Dr. Chang fails to acknowledge the absence of prenatal or early postnatal fluoride exposure assessments in the New Zealand studies, nor any of the other serious shortcomings of these studies. Instead, Dr. Chang focused on non-differential measurement uncertainties of the urine-fluoride data in the far superior ELEMENT and MIREC cohorts to cast doubt on the findings of these studies. As already discussed in my report, however, the imprecision of the fluoride exposure parameters would likely *bias the results toward the null*, not the reverse. The temporality requirement is thus met with fluoride, as each of the prospective birth cohort studies has found a significant association between early-life exposure to fluoride and the offspring's subsequent performance on neurobehavioral testing. The exposure preceded the effect in these studies, which is

what the temporality factor is supposed to assess.

119. *Biological Gradient*: The ELEMENT and MIREC studies have reported monotonic dose-response relationships between elevated prenatal fluoride exposure and IQ deficits in the offspring (Bashash et al. 2017, Green et al. 2019), as well as ADHD behaviors (Bashash et al. 2018). Dr. Chang dismissed the biological gradient of these effects by showing scatterplots from the ELEMENT and MIREC cohorts without the trend lines. However, this approach proves little insight, other than illustrating the undisputed fact that there is substantial natural variation in IQ across the population and that an appropriate statistical analysis is needed to extract a reliable estimate of the average effect of the toxicant exposure. Similar scatterplots have been published showing the effects of lead and IQ, as can be seen in the figure to the right (Rothenberg & Rothenberg 2005, Figure 1). Lead would thus fail the biological gradient test that Dr. Chang has used for fluoride. Dr. Chang also argued that outliers may have distorted the effects seen in the ELEMENT and MIREC cohorts (p. 77-78), without acknowledging that statistical analyses on the impact of outliers have been conducted and that the results did not meaningfully change (Bashash et al. 2017).

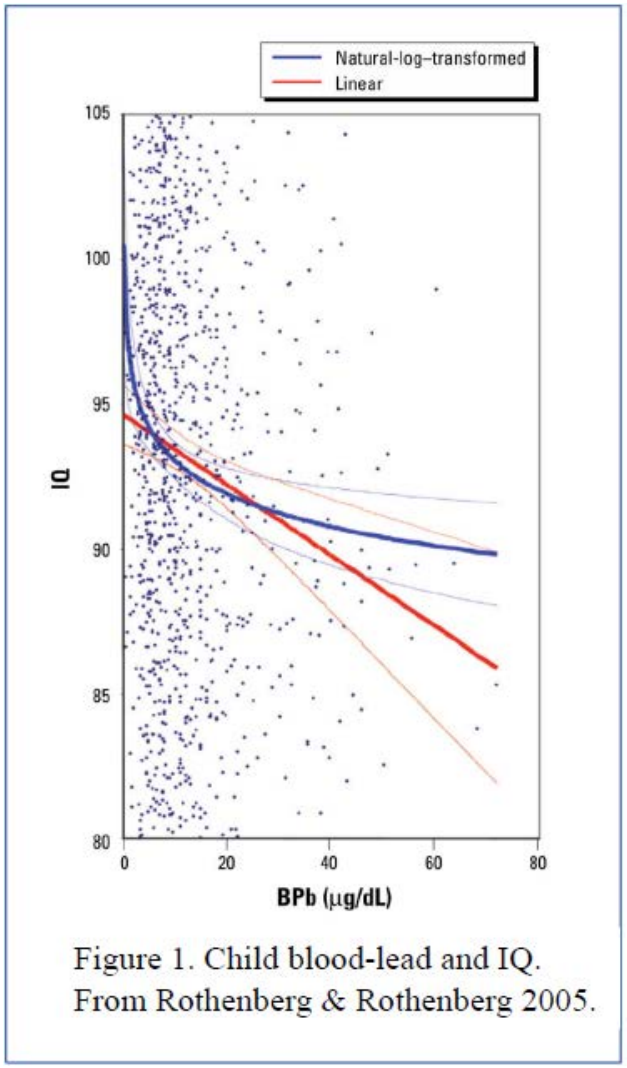


Figure 1. Child blood-lead and IQ. From Rothenberg & Rothenberg 2005.

120. *Plausibility*: Dr. Chang limited her assessment of biologic plausibility to NTP's assessment of learning and memory (NTP 2016) in animal models, and to Dr. Tsuji's expert report. In so doing, Dr.

Chang completely ignored the large body of animal literature showing adverse neuroanatomical and neurochemical effects from fluoride exposure, as already reviewed by the National Research Council (NRC 2006) and by Dr. Thiessen in her report. The NRC concluded that the neuroanatomical and neurochemical effects are sufficient to determine that fluoride interferes with brain function (NRC 2006). Dr. Chang ignored this information in favor of the NTP's more narrow assessment on learning/memory, but even the NTP assessment found suggestive evidence that fluoride impairs learning and memory. In contrast to Dr. Chang's assessment, EPA's own experts on developmental neurotoxicity, including internationally recognized scientists such as William R. Mundy and Kevin M. Crofton (Mundy et al. 2015), have identified fluoride as a chemical with substantial evidence of developmental neurotoxicity.

121. *Coherence*: Dr. Chang dismissed the coherence of fluoridated water reducing IQ on the grounds that IQ scores in US children steadily improved throughout the 20th century (the so-called "Flynn Effect"). Dr. Chang even went so far as to suggest that fluoridation may be responsible for the increased scores, although more plausible explanations are known. Under Dr. Chang's simplistic framework, leaded gasoline could not have reduced IQ and may have increased it, as it was introduced in the early part of the 20th century and IQ scores continued to increase during the entire duration of its use. It is well accepted, however, that low-level lead exposure reduces IQ, and thus the Flynn Effect argument—while perhaps superficially appealing—does *not* demonstrate "incoherence."

122. In her assessment of coherence, Dr. Chang failed to consider other relevant considerations, including the association between neonatal fluoride exposure mediated by infant formula feeding and reduced IQ (Till et al. 2020), as further discussed below. While the studies prior to the recent Canadian analysis did not evaluate the potential role of neonatal fluoride exposure, formula feeding is well established to increase a baby's fluoride exposure, even in areas without fluoridated water (Harriehausen

et al. 2019; Zohoori et al. 2019). Although other factors are of likely importance, the relationship between formula-feeding and reduced IQ is coherent with maternal fluoride exposure during pregnancy being associated with a lowered IQ in the child and supports a causative relationship between early-life exposure to fluoride and IQ deficits.

123. *Experiment*: Dr. Chang ignored the NRC's observation (NRC 2006) that case reports of fluoride toxicity constitute "experimental studies" of neurologic symptomatology following fluoride exposure (NRC, p. 208). The case reports involve "one or more individuals who underwent withdrawal from their source of fluoride exposure and subsequent re-exposures under 'blind' conditions." In most cases, the symptoms (which included lethargy, weakness, and impaired ability to concentrate) "disappeared with the elimination of exposure to fluoride and returned when exposure was reinstated." Although experimental support is not an obligatory criterion (Neutra 2018), the existence of such support should not be missed in what is dubbed a systematic assessment.

124. *Analogy*: I agree with Dr. Chang that "analogies can be drawn to other naturally occurring elements, especially certain metals" like lead (p. 85). As discussed above, many of the exaggerated criteria that she uses to reject a causal relationship between fluoride exposure and IQ could be equally used to erroneously dismiss the causal relationship between low-level lead exposure and IQ.

125. In summary, after correcting for Dr. Chang's errors and biases in judgment, the Bradford-Hill aspects support, rather than detract from, a causal relationship between fluoride in water and neurotoxicity. After analyzing and considering Dr. Chang's systematic review, I have more, not less, confidence that developmental neurotoxicity is a serious risk of elevated fluoride exposure.

VIII. BENCHMARK DOSE (BMD) ANALYSIS

A. Selection of Source Data

126. Regulatory agencies are in overall agreement in using Benchmark Dose (BMD) analyses to

calculate non-cancer health-based limits for dietary intakes of contaminants, such as those found in drinking water (EFSA 2009; EPA 2012).

127. As with the Faroe Islands cohort that the EPA relied upon in its risk assessment for methylmercury, the ELEMENT and MIREC studies are high-quality birth cohorts suitable for dose-response analysis (Bashash et al. 2017; Green et al. 2019). Further, as the data refer to the critical effect in a highly vulnerable population, they constitute appropriate data to use for identifying a safe exposure limit for fluoride. I worked, therefore, with my colleague, Dr. Budtz-Jorgensen, on BMD analyses of these studies, which I describe below.

128. Our selection of the ELEMENT and MIREC studies for BMD analysis is consistent with an analogous assessment conducted by both Dr. Chang and her colleague, Dr. Joyce Tsuji (Tsuji et al. 2015) for another neurotoxicant. In their paper, Drs. Chang and Tsuji sought to determine if the existing RfD for arsenic is adequately protective of neurotoxicity. To answer this question, they conducted a systematic review of the literature to see if there were any studies that would permit a dose-response analysis for quantitative risk assessment. After reviewing the literature, they found a study that, in their judgment, was suitable for the purpose: a study from Bangladesh by Hamadani et al. (2011).

129. The ELEMENT and MIREC studies are at least equally suitable for dose-response analysis as the one study Dr. Chang and Dr. Tsuji found sufficiently reliable to use for their risk assessment of arsenic exposure. As with the Hamadani study, the ELEMENT and MIREC studies have a (i) prospective birth cohort design; (ii) large sample size; (iii) control for potential confounders;[20] (iv) urine measurements[21] of the toxicant of interest during pregnancy; (v) and extended follow-up (up to 5 years

[20] Drs. Chang and Tsuji considered studies to have sufficiently controlled for potential confounders if they controlled for SES or HOME Score and parental education/IQ (Tsuji et al. 2015, p. 93).

[21] As with the ELEMENT and MIREC studies, the Bangladesh study measured prenatal exposure through several samples of maternal urine (adjusted for specific gravity) (Hamadani 2011). The Bangladesh study collected urine twice during the pregnancy (at gestational weeks 8 and 30), which

after birth). In fact, the ELEMENT and MIREC studies have an important advantage: the average arsenic exposure in Bangladesh substantially exceeded exposures in the U.S.,[22] which is not the case with the North American fluoride cohort studies.

130. My calculations of benchmark values for fluoride from the ELEMENT and MIREC cohorts are therefore in accordance with the criteria that Drs. Chang and Tsuji have previously used when generating benchmark calculations for arsenic (where adverse effects were seen in girls, but not boys, at 5 years of age).

B. Selection of Benchmark Response (BMR)

131. The benchmark dose (BMD) is defined as the dose that leads to a specific loss (or degree of abnormality) known as the benchmark response (BMR) in the outcome variable. The BMR must be defined before the analysis (EPA 2012), and general guidelines been developed for the selection of a BMR (EFSA 2009).

132. According to the EPA Clean Air Scientific Advisory Committee, a 1-to-2 IQ point reduction at the population level is "highly significant from a public health standpoint," and should be prevented in up to 99.5% of the population (EPA 2008). Consistent with this, previous BMD analyses of human neurotoxicity have selected 1 IQ point as the BMR (Budtz-Jorgensen et al. 2000; Budtz-Jorgensen et al. 2013; EFSA 2010; Tsuji et al. 2015).

133. Economists have calculated the substantial losses in lifetime incomes from a decrease of 1 IQ point[23] (Gould 2009), as also practiced by economists at the EPA in regulatory impact analyses (EPA 2008).

134. Research on other neurotoxicants (Grandjean 2013) has shown that shifts to the left of IQ

is a lower number of samples than the MIREC cohort, and roughly the same as the ELEMENT study.

[22] The Bangladesh study addressed a population with mean urinary arsenic levels ranging from 35 to 80 ug/L, which is about 10-to-40 times the levels measured in the US population.

[23] In terms of 2006-dollars, the value of 1 IQ point was calculated to be about $18,000 (Gould 2009; Spadaro and Rabl 2008).

distributions in a population (i.e., reductions in average IQ) can have substantial impacts, especially among those in the high and low ranges of the distribution (Bellinger 2007).

135. Consistent with prior analyses, including our own, we therefore selected 1 IQ point as the BMR (Budtz-Jorgensen et al. 2000; Budtz-Jorgensen et al. 2013).

C. Analyses of ELEMENT and MIREC Data

136. For our BMD analysis, we used the same formula that we used in our prior assessment of lead (Budtz-Jorgensen et al. 2013). The formula is as follows:

> The BMD is defined by
>
> $$f(0) - f(BMD) = BMR \rightarrow BMD = f^{-1}(-BMR)$$
>
> In a linear model, $(Y = \alpha + \beta d + \varepsilon)$, from which we get $BMD = -BMR/\beta$.
>
> Likewise, the BMDL is defined as a lower one-sided 95% confidence limit of the BMD. In the linear model,
>
> $$BMDL = -BMR/\beta_{lower}$$
>
> where β_{lower} is the one-sided lower 95% confidence limit for β. Information on the (linear) regression coefficients and their standard deviations, from which the confidence intervals can be calculated, is available from the published articles on the two major prospective cohort studies.

137. For the ELEMENT study (Bashash et al. 2017), a linear dose-response model could be used for the effect of urine-fluoride concentrations on both measures of childhood IQ (i.e., the General Cognitive Index (GCI) results at age 4 and IQ results at ages 6-12). In this model, the BMD and BMDL can be calculated based only on the regression coefficient and its precision. In Table 4 of the publication (Bashash et al. 2017), this information is available both for a crude model and for a model A with confounder adjustment. The table below shows the benchmark results for these two models for both the age-4 GCI and school-age IQ.

***Table 2. Benchmark dose results (mg/L urine adjusted for creatinine) obtained from the ELEMENT study results* (Bashash et al. 2017).**

	GCI		IQ	
Model	BMD	BMDL	BMD	BMDL
Crude	0.133	0.085	0.211	0.121
Adjusted	0.159	0.099	0.200	0.130
Read from plot	0.159	0.102	-	-

138. As these calculations are based on assumptions of Gaussian distributions, we checked the validity by scanning the numbers from the plot in the published article. We tentatively used the *WebPlotDigitizer* software to read the plot shown in the published paper (see Figure 1, page 22) (Bashash et al. 2017), to obtain the individual adjusted GCI results for more accurate BMD calculations. Of the original 287 observations, the software provided 286 observations, probably due to two overlapping observations. Thus, missing a single point only, our calculations based on the scanned data should be considered fairly reliable.

139. Using the standard benchmark approach to epidemiological data and a linear dependency, we find that the BMD for GCI is approximately 0.16 mg/L, and that the BMDL is 0.10 mg/L (bottom line of Table 2). These results are in excellent agreement with the results calculated only from the regression data presented in Table 4 of Bashash et al. (2017).

140. To assess the robustness of the calculation, we included a logarithmic conversion of the exposure parameter. We also used a split linear dose-response curve as in one of our previous studies (Budtz-Jorgensen et al., 2013). These sensitivity analyses showed BMD results that deviated only marginally from the calculation using the default linear association. In conclusion, Table 2 shows

reliable BMD results that have been calculated in accordance with standard EPA procedures.

141. We also conducted a BMD analysis of the MIREC data. As with the ELEMENT study, we calculated the BMD and BMDL from the reported regression coefficients and standard deviations, with the assumption of a Gaussian distribution (Green 2019, Table 2). In addition to calculating the BMD and BMDL from the urine-fluoride data (U-F), we also calculated a BMD and BMDL from the maternal fluoride intake data. Our results are shown in the table below:

Table 3. Benchmark dose results (mg/L urine adjusted for specific gravity, or mg estimated daily intake) obtained from MIREC study results on IQ (Green et al. 2019).

Study	Exposure	Sex	BMD	BMDL
MIREC	Maternal U-F	Both sexes	0.51	0.21
	Maternal U-F	Boys	0.22	0.13
	Maternal U-F	Girls	(–)	0.58
	Maternal F intake	Both sexes	0.27	0.15

142. As shown in the above table, the prenatal BMD for girls is not defined when relying on urine-fluoride, but the BMDL is still meaningful and is, as expected, higher than the other estimates obtained. No sex difference was found when relying on estimated fluoride intake.

143. Overall, the results derived from the two studies are comparable. In the ELEMENT study, the BMDL for maternal urine among ~4-year olds is approximately **0.1 mg/L** (both sexes), while in the MIREC study, it is **0.13 mg/L** (boys) and **0.21 mg/L** (both sexes).[24] The respective BMDL for the 6-to-12-year olds from the ELEMENT study is **0.13 mg/L**, thus overall approximately 0.15 mg/L. Consistent with these maternal urinary excretion values, the BMDL for maternal fluoride *intake* in the MIREC

[24] Based on how the authors reported the data, our BMDL values from the ELEMENT cohort are creatinine-adjusted, while our BMDL values from the MIREC cohort are specific gravity-adjusted.

study is **0.15 mg/day** (both sexes).

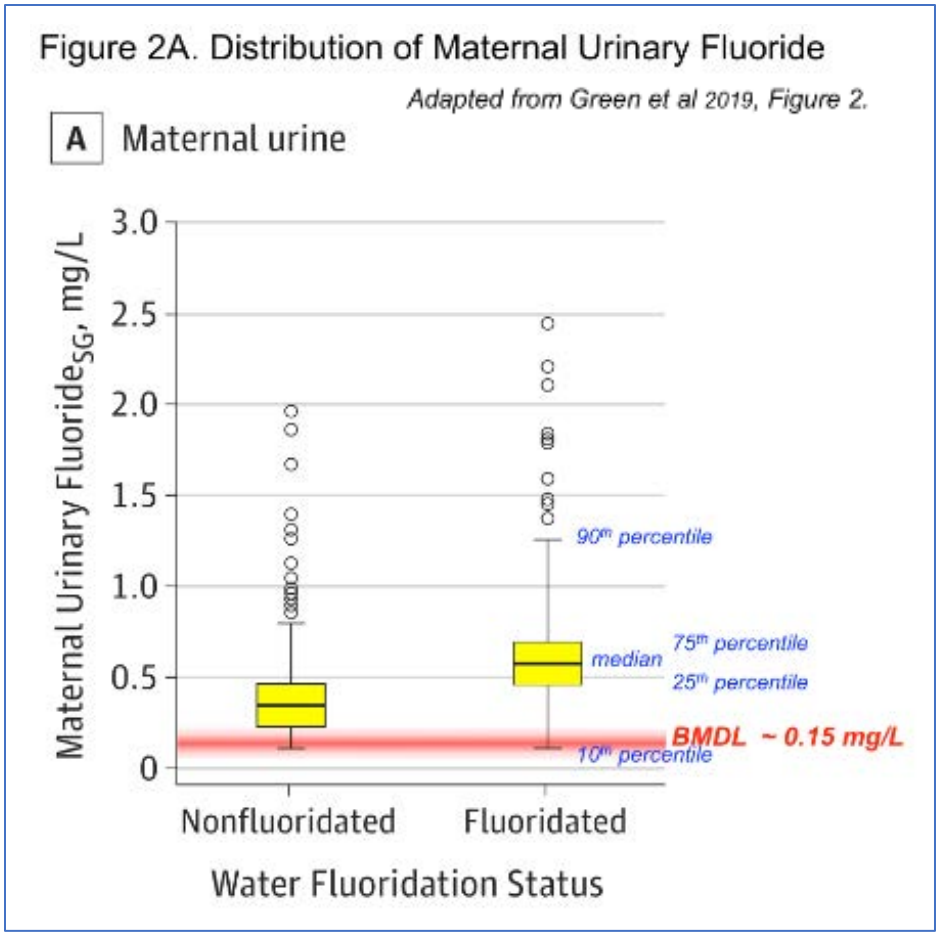
IX. ASSESSMENT OF RISK

A. Comparing BMDLs with Current Exposures in Fluoridated Areas

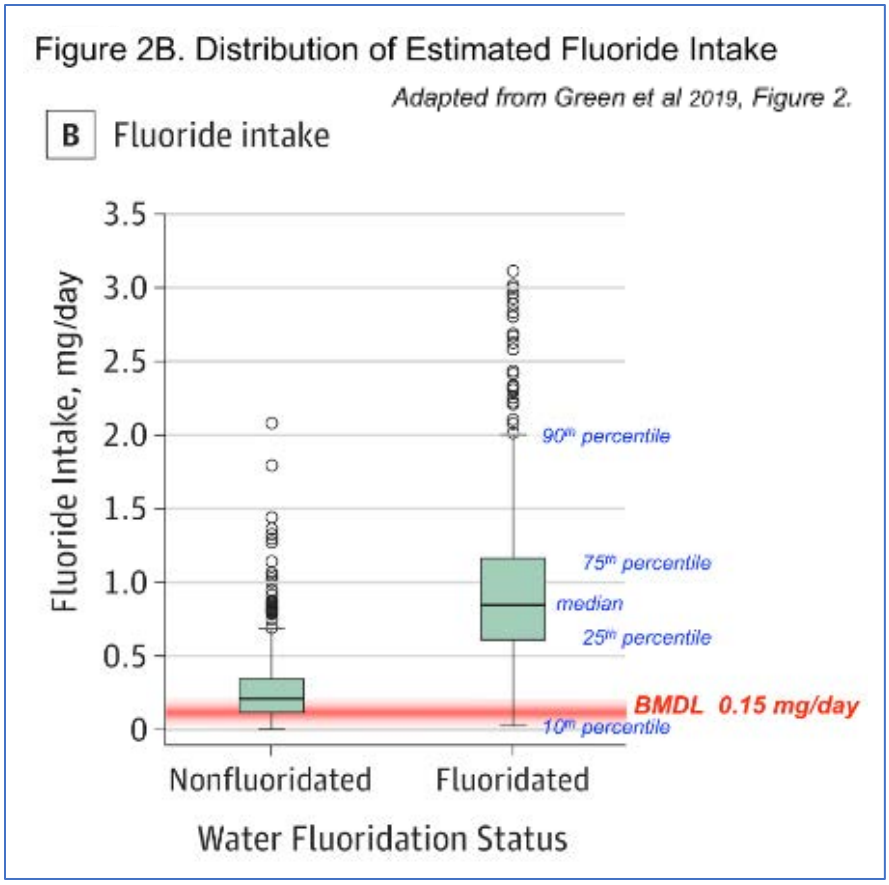
144. As benchmark dose calculations constitute a routine approach applied by the EPA for establishing safe limits on chemical exposure, the above calculations that rely on overall associations between fluoride exposure and cognitive deficits provide a basis for assessing the risk of cognitive deficits from current fluoride exposure levels.

145. Typically, the EPA uses the BMDL to calculate a Reference Dose (RfD) by dividing by an uncertainty factor for the purpose of accounting for variations in human susceptibility. The default value that EPA uses for the uncertainty factor is 10. Here, if we round up the overall BMDL to **0.2 mg/L**, or about 0.2 mg/day, the RfD would likely be 0.02, which is very much below current exposure levels, especially in communities with fluoridation programs (Till et al. 2018). But, *even if no uncertainty factor is applied, and even if relying on the BMD rather than the BMDL* (both of which would be unusual), the RfD would still be well below current exposure levels in fluoridated areas (Till et al. 2018).

146. The serious risk that we are confronted with can be appreciated by visually comparing the BMDLs against documented exposure levels in fluoridated communities. The following Figure 2A, adapted from Green et al. (2019), compares an overall BMDL for maternal urine-fluoride (0.15 mg/L) with the maternal urine-fluoride concentrations reported in the study. As can be seen, the urine-fluoride levels far surpass the levels associated with IQ loss.



147. The below Figure 2B compares the approximate BMDL for maternal fluoride *intake* from beverages (0.15 mg/day) against the reported fluoride intakes in Green et al (2019). As can be seen, the estimated fluoride intakes in fluoridated areas far surpass the fluoride intake level associated with a clear IQ loss.



148. There are no contemporary large-scale studies of urine-fluoride concentrations in the United States, as the CDC has not yet reported urinary fluoride excretion levels as part of its ongoing National Health and Nutrition Examination Survey (NHANES) studies. One can reasonably infer, however, that urinary fluoride excretion levels in fluoridated areas of the U.S. are generally comparable to those in fluoridated areas of Canada. The reasonableness of this inference is supported by the following facts:

149. Canada and the U.S. add fluoride to water to reach the same target concentration (0.7 mg/L), although empirical data suggests Canadian cities only reach 0.6 mg/L which is slightly less than the U.S. (Till et al. 2018).

150. Fluoridated water is recognized as the largest source of fluoride exposure for adults, particularly when indirect sources are accounted for, such as beverages and foods prepared with the

water, including commercially prepared beverages such as soda and reconstituted juice (EPA 2010).

151. Urine-fluoride has been shown to be a good indicator of total daily fluoride intake, and has a close, linear correlation with the fluoride content in water (Villa et al. 2000; McClure 1944; Smith et al. 1950).

152. The largest study of urine-fluoride levels in the U.S. found that pooled urine samples from healthy young males generally mirrored the fluoride concentration in the drinking water (McClure 1944). Based on U.S. data, therefore, a person drinking water with 0.7 mg/L fluoride would be expected to have about 0.7 mg/L in their urine, which is similar to what was found in the MIREC cohort (Till et al. 2018). Although these U.S. data were published prior to widespread fluoridation, the levels today would, if anything, tend to be *higher* today, not lower because fluoride is now available from more sources than was the case in the 1940s (e.g., including commercial beverages made with fluoridated water, dental products, etc.).

153. To address the lack of contemporary US data on fluoride exposures in pregnant women,[25] the recent UCSF study measured the concentrations of fluoride in urine (and blood[26]) of 48 pregnant women living in fluoridated and non-fluoridated areas of California. As with the Canadian study, the UCSF team had the urine tested by Dr. Angeles Martinez-Mier at the University of Indiana and adjusted the fluoride measurements for specific gravity. The study found an average (specific gravity-adjusted) urine-fluoride concentration of **0.69 mg/L** among pregnant women in areas with at least 0.7 mg/L in the community water, which is clearly in the same range as the MIREC team found in Canada (Uyghurturk

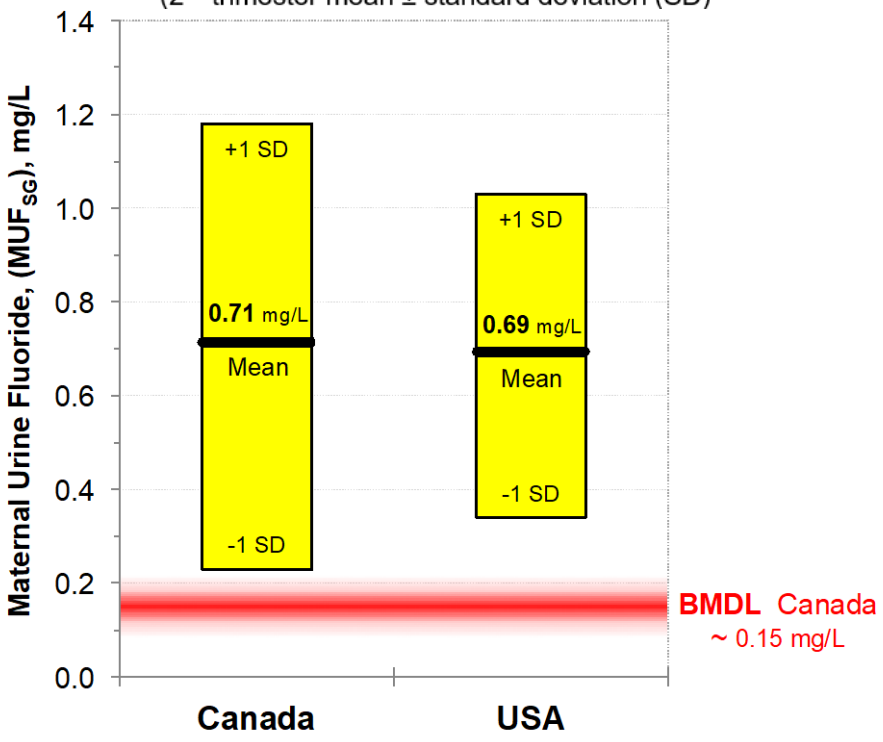
[25] As noted by the UCSF team, there is only one prior published study of urine-fluoride levels among pregnant women in the US: this is the study by Shen & Taves (1974) that I discussed in my expert report. This study found an average of 1.02 mg/L in maternal urine among a group of 16 pregnant women, but the authors did not report the concentrations of fluoride in water.

[26] The study found an average of 0.021 mg/L fluoride in the blood (=1.1 µmol/L) of the women from fluoridated areas (~0.8 mg/L), which is higher than the predicted value (0.015 mg/L = 0.8 µmol/L). As discussed by the NRC, it has been historically estimated that adult populations will have 1 µmol/L in their blood for each 1 mg/L of fluoride in the water (NRC 2006).

2020, Table 2). While the small-scale nature of the study likely introduced some random scatter in the results of the UCSF study,[27] the study supports the general similarity in fluoride exposures in the Canadian and U.S. populations.

154. Finally, the relevance of the Canadian IQ data (Green et al., 2019) to the US can be appreciated by comparing the BMDL to the maternal urine-fluoride concentrations reported by the UCSF team (Uyghurturk 2020). As can be seen in the following Figure 3, maternal urine-fluoride concentrations found in pregnant women in the Californian cohort greatly exceed the BMDL for fluoride-associated IQ loss. This, ultimately, is the most important consideration.

Figure 3. Specific gravity adjusted urine-fluoride concentrations in fluoridated communities of Canada and the U.S. (2nd trimester mean ± standard deviation (SD)



Urine F in Canada from Till 2018, Suppl., Table S4; urine F in USA from Uyghurturk 2020, Table 2.

[27] The study found some high levels of urine-fluoride in the mid-range fluoride communities (0.3-0.5 mg/L), which slightly skewed the distribution (Uyghurturk 2020, Fig. 2). As the authors note, this may be the result, in part, of the fact that the women had their urine tested while visiting a clinic in San Francisco, which is fluoridated (Uyghurturk 2020, p. 6-7). In the areas with >0.3 mg/L in water, the average (specific-gravity adjusted) fluoride level was 0.74 mg/L (Uyghurturk 2020, Table 5).

B. Comparing Fluoride's Population-Level Effects with Other Causes of IQ Loss

155. In order to compare fluoridation's population-level effects with other neurotoxicant exposures, some approximate estimates of fluoride-associated IQ losses can be made. The calculations rely on several assumptions that are necessary in the absence of actual data and are therefore meant only to identify relative orders of magnitude. On the conservative side, I shall assume that all children are equally vulnerable and that the dose-dependent IQ losses observed in the recent prospective studies can be used to assess the impact on the population at large (i.e., that genetic and other predisposition can be ignored).

156. My analysis focuses on the average difference in maternal urine-fluoride levels between fluoridated and non-fluoridated areas. The Canadian study (Till et al. 2018) showed that this difference is approximately 0.4 mg/L. It bears emphasizing that this difference likely understates the true contribution of fluoridated water because part of the exposure in "non-fluoridated" areas comes from the "halo" effect. The halo effect refers to the fact that many commercial beverages and foods made in fluoridated areas are shipped to and consumed in non-fluoridated areas and that residents from non-fluoridated communities may work or spend time in fluoridation areas.[28]

157. Given the BMD results, an average increase of 0.4 mg/L in maternal fluoride concentrations is above the threshold for developmental neurotoxicity, even if assuming a zero background exposure. Using the dose-dependent losses observed in the recent prospective studies (Bashash et al. 2017; Green et al. 2019), this elevated exposure will correspond to an IQ loss of approximately 2 IQ points.

158. Because about two-thirds of the U.S. population receives fluoridated drinking water, one can assume that a similar proportion of the 4 million annual U.S. births (i.e., more than 2.5 million

[28] This widespread dispersal of fluoridated water in commercial products helps to explain the relatively high urine-fluoride levels now seen in non-fluoridated communities versus the situation back in the 1940s (Till et al. 2018).

births) are affected by fluoridation-associated exposure increases. With the 2-point average IQ loss associated with fluoridation, the 2.5 million births will lose a total estimated number of 5 million IQ points annually.

159. This approximate estimate can be compared with calculations made by Professor David Bellinger on IQ losses due to major pediatric diagnoses affecting 0-to-5-year-old children (Bellinger 2012). According to CDC data and Bellinger's calculations, the top pediatric etiologies for IQ loss are preterm birth at 34 million IQ points lost and lead exposure representing 23 million IQ points lost. For fluoridation, the estimate for children aged 0 to 5 years is approximately 25 million IQ points. Even if this estimate is somewhat imprecise, and unevenly distributed, the order of magnitude is likely to be correct and is very considerable.

160. Finally, even if we assume that a threshold exists at approximately 0.8 mg/L in maternal urine (as suggested by mere inspection of the IQ plots in the ELEMENT study for the 6-to-12-year-old cohort members), water fluoridation would still result in substantial IQ losses. As documented in the MIREC study, the 75th percentile maternal urine-fluoride levels (adjusted for creatinine) are 1.04 mg/L in the fluoridated areas versus 0.52 mg/L in the non-fluoridated areas (Till et al. 2018, Table S4). In fluoridated areas, pregnant women above the 75th percentile are already at least 0.29 mg/L above the hypothetical threshold, and thus 25% of the children would then experience an average IQ loss of at least 1.5 points. This would amount to over 4.5 million lost IQ points among 0-to-5-year-olds. Even this smaller amount of IQ losses exceeds the IQ losses attributed to methylmercury exposure in the U.S. (Grandjean et al. 2012).

161. I have made these calculations only to illustrate the significance and impact of neurotoxicity outcomes from fluoridation exposures, and I offer these crude estimates to emphasize my concern that developmental neurotoxicity due to early-life exposure to fluoride is a serious public health

hazard with substantial societal impacts that must be controlled.

X. CONCLUSIONS

162. Recent research has shown that the most vulnerable life stage for many toxicants, particularly those that adversely affect the brain, is during intrauterine and early postnatal development. Fluoride fits into this paradigm, and efforts to control human fluoride exposures must therefore focus on pregnant women and small children.

163. Research on fluoride-exposed workers and laboratory animals suggest that elevated fluoride exposure is toxic to the brain and nerve cells. Epidemiological studies have identified links to learning, memory, and intelligence deficits, though most of the past studies focused on populations with fluoride exposures higher than those typically provided by U.S. water supplies.

164. Epidemiology studies of birth cohorts from the most recent years document that adverse effects on brain development happen at elevated exposure levels that occur widely in North America, in particular in communities with fluoridated drinking water. These new prospective studies are of very high quality and show very similar results, thus leaving little doubt that developmental neurotoxicity is a serious risk associated with elevated fluoride exposure. This evidence shows that community water fluoridation is associated with IQ losses that are substantial and of economic and societal concern.

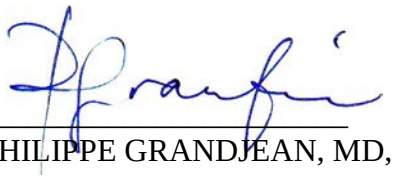
165. Applying methods for standards setting routinely used by the EPA (i.e., Benchmark Dose analysis), the recent studies on IQ deficits in children allow the estimation of a recommended limit that would protect against neurotoxicity. Such calculations show that current allowable limits for fluoride in drinking water and the levels of fluoride added in community water fluoridation programs both greatly exceed a science-based limit that would protect against developmental neurotoxicity.

166. The evidence on fluoride neurotoxicity in the general population is fairly recent and

unlikely to represent the full toxicological perspective, including adverse effects that may occur at longer delays. As has been seen on numerous occasions, the evidence available today may well underestimate the true extent of the fluoride toxicity. With a reasonable degree of scientific certainty, I therefore consider the elevated levels of fluoride exposure in the U.S. population as a serious public health concern.

I declare under penalty of perjury, under the laws of the United States, that the foregoing is true and correct to the best of my knowledge and belief.

Executed on May 20, 2020, in Copenhagen, Denmark.



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Academic degrees

1974, M.D., University of Copenhagen
1975, Diploma in basic medical research, University of Copenhagen
1979, D.M.Sc. (dr.med.), University of Copenhagen

Chronology of employment

1974-1975	Postgraduate training fellowship, University of Copenhagen
1975-1978	Research fellow, Institute of Hygiene, Univ. Copenhagen
1978-1980	Senior research fellow, University of Copenhagen Visiting fellow, Department of Community Medicine, Mount Sinai School of Medicine, New York
1980-1982	Director, Department of Occupational Medicine, Danish National Institute of Occupational Health
1982-	Professor of Environmental Medicine, Odense University
1983-2017	Consultant in Toxicology, Danish Health Authority
1994-2002	Adjunct Professor of Public Health (Environmental Health) and Neurology, Boston University School of Medicine, Boston
2003-	Adjunct Professor of Environmental Health, Harvard T.H. Chan School Public Health, Boston

Awards and honors

Prize essay in medicine, University of Copenhagen (1972)
Fulbright senior research scholarship (1978)
Keynote speaker, Odense University anniversary (1983)
Gitlitz Memorial Lecture, Association of Clinical Scientists, USA (1985)

Fellow, Collegium Ramazzini (1987)
Knight of the Dannebrog, awarded by the Queen of Denmark (1990)
The Dannin prize for medical research (1991)
Fellow, American Association for the Advancement of Science (1994)
Irish Congress Lecturer, Royal College of Physicians of Ireland and Irish Society of Toxicology (1996)
Knight of the Dannebrog, First Degree, awarded by the Queen of Denmark (2003)
'Mercury madness award' for excellence in science in the public interest from eight US environmental organizations (2004)
Emeritus Fellow, International Union of Pure and Applied Chemistry, IUPAC (2009)
Honorary Research Award, International Order of Odd Fellows (2010)
Science Communication Award, University of Southern Denmark (2012)
Bernardino Ramazzini Award (2015)
Basic & Clinical Pharmacology & Toxicology Nordic Award (2015)
Margrethegaarden honorary prize (2016)
John R. Goldsmith Award, International Society for Environmental Epidemiology (2016)

Editorial boards
American Journal of Industrial Medicine (1987-2017)
Applied Organometal Chemistry (1985-1991)
Arbejdsmiljø (Occupational Environment, in Danish, 1983-1990)
Archives of Environmental Health (European Editor, 1986-1992)
Archives of Toxicology (1987-)
Biomarkers (1996-2001)
Central European Journal of Occupational and Environmental Medicine (2015-)
Critical Reviews in Toxicology (1985-2012)
Danish Medical Bulletin (1994-2003)
Environmental Health (Editor-in-Chief, 2002-)
Environmental Health Perspectives (2003-)
Environmental Research (1981-1994 and 2014-2017, Associate Editor, 1995-2014)
Industrial Health (2000-2005)
International Journal of Hygiene and Environmental Health (2001-)
International Journal of Occupational and Environmental Health (1994-2011)
International Journal of Occupational Medicine & Environ Health (1991-
Journal of Clean Technology, Environmental Toxicology, and Occupational Medicine (1992-1998)
Journal of Environmental Medicine (1998-1999)
Naturens Verden (Natural Science, in Danish) (1987-1991)
Ugeskrift for Læger (Danish Medical Journal, in Danish) (1991-2007)

Scientific societies
American Association for the Advancement of Science (Fellow, 1994)
American Public Health Association
Collegium Ramazzini (Fellow, 1987; Member of the Council, 2005-2013)
Danish Medical Association

Danish Societies of Clinical Chemistry, Epidemiology, Occupational and Environmental Medicine, and Public Health
Faroese Society of Science and Letters
International Society for Environmental Epidemiology

Teaching experience

Professor of Environmental Medicine, Odense University (University of Southern Denmark) (1982-). Member of curriculum committee. Coordinator, Global Health class.
Adjunct Professor of Public Health (Environmental Health) and Neurology, Boston University School of Medicine, Boston (1994-2002)
Adjunct Professor of Environmental Health, Harvard T.H.Chan School of Public Health, Boston (2003-)
Invited teacher, École des hautes études en santé publique (EHESP, French school of public health) (2009-)
International: Numerous teaching assignments, including guest lectures at universities and related tasks, e.g. as external examiner, National University of Singapore (1995). External evaluator of PhD theses from other universities, including University of Sydney and University of South Pacific (Fiji).

Research support as Principal Investigator since 2000

2000-2006 NIEHS
Mercury associated neurobehavioral deficit in children
2001-2003 Nordic Arctic Research Programme (NARP)
Changing patterns of biomagnified pollutants in the northern marine environment
2001-2004 Danish Medical Research Council
Exposure assessment for endocrine disruptors
2002-2004 Danish Medical Research Council
Environmental epidemiology research
2003-2004 European Commission
Assessment of Neurobehavioral Endpoints and Markers of Neurotoxicant Exposures (ANEMONE)
2003-2005 Danish Medical Research Council
Research in hormone related substances
2003-2006 NIEHS ES11687
Effects of perinatal disruptors in children
2003-2007 EPA STAR RD-83075801-0
Children's vulnerability to environmental immunotoxicant
2004-2011 NIEHS ES12199
Epidemiology of immunotoxicant exposure in children
2006-2011 NIEHS ES13692
Health effects of lifetime exposure to food contaminants
2006-2012 NIEHS ES14460
Three-generation human study of reproductive effects of marine food contaminants
2008-2012 Danish Council for Strategic Research
Environmental pollutant impact on antibody production against current and new childhood vaccines
2007-2013 NIEHS ES009797

Mercury associated neurobehavioral deficit in children
2011-2017 NIEHS ES012199
Epidemiology of immunotoxicant exposure in children
2012-2020 NIEHS ES021993 and NSF OCE-1321612
Immunotoxity in Humans with Lifetime Exposure to Ocean Pollutants
2013-2019 NIEHS ES021477
Glucose Metabolism in Adults Prenatally Exposed to Diabetogenic Pollutants
2013-2018 NIEHS ES021372
Pollutant-related diabetes in the Nurses' Health Study II
2014-2020 NIEHS ES023376
Gut Microbiome in Adults with Early Life Exposures to Environmental Chemicals

Major Current Funding as Principal Investigator
2017-2020 NIEHS ES026596
Inflammation and metabolic abnormalities in pollutant-exposed children
2017-2022 NIEHS P42ES027706
Sources, Transport, Exposure and Effects of PFASs (STEEP)
2019-2024 ATSDR TS000313
Assessment of PFAS exposures and health effects in two Massachusetts communities with PFAS drinking water contamination
2019-2023 NIEHS ES030394
Vulnerability During Infancy to Immunotoxic Contaminant Exposures

Major committees, boards and elective offices
Danish:
Danish Medical Association: Member, Prevention Council (2011-2014)
Danish Medical Research Council: Consultant on environmental medicine (1985-1990); Member, Joint Research Council Committee on Environmental Research (1986-1991); Member of DMRC (1992-1998)
Danish Society of Community Medicine: Secretary (1977-1978)
Danish Society of Industrial Medicine: Board Member (1974-1983)
Ministry of Education: Member, Committee on Toxicology (1984-1986); Member, Committee on Environmental Education (1986-1987)
Ministry of the Environment: Member, Council on Environmental Chemicals (1983-1989); Member, Environmental Appeal Board (1986-2010); Member, Environmental Research Council (1990-1992); Member, Advisory Committee on Pesticide Research (1995-2004 and 2018-2020); Member, Advisory Committee on Arctic Research (1996-2004)
Ministry of Health: numerous committee appointments; Chair, Committee on Risk Perception (2000-2001)
Ministry of Labour: Consultant on Occupational Health, Council on Occupational Safety and Health (1983-1993); Member, Occupational Health Council Research Committee (on behalf of the Danish Medical Research Council) (1984-1990 and 1999-2003)
Ministry of Research: Chair, Committee on Research at the Faroe Islands (1995-1996); Member, Committee on Scientific Dishonesty (2004-2006); Chair, Program Committee on Non-Ionizing Radiation (2004-2009)
Odense University (from 2000 University of Southern Denmark), elected

offices: Chairman, Institute of Community Health (1982-1985; 1996-1999); Member of Executive Committee, Institute of Community Health (from 2000 Institute of Public Health) (1986-1995; 2000-2005); Member, Faculty Research Committee (1983-1985); Member, Curriculum Committee (1984-1986); Member, Faculty Council (1985-1993); Vice-Dean (1991-1993); Member, Scientific Integrity Committee (2003-2022)

United States and international:

Academy of Finland: member of panel evaluating the National Institute of Public Health (1995), site visit of center of excellence (2001)

Agency for Toxic Substances and Disease Registry: Workshop Rapporteur, Neurobehavioral Test Batteries for Use in Environmental Health Field Studies (1992); Member, Expert Panel of Mercury (1998)

Association of Schools of Public Health in the European Region: Treasurer (1975-1977)

BioMedCentral: Member, Editors Advisory Group (2011-2013)

Boston Environmental Hazards Center: Consultant (1994-1999)

Collegium Ramazzini: President, International Conference, The precautionary principle: Implications for research and prevention in environmental and occupational health (2002); Member, Executive Council (2005-2013)

Commission of the European Communities: National Expert, Working Party on Environmental and Lifestyle-Related Diseases (1988-1990); ad hoc Consultant for evaluation of research applications; ad hoc Scientific Advisor on Risk Assessment (2009-); Member, Scientific Committee on Emerging and Newly Identified Health Risks; – Working group on Dental Amalgam (Human Health)(2012-2013)

European Environment Agency: Member, Scientific Committee (2012-2020)

European Food Safety Authority: Member, Panel on Contaminants in the Food Chain responsible for 85 opinions (2003-2009); Member of Working Groups on mercury, polychlorinated biphenyls, cadmium, lead, and benchmark dose

Food Advisory Committee, U.S.FDA, Methylmercury: invited expert (2002)

INMA (Infancia y Medio Ambiente), Spain: Member, Project Steering Committee (2010-)

Institut de Recherche Santé, Environnement et Travail, France: Member, Board of Advisers (2015-)

International Agency for Research on Cancer: Member of Task Group, Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 47 (1988), Vol. 49 (1989), as chairman, Vol. 58 (1993), and as Subgroup chair, Vol. 100C (2009)

International Commission on Occupational Health: Danish Delegation Secretary (1982-90); Member, Scientific Committee on the Toxicology of Metals (1987-); Member of the Board (1990-1996)

International Programme on Chemical Safety: Member of Task Group, Environmental Health Criteria, Vol. 36 (1984) and 72 (1986)

International Society for Environmental Epidemiology: Councillor (1991-1994)

International Union of Pure and Applied Chemistry: Member, Subcommittee on the Toxicology of Nickel (1979-1989); Titular

Member (1985-1991) and Chairman (1987-1991), Commission on Toxicology; Chairman, Subcommittee on Risk Assessment (1985-1989)
Instituto de Saude Ambiental, Lisboa, Portugal: Member, External Advisory Committee (2018-2020)
Karolinska Institute (Stockholm, Sweden): Member of international evaluation panel on environmental medicine (1993)
Ministry for Scientific Policy (Belgium): Consultant on national research program on health hazards (1990 and 1994)
National Institutes of Health (USA): Member of Special emphasis panels (2009-)
NATO Priority Area Panel on Environmental Security: Member (1996-1997)
Norwegian Research Council: ad hoc reviewer (2001-2008); Chairman of Environment and Health Review Group (2009-2010); member of steering committee (2011-2015)
Prenatal Programming and Toxicity (PPTOX) conferences: Organizer/ Chair/Co-chair, Torshavn (2007), Miami (2009), Paris (2012), Boston (2014), Kita-Kyushu (2016), Torshavn (2018)
Society of Occupational and Environmental Health: Member, Governing Council (1990-1993)
Swedish Council for Work Life Research: Member, Priority Committee on Chemical Health Risks (1997-1998)
U.N.Environment Programme: Member, Global Mercury Assessment Working Group (2002)
U.S. Environmental Protection Agency: Member, SAB/SAP Endocrine Disruptor Screening Program Subcommittee (1998-1999); Member, Food Quality Protection Act (FQPA) Science Review Board (SRB)(1999-2003)
White House Office of Science and Technology Policy: Team leader and presenter, Workshop on Scientific Issues Relevant to Assessment of Health Effects from Exposure to Methylmercury (1998)
World Health Organization: Temporary Adviser or Consultant on several occasions, five times elected Rapporteur; Member, European Advisory Committee on Health Research (2011-2017)

Books

1. Grandjean P, ed. Standards setting. Copenhagen: Occupational Health Foundation, 1977, 210 pp.
2. Grandjean P, Nielsen T. Organiske blyforbindelser, forurening og toksikologi (Organolead compounds, pollution and toxicology, in Danish). Report No. SNV PM 879. Stockholm: Naturvårdsverket, 1977, 78 pp.
3. Grandjean P. Occupational health aspects of construction work. EURO Reports and Studies 86. Copenhagen: World Health Organization, Regional Office for Europe, 1983, 28 pp. (also published in German, French and Russian)
4. Grandjean P, ed. Biological effects of organolead compounds. Boca Raton, FL: CRC Press, 1984, 278 pp.
5. Grandjean P, Tarkowski S, eds. Toxic oil syndrome: mass food poisoning in Spain. Copenhagen: World Health Organization, Regional Office for Europe, 1984, 92 pp. (also published in Spanish)
6. Grandjean P. Miljø og forebyggelse. (Environment and prevention, student's guide in Danish). Copenhagen: F.a.d.L.'s Forlag, 1984, 109 pp.
7. Gilioli R, Grandjean P, Johnson B, Seppäläinen AM, Tarkowski S, eds. Neurobehavioural methods in occupational and environmental health. Environmental Health No. 3. Copenhagen: World Health Organization, Regional Office for Europe, 1985, 209 pp.
8. Grandjean P, ed. Neurobehavioural methods in occupational and environmental health. Environmental Health No. 6. Copenhagen: World Health Organization, Regional Office for Europe, 1985, 72 pp.
9. Grandjean P, ed. Miljømedicin (Environmental medicine, textbook in Danish). Copenhagen: F.a.d.L.'s Forlag, 1986, 257 pp.
10. Grandjean P, ed. Trace elements in human health and disease: extended abstracts. Environmental Health No. 20. Copenhagen: World Health Organization, Regional Office for Europe, 1987, 230 pp.
11. Grandjean P, ed. Trace elements in human health and disease: symposium report. Environmental Health No. 26. Copenhagen: World Health Organization, Regional Office for Europe, 1987, 134 pp.
12. Grandjean P, Kimbrough RD, Rantanen J, Tarkowski S, Yrjänheikki E. Assessment of health risks in infants associated with exposure to PCBs, PCDDs and PCDFs in breast milk. Environmental Health No. 29. Copenhagen: World Health Organization, Regional Office for Europe, 1988, 116 pp.
13. Grandjean P, ed. Miljømedicin, 2. udg. (Environmental medicine, 2nd ed., textbook in Danish). Copenhagen: F.a.d.L.'s Forlag, 1988, 311 pp.
14. Kimbrough RD, Mahaffey KR, Grandjean P, Sandø SH, Ruttstein DD. Clinical Effects of Environmental Chemicals: A Software Approach to Etiologic Diagnosis. New York: Hemisphere, 1989, 110 pp. and one floppy disk.
15. Grandjean P. Skin Penetration: Hazardous Chemicals at Work. (Published on behalf of the Commission of the European Communities.) London: Taylor and Francis, 1990, 187 pp.
16. Grandjean P, ed. Ecogenetics: Genetic Predisposition to Toxic

Effects of Chemicals. London: Chapman & Hall, 1991, 288 pp.
17. Grandjean P, ed. Miljø, sundhed og samfund (Environment, health and society, in Danish). Copenhagen: Nyt Nordisk Forlag, 1991, 453 pp.
18. Grandjean P, Brown SS, Reavey P, Young DS, Rej R (eds). Biomarkers of Chemical Exposure. Proceedings of the Arnold O. Beckman/IFCC European Conference on Environmental Toxicology. Clin Chem 1994; 40 (issue 7B).
19. Toppari J, Larsen JC, Christiansen P, Giwercman A, Grandjean P, Guillette LJ, Jr, Jégou B, Jensen TK, Jouannet P, Keiding N, Leffers H, McLachlan JA, Meyer O, Müller J, Rajpert-DeMeyts E, Scheike T, Sumpter J, Skakkebaek N. Male reproductive health and environmental chemicals with estrogenic effects. Copenhagen: Danish Environmental Protection Agency, 1995, 166 pp.
20. Grandjean P, Brown SS, Reavey P, Young DS, Sampson E (eds). Biomarkers. Proceedings of the Second Arnold O. Beckman/IFCC European Conference on Environmental Toxicology. Clin Chem 1995; 41 (issue 12B).
21. Grandjean P. Farlig forurening (Dangerous pollution, in Danish). Copenhagen: Nyt Nordisk Forlag and National Board of Health, 1998, 174 pp.
22. Grandjean P ed. Human health effects of environmental mercury exposure (special issue). Environ Res 1998; 77 (67-177).
23. Grandjean P, Sofritti M, Minardi F, Brazier J (eds). The Precautionary Principle. Implications for research and prevention in environmental and occupational health. Eur J Oncol Library 2003; 2: 1-245. Also published in Int J Occup Med Environ Health 2004; 17: 3-201.
24. Grandjean P (ed). Prenatal programming and toxicity. Basic Clin Pharmacol Toxicol. 2008; 102(2): 71-273.
25. Gee D, Grandjean P, Hansen SF, van den Hove S, MacGarvin M, Martin J, Nielsen G, Quist D, Stanners D, eds. Late Lessons from Early Warnings, volume II (EEA Report No 1/2013). Copenhagen, European Environment Agency, 2013, 746 pp.
26. 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 (232 pp.).
27. Grandjean P, Hermann P. Kemi på hjernen – går ud over enhver forstand. København: Gyldendal, 2015 (334 sider).
28. Grandjean P. Cerveaux en danger (Brains in danger, in French). Translated by Odile Demange. Paris: Buchet Chastel, 2016 (336 pp.).
29. Kishi R, Grandjean P, eds. Health Impacts of Developmental Exposure to Environmental Chemicals. Singapore: Springer, 2020 (555 pp.)

Publications in international peer-reviewed journals

1. Grandjean P, Holma B. A history of lead retention in the Danish population. Environ Biochem Physiol 1973; 3: 268-73.
2. Grandjean P. Lead in Danes, historical and toxicological studies. Environ Qual Saf 1975; Suppl. Vol. 2: 6-75.
3. Grandjean P. Possible effect of lead on egg-shell thickness in kestrels 1874-1974. Bull Environ Contam Toxicol 1976; 16: 101-6.
4. Grandjean P. Regional distribution of lead in human brains. Toxicol Lett 1978; 2: 65-9.
5. Nielsen T, Jensen KA, Grandjean P. Organic lead in normal human brains. Nature (Lond.) 1978; 274: 602-3.
6. Grandjean P. Lead concentration in single hairs as a monitor of occupational lead exposure. Int Arch Occup Environ Health 1978; 42: 69-81.
7. Grandjean P, Lintrup J. Erythrocyte-Zn-protoporphyrin as an indicator of lead exposure. Scand J Clin Lab Invest 1978; 38: 669-75.
8. Grandjean P, Arnvig E, Beckmann J. Psychological dysfunctions of lead-exposed workers: Relation to biological parameters of exposure. Scand J Work Environ Health 1978; 4: 295-303.
9. Grandjean P. Widening perspectives of lead toxicity, a review of health effects of lead exposure in adults. Environ Res 1978; 17: 303-21. (Also published as a special report to the U.S. National Institute of Environmental Health Sciences)
10. Grandjean P. Occupational lead exposure in Denmark: Screening with the haematofluorometer. Br J Ind Med 1979; 36: 52-8.
11. Grandjean P, Nielsen OV, Shapiro IM. Lead retention in ancient Nubian and contemporary populations. J Environ Path Toxicol 1979; 2: 781-7.
12. Grandjean P, Nielsen T. Organolead compounds, environmental health aspects. Residue Rev 1979; 72: 97-148.
13. Arnvig E, Grandjean P, Beckmann J. Neuropsychological effect of heavy lead exposure determined with psychological tests. Toxicol Lett 1980; 5: 399-404.
14. Hertz MM, Bolwig TG, Grandjean P, Westergaard E. Lead poisoning and the blood-brain barrier. Acta Neurol Scand 1981; 63: 286-96.
15. Grandjean P, Selikoff IJ, Shen SK, Sundermann FW Jr. Nickel concentrations in plasma and urine of shipyard workers. Am J Ind Med 1981; 1: 181-9.
16. Olsen NB, Hollnagel H, Grandjean P. Indicators of lead exposure in an adult Danish suburban population. Dan Med Bull 1981; 28: 168-76.
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18. Grandjean P, Kon SH. Lead exposure of welders and bystanders in a ship repair yard. Am J Ind Med 1981; 2: 65-70.
19. Grandjean P, Lintrup J. Sources of variation in fluorometry of zinc-protoporphyrin in blood. Scand J Work Environ Health 1981; 7: 311-2.
20. Grandjean P, Olsen NB, Hollnagel H. Occupationally related lead exposure in the general population. Scand J Work Environ Health 1981;

7: 298-301.
21. Grandjean P. Occupational fluorosis through 50 years: clinical and epidemiological experiences. Am J Ind Med 1982; 3: 227-36.
22. Nielsen OV, Grandjean P, Bennike P. Chemical analyses of archaeological bone samples: Evidence for high lead exposure on the Faroe Islands. J Dan Archaeol 1982; 2: 145-8. (also published in Faroese: Blyggj i føroyingum, Mondul 1983; 9: 27-31)
23. Grandjean P. Storage depots in the body: Passive retention or time bomb? (Editorial) Am J Ind Med 1983; 4: 489-90.
24. Grandjean P, Wulf HC, Niebuhr E. Sister chromatid exchange in response to variations in occupational lead exposure. Environ Res 1983; 32: 199-204.
25. Grandjean P, Thomsen G. Reversibility of skeletal fluorosis. Br J Ind Med 1983; 40: 456-61.
26. Grandjean P. Lead poisoning: Hair analysis shows the calendar of events. Hum Toxicol 1984; 3: 223-8.
27. Grandjean P, Hansen ON, Lyngbye K. Analysis of lead in circum-pulpal dentin of deciduous teeth. Ann Clin Lab Sci 1984; 14:270-5.
28. Eskildsen J, Grandjean P. Lead exposure from lead pellets: Age-related accumulation in mute swans. Toxicol Lett 1984; 21: 225-9.
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33. Grandjean P, Lyngbye T, Hansen ON. Lead concentration in deciduous teeth: Variation related to tooth type and analytical technique. J Toxicol Environ Health 1986; 19: 437-45.
34. Grandjean P. After Chernobyl (Editorial). Arch Environ Health 1986; 41: 277.
35. Andersen O, Grandjean P. Effects of inorganic and organic lead compounds on chromosomal length in human lymphocytes. Appl Organomet Chem 1987; 1: 15-19.
36. Grandjean P, Andersen O, Nielsen GD. Carcinogenicity of occupational nickel exposures: An evaluation of the epidemiological evidence. Am J Ind Med 1988; 13: 193-209.
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38. Grandjean P, Berlin A, Gilbert M, Penning W. Preventing percutaneous absorption of industrial chemicals: The "skin" denotation. Am J Ind Med 1988; 14: 97-107.
39. Lyngbye T, Hansen ON, Grandjean P. Bias resulting from non-participation in childhood epidemiological studies: A study of low-level lead exposure. Scand J Soc Med 1988; 16: 209-15.

40. Grandjean P. Ancient skeletons as silent witnesses of lead exposures in the past. CRC Crit Rev Toxicol 1988; 19:11-21.
41. Madsen HHT, Skjødt T, Jørgensen PJ, Grandjean P. Blood lead levels in patients with lead shot retained in the appendix. Acta Radiol 1988; 29: 745-6.
42. Andersen O, Grandjean P. Effects of tetraethylthiuram disulfide on the toxicokinetics of cadmium in mice. Pharmacol Toxicol 1989; 64: 210-5.
43. Lyngbye T, Hansen ON, Grandjean P. Neurological deficits in children: Medical risk factors and lead exposure. Neurotoxicol Teratol 1989; 10: 531-7.
44. Grandjean P, Hollnagel H, Hedegaard L, Christensen JM, Larsen S. Blood lead-blood pressure relationships: Alcohol intake and hemoglobin as confounders. Am J Epidemiol 1989; 129: 732-9.
45. Hansen ON, Trillingsgaard A, Beese I, Lyngbye T, Grandjean P. A neuropsychological study of children with elevated dentine lead level: Assessment of the effect of lead in different socioeconomic groups. Neurotoxicol Teratol 1989: 11: 205-13.
46. Grandjean P, Jensen BM, Sandø SH, Jørgensen PJ, Antonsen S. Delayed blood regeneration in lead exposure: An effect on reserve capacity. Am J Publ Health 1989; 79: 1385-8.
47. Grandjean P. Bone analysis: Silent testimony of lead exposures in the past. Medd Grønland Man Soc 1989; 12: 156-60.
48. Grandjean P, Hørder M, Thomassen Y. Fluoride, aluminum and phosphate kinetics in cryolite workers. J Occup Med 1990;32:58-63.
49. Grandjean P, Kristensen K, Jørgensen PJ, Nielsen GD, Andersen O. Trace element status in alcoholism before and during disulfiram treatment. Ann Clin Lab Sci 1990; 20: 28-35.
50. Nielsen GD, Jepsen LV, Jørgensen PJ, Grandjean P, Brandrup F. Nickel-sensitive patients with vesicular hand eczema: Oral challenge with a diet naturally high in nickel. Br J Dermatol 1990; 122: 299-308.
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53. Lyngbye T, Grandjean P, Hansen ON, Jørgensen PJ. Validity and interpretation of blood lead levels: A study of Danish school children. Scand J Clin Lab Invest 1990; 50: 441-9.
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55. Lyngbye T, Hansen ON, Grandjean P. Predictors of tooth-lead level with special reference to traffic. Int Arch Occup Environ Health 1990; 62: 417-22.
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57. Lyngbye T, Hansen ON, Grandjean P. Lead concentration in deciduous teeth from Danish school children. Dan Med Bull 1991; 38: 89-93.

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60. Grandjean P, Sandoe SH, Kimbrough RD. Nonspecificity of clinical signs and symptoms caused by environmental chemicals. Hum Exp Toxicol 1991; 10: 167-73.
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62. Grandjean P, Andersen O. Lung cancer in filling station attendants. Am J Ind Med 1991; 20: 763-8.
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64. Grandjean P, Nielsen GD, Jørgensen PJ, Hørder M. Reference intervals for trace elements in blood: Significance of risk factors. Scand J Clin Lab Invest 1992; 52: 321-337.
65. Grandjean P, Olsen JH, Jensen OM, Juel K. Cancer incidence and mortality in workers exposed to fluoride. J Natl Cancer Inst 1992; 84: 1903-9.
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intrauterine and postnatal exposures. Clin Chem 1994; 40: 1395-1400.
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88. Toppari J, Larsen JC, Christiansen P, Giwercman A, Grandjean P, Guillette LJ, Jr, Jégou B, Jensen TK, Jouannet P, Keiding N, Leffers H, McLachlan JA, Meyer O, Müller J, Rajper-DeMeyts E, Scheike T, Sharpe R, Sumpter J, Skakkebaek NE. Male reproductive health and environmental xenoestrogens. Environ Health Perspec 1996; 104 (Suppl.4): 741-803.
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FOR THE NORTHERN DISTRICT OF CALIFORNIA
AT SAN FRANCISCO

FOOD & WATER WATCH, et al., Plaintiffs, vs. U.S. ENVIRONMENTAL PROTECTION AGENCY, et al. Defendants.	Civ. No. 17-CV-02162-EMC **DECLARATION OF HOWARD HU, MD, MPH, ScD**

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I, Howard Hu, MD, MPH, ScD, declare that:

1. I am a physician-scientist trained in internal medicine, occupational/environmental medicine, epidemiology and general public health who has held leadership positions in science and academia for over 2 decades.

2. I am also the Principal Investigator of ongoing research that is examining the impact of early-life exposures to fluoride on neurobehavioral development in the offspring participating in the Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) project.

I. SUMMARY OF QUALIFICATIONS

3. A complete summary of my qualifications and publications can be found in my Curriculum Vitae, which has been marked as Plaintiffs' Exhibit 5 and attached herein.

4. As relevant to my testimony here, I am an epidemiologist with decades of research experience investigating the impact of environmental toxicants on human health. In 1990, I received a Doctor of Science degree in Epidemiology from the Harvard School of Public Health, and since that time have taught epidemiology at Harvard, University of Michigan, and University of Toronto, where I served as Dean of the School of Public Health.

5. I hold editorial positions on leading environmental and occupational health journals, including the *American Journal of Industrial Medicine, Current Environmental Health Reports* and *Environmental Health Perspectives*, and serve as a peer reviewer for the *American Journal of Epidemiology*, *Epidemiology*, *Journal of the American Medical Association*, *Lancet*, *New England Journal of Medicine*, and *Pediatrics,* amongst others.

6. My own epidemiological research has resulted in hundreds of peer-reviewed publications in leading scientific journals. For the past 29 years, this research has been continuously funded by the National Institutes of Health (NIH) through a number of competitive R01 grants.

7. The Environmental Protection Agency (EPA) has funded several of my epidemiological studies, including a $7.8 million research grant to study the effects of metals mixtures on children's health. I have also served as an expert advisor to the EPA, including as a member of EPA's Science Advisory Board on Relative Risk Reduction Strategies and as an expert reviewer of EPA's recent draft report on the concentration-response functions between lead exposure and cardiovascular disease.

8. In 1993, I co-founded the ELEMENT research project, a pregnancy and birth cohort that has been funded by both the EPA and NIH. Since its inception, ELEMENT has evolved into a highly successful, award-winning project involving collaborators at the University of Michigan, Harvard, and other academic institutions in the U.S., Canada, and Mexico.

9. Through the ELEMENT cohort, we have studied how prenatal exposure to environmental toxicants—including lead, mercury, and fluoride—affect children's health, including their neurodevelopment. Thus far, the ELEMENT cohort has generated over 80 high-impact publications and provided evidence contributing towards environmental health policies around the world, including the EPA's national air standard for lead and the CDC's "Guidelines for the Identification and Management of Lead Exposure in Pregnant and Lactating Women."

10. In 2012, following the National Research Council's (NRC) call for more research to investigate the neurobehavioral risks of fluoride exposure, the team I lead successfully competed for a peer-reviewed NIH RO1 grant to study the neurodevelopmental effects of pre- and post-natal fluoride exposures. This research was funded with an understanding that it would provide a major contribution to fluoride risk assessment and policy decision-making on the neurotoxicity concerns identified by the NRC.

11. To date, my team has published five peer-reviewed studies on fluoride, including two prospective studies on fluoride and neurodevelopment that were published in the world's two most

prominent environmental health journals: *Environmental Health Perspectives* and *Environment International* (Bashash 2017, Bashash 2018, Cantoral 2019, Liu 2019, Thomas 2016). As with our own research, the journal *Environmental Health Perspectives* is funded by the NIH.

II. SUMMARY OF OPINIONS

12. The ELEMENT prospective cohort studies of fluoride's neurodevelopmental effects are methodologically rigorous studies that provide scientifically reliable and robust results.

13. The results of the ELEMENT prospective cohort studies are consistent with and support the conclusion that fluoride is a developmental neurotoxicant at levels of exposure seen in the general population in water-fluoridated communities.

III. BASIS FOR OPINIONS

A. The Methodological Strengths of the ELEMENT Studies

14. ***Prospective Birth Cohort Study Design***: One of the key strengths of our ELEMENT research is that it has utilized a prospective birth cohort design. Prospective studies (aka longitudinal cohort studies designed at the outset to enable research on the topics of interest and that follow a defined group of individuals) are recognized by epidemiologists as the ideal study design for investigating the impact of environmental toxicants on human health, in part, because the measurement of exposure precedes the development of disease/dysfunction. This is important because it permits greater confidence in the causal relationship of an association since the requirement of temporality is satisfied i.e., the exposure precedes the effect, which, in turn, is one of the components of the Bradford Hill criteria. Where there is suspicion that a chemical may exert a toxic effect *in utero*, a birth cohort study design is critical because it allows an assessment of exposure during the prenatal period.

15. ***Effective Control for Other Factors that Influence IQ:*** Our ELEMENT studies have considered and controlled for a large number of factors known to affect neurodevelopment, which

increases the rigor of the results. First, we excluded women from the study who had characteristics known to affect neurodevelopment, including gestational diabetes, renal disease, hypertension, circulatory diseases, use of illicit drugs, and alcohol consumption. Second, our analyses of fluoride and neurodevelopment controlled for a large number of potential confounders, including maternal age, maternal education, maternal IQ, birth weight, gestational age at time of delivery, sex of child, birth order, maternal smoking, and marital status. Third, we performed sensitivity analyses which controlled for the quality of the child's home environment (i.e., HOME),[1] as well as prenatal lead and mercury exposures.

16. ***Blinded Assessments***: Our studies employed a "blinded" study design where neither the examiners nor the subjects were aware of the subject's fluoride exposure status at the time of the neurodevelopmental exams. A blinded study design is superior to a non-blinded study because it helps protect against bias, including unconscious bias, in the assessment.

17. ***Individual Biomarkers of Both Prenatal and Postnatal Exposure***: As cohort studies, our investigations have collected and utilized individual measurements of fluoride exposure, covariates, and the outcomes of interest. Cohort studies with individual measurements of exposure, covariates and outcomes are considered much more robust than studies with group-level metrics (otherwise known as "ecological studies") because the accuracy and precision of individual-level measures are far superior to the estimates of these parameters that are associated with ecological studies. In our studies, we measured prenatal fluoride exposure by testing archived samples of the mother's urine that were collected during pregnancy. Urine fluoride is a well-accepted biomarker of total fluoride exposure. As the EPA has

[1] The HOME Score is a rating that is performed by a research observer who gains permission to enter the home and observe the interactions between the offspring and other family members, as well as other characteristics of the home environment. It is intended to try to capture the ability of the home to enrich a child's educational development and skill development. It is often highly correlated with socio-economic status, but it also has some independent value of its own in determining a child's neurodevelopmental trajectory.

recognized, "archives of biological samples from birth cohort studies . . . provide critical information on the prenatal and childhood determinants of adult disease" (EPA-NIEHS 2017, p. 9). The archived urine samples in our studies were tested under the oversight and direction of Dr. Angeles Martinez-Mier, a leading authority on the measurement of fluoride in urine and plasma.

18. As I acknowledge and discuss further below, there are some limitations with our urine-based exposure estimates. These limitations, however, do not provide a plausible explanation for the results we have observed as they create *non-differential* imprecision in the exposure variable (in this case, the non-differential exposure misclassification is sometimes referred to as "random" or "classical" measurement error associated with exposure). It is a basic epidemiologic axiom that non-differential errors, such as non-differential exposure misclassification, bias the results towards the null (i.e., no association exists), rather than create spurious associations where none otherwise exist. I discuss this further below.

19. ***Large Cohort Sizes***: Our studies have involved a sufficiently large number of mother-offspring pairs to permit statistical analyses that are stable and robust. In our 2017 study ("Bashash 2017"), we investigated fluoride's relationship with intelligence among 299 mother-offspring pairs. This included 287 mother-offspring pairs for the analysis of intelligence at age 4, and 211 mother-offspring pairs for an analysis of intelligence at ages 6-12. In our 2018 study ("Bashash 2018"), we investigated the relationship between fluoride and symptoms of Attention-Deficit Hyperactivity Disorder (ADHD) among a total of 213 mother-offspring pairs, with the ADHD assessment conducted between the ages of 6 and 12.

20. ***Reliable Neurocognitive Tests:*** Our 2017 study on intelligence used validated, standardized neurocognitive tests that were administered by a team of psychologists. For the 4-year old children, we used the McCarthy Scales of Children's Abilities (MSCA), and focused on the General

Cognitive Index (GCI) score. For the 6-12 year old children, we used the Spanish version of the Wechsler Abbreviated Scale of Intelligence (WASI)[2] to assess Full-Scale IQ. All raw scores were standardized for age and sex. The examining psychologists were trained and supervised by an experienced developmental psychologist, and independent testing confirmed a very high correlation (0.99) in the scoring, thus confirming a high degree of inter-examiner reliability.

21. ***Reliable Neurobehavioral Tests:*** Behaviors associated with ADHD were assessed using the Spanish version of the Conners' Rating Scales-Revised (CRS-R)[3] and Conners' Continuous Performance Test (CPT-II, 2nd Edition).[4] All measures of ADHD-behaviors were standardized for age- and sex. Higher T-scores (mean of 50, SD of 10) indicate poorer performance. All psychometric tests were applied under the supervision of an experienced psychologist.

22. ***Appropriate Statistical Analyses that Did Not Assume Linearity***: We used the same standard statistical analyses for our fluoride studies as we have used for our other ELEMENT studies. These included regression analyses that appropriately adjusted for potential confounders, as well as Generalized Additive Models (GAM) that visualized adjusted associations between fluoride and neurodevelopment for purposes of assessing the linearity of the relationship. We did *not* assume

[2] The WASI shows strong criterion validity with the full-length Wechsler Intelligence Scale for Children (WISC-III; ages 6-16 yrs), and the Wechsler Adult Intelligence Scale (WAIS; ages 16+ yrs). The correlation coefficient between the Full Scale IQ of the WASI and WISC-III is 0.81 (Wechsler, 1991), and 0.92 between the WASI and the WAIS-III (Wechsler, 1999), indicating a high covariance between the abbreviated and full-length measures of intellectual ability. The WASI is also correlated with another abbreviated IQ test, the Kaufman Brief Intelligence Test (r = 0.89), providing evidence for convergent validity (Hays et al., 2002). Finally, the WASI demonstrates excellent internal consistency (reliability=0.976) (based on data from Tables 5.1 and 5.8 of the WASI manual).

[3] The CRS-R contains three ADHD scales that correspond with the Diagnostic and Statistical Manual of Mental Disorders – 4th edition (DSM-IV) criteria for ADHD: 1) DSM-IV Inattention Index, 2) DSM-IV Hyperactive-Impulsive Index, and 3) DSM-IV Total Index (inattentive and hyperactive-impulsive behaviors combined). It also examines seven types of behavior problems that were derived through factor analysis, including: Oppositional, Anxious-Shy, Cognitive Problem/Inattention, Hyperactivity, Perfectionism, Psychosomatic, and Social Problems. For our study, we examined the three DSM-IV ADHD scales as our primary outcomes because these scales are intended to screen for ADHD, and are commonly used to study the association between diverse environmental contaminants and ADHD- behavior problems.

[4] The CPT-II is a computer-administered signal detection paradigm. Using the CPT-II, we measured errors of omission and commission, and hit reaction time (response latency).

linearity in the dose-response relationship. Additionally, we took appropriate steps to eliminate the influence of outliers and influential points.

B. Prenatal Fluoride Exposure Is Associated with Substantial and Significant Adverse Effects on IQ and ADHD-Behaviors in the ELEMENT Cohort

23. In the ELEMENT cohort, we found that prenatal fluoride exposure has a linear, dose-response relationship with reduced IQ among both 4-year old and 6-12 year old children (Bashash 2017).[5] In our main model that adjusted for potential confounders, we found that each 0.5 mg/L increase in maternal urinary fluoride (which approximates the interquartile range, i.e., the difference between the 25th v. 75th percentile) was significantly associated with a loss of 3.15 GCI points among the 4-year-olds, and a loss of 2.5 IQ points among the 6-to-12 year olds. These are substantial reductions in intelligence that rival the effect sizes associated with lead exposure. As one measure of practical impact developed and published in 2009 by an expert from the Economics Policy Institute, each IQ point lost due to lead exposure was estimated to represent a loss of $17,815 in present discounted value of lifetime earnings (in 2006 USD) (Gould 2009).

24. Visual assessment of the adjusted associations between fluoride and intelligence confirmed the monotonic, mostly linear nature of the relationships (see Figures A and B). Notably, there was no evidence of a threshold among the 4-year olds, although there was some suggestion of a threshold at approximately 0.8 mg/L among the 6-12 year olds.

[5] We have subsequently reported an analysis, in abstract form, of neurocognitive outcomes at ages 1 to 3, as measured through the Mental Development Index (Thomas 2018). These results are consistent with the age 4 and age 6-12 analyses in that they show significant adverse associations with maternal urinary fluoride. I do not rely on these results here, however, since they have not yet been published in full

Figure A: Visual Association Between Maternal Urinary Fluoride and Intelligence at Age 4

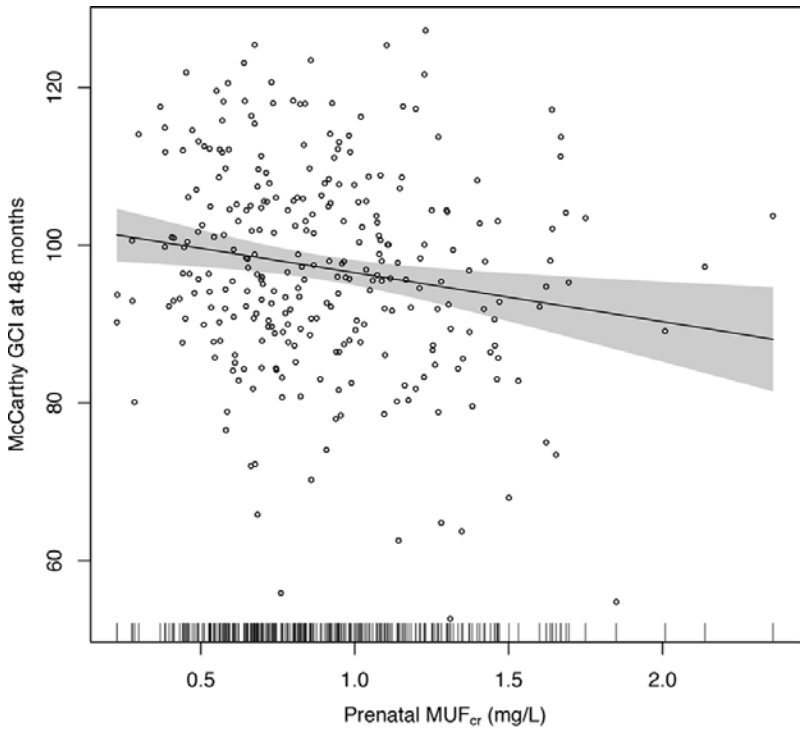
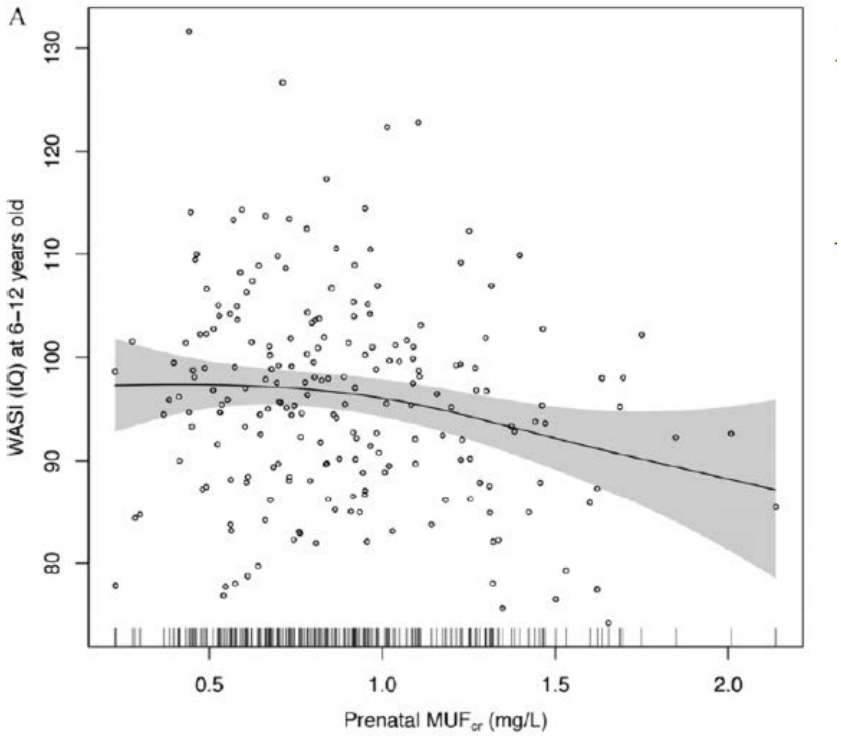


Figure B: Visual Association Between Maternal Urinary Fluoride and Intelligence at Ages 6-12

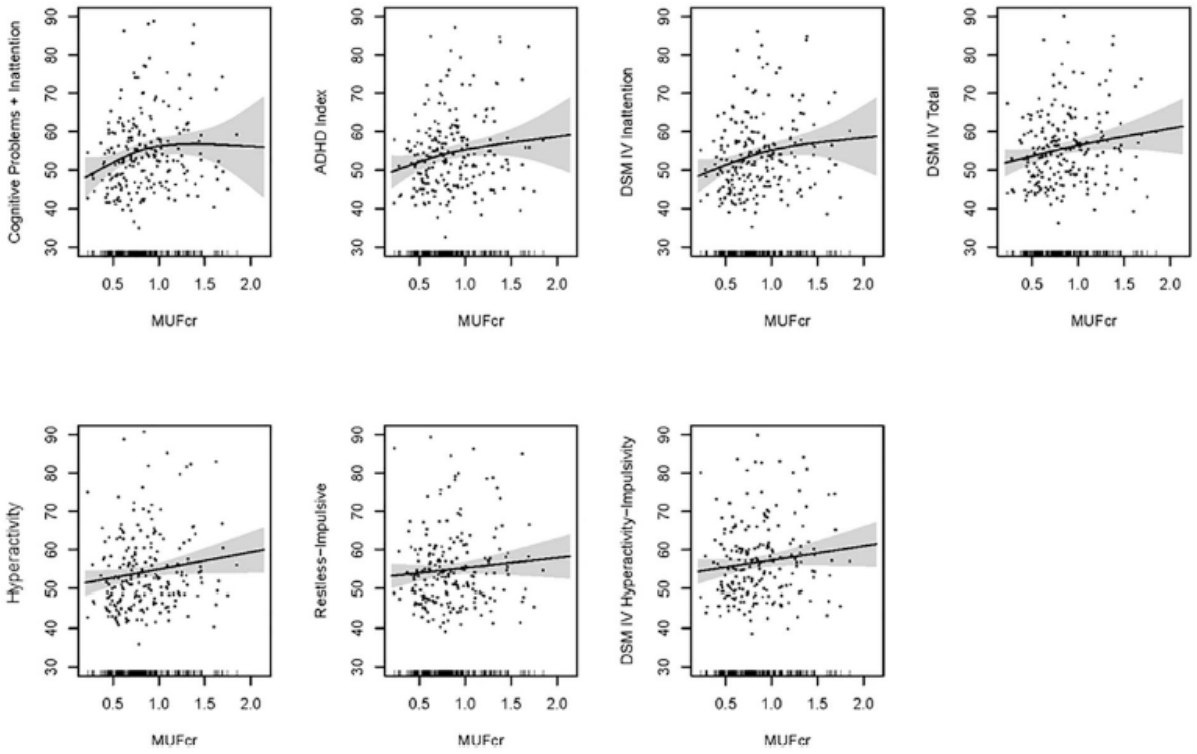


25. In contrast with prenatal exposures, we did not find statistically significant associations between IQ and childhood urinary fluoride levels at ages 6 to 12, although there was some suggestion of an adverse effect. This suggests that the timing of fluoride exposure is an important determinant of fluoride's neurodevelopmental effects, and is consistent with exposures occurring prenatally being more detrimental than those occurring during school-aged years. This is plausible given fluoride's passage through the placental barrier, and the known enhanced vulnerability of the developing brain to neurotoxicants during the *in utero* period.

26. In addition to IQ, we have also found a significant association between prenatal fluoride exposure and some attention deficit hyperactivity disorder (ADHD)-like behaviors on the CRS-R test, including cognitive problems and inattention (Bashash 2018). As with our IQ analyses, the associations were linear, although—as we have found for lead (Huang 2016)—there was some indication in some of the analyses of a ceiling effect at higher doses (i.e., the dose-response curve for cognitive problems and inattention began to flatten above 1 mg/L).

27. The effect sizes between prenatal fluoride and ADHD behaviors in our cohort were substantial. For those effects which reached statistical significance, increases of 0.5 mg/L in maternal urinary fluoride were associated with 2.4 to 2.8-point higher scores (higher scores reflect indicate poorer performance). Whereas IQ is standardized to a mean of 100, the ADHD behavior scales are standardized to a scale of 50. The effect sizes that we found for prenatal fluoride are similar to what we have found for childhood blood lead levels (Huang 2016).

Figure C: Association Between Maternal Urinary Fluoride & ADHD Behaviors



28. We did not find statistically significant associations between fluoride and ADHD-behaviors on the CPT-II test. Other studies of environmental chemicals have reported similar discrepancies between the two tests, suggesting that they are assessing different constructs. The stronger association that we found between fluoride and ADHD behaviors on the CRS-R scale may be explained by the CRS-R's focus on constructs that rely on attention (e.g., new learning, ability to hold information and complete tasks, organizational skills, etc).

29. The relationship we observed between fluoride and inattention is consistent with some animal research that has reported a relationship between prenatal fluoride exposure and hypoactive behavioral patterns (Mullenix 1995), as well as prior epidemiological research associating fluoride with impaired working memory (Choi 2015). Working memory is linked with the ability to control attention and it is common for youth with ADHD to have weaknesses in working memory (Kasper 2012).

Fluoride's effect on working memory may relate to an effect on the dopamine system, which fluoride has been found to alter in animal studies (Pal & Sarkar 2014). Dopamine is an important modulatory neurotransmitter in planning and initiation of motor responses, activation, switching, reaction to novelty and processing of reward (Fararone 2015).

30. Some have suggested that the "scatter" in the above scatterplots is a basis to doubt the relation between fluoride and the neurodevelopmental outcomes. Such scatter, however, is typical in epidemiological studies of neurotoxicants, as can be seen in the following figure from our study on lead and neurocognitive effects which the EPA relied upon as evidence of low-level lead neurotoxicity when the Agency set the national air standard for lead (Tellez-Rojoz 2006, Fig 1, reproduced as Figure D below). We also found similar scatter in our analysis of blood lead and ADHD behaviors, as measured by CRS-R (Huang 2016, Fig. 1, reproduced as Figure E below). The scatter relates to the fact that there are multiple factors that impact on intelligence and behavior; however, unless they are confounders (which we controlled for), they do not preclude the ability to focus on the specific effect of fluoride.

Figure D: Association Between Childhood Blood Lead Levels and Mental Development Index

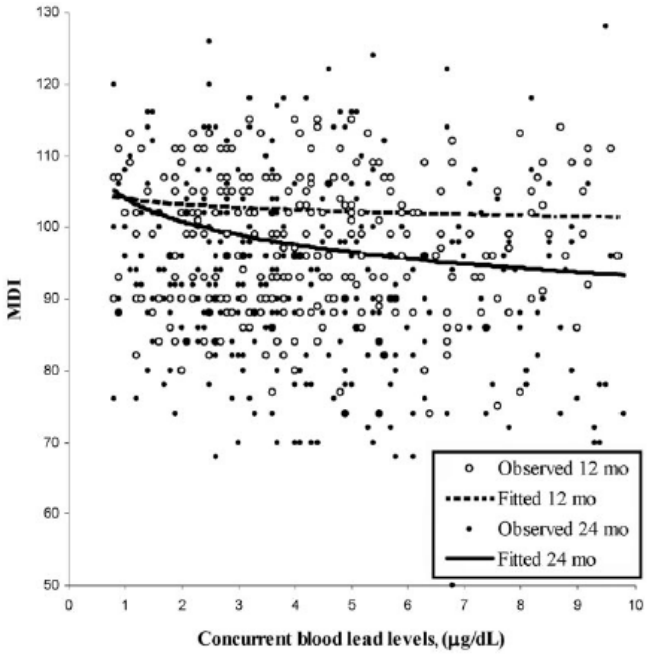
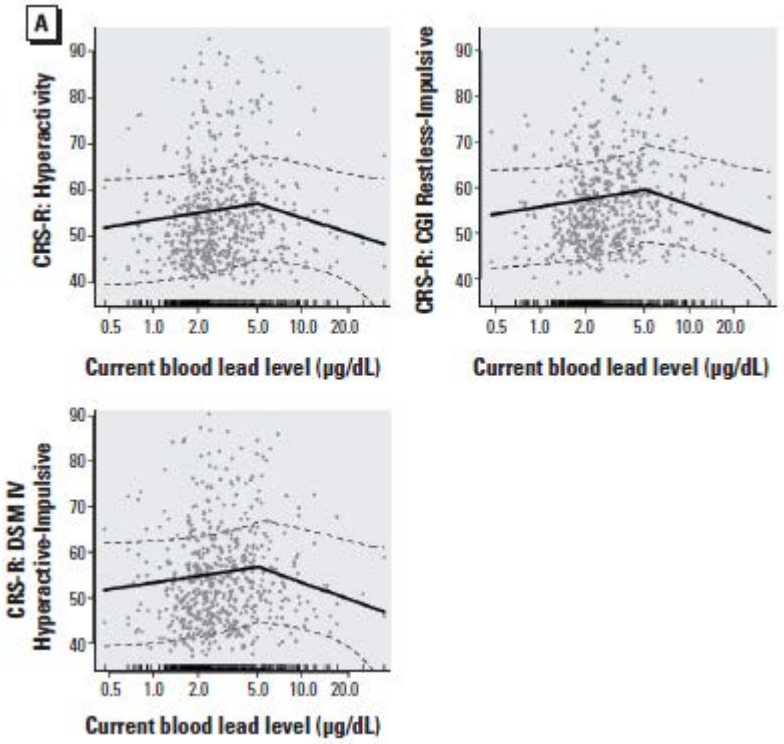


Figure E: Association Between Childhood Blood Lead Levels and ADHD Behaviors



C. The Limitations of Our Studies Do Not Provide Plausible Alternative Explanations for the Results

31. Every epidemiological study, including our studies on fluoride and neurodevelopment, has its limitations. Some of these limitations could theoretically be avoided through the use of human experiments where the toxicant is delivered to the study participants in a controlled and randomized manner. Human experimentation on neurotoxicants, however, is strictly prohibited for obvious ethical reasons. We are thus left with "observational" studies to investigate the impact of environmental toxicants on human health, with prospective cohort studies being the study design best suited for this purpose.

32. As is often the case with epidemiological studies of environmental toxicants, there are limitations in the exposure measurements that we have used in the ELEMENT studies. Our use of spot samples to collect the urine introduces some imprecision into the exposure measurement because urinary

fluoride concentrations can fluctuate somewhat throughout the day. This imprecision would have been reduced through the use of 24-hour urine collection samples, and, to a lesser extent, fasting first-morning voids, which are both considered more rigorous measures of fluoride exposure. We compensated for this limitation by using "timed" samples (i.e., second void in the morning) and adjusting for urinary creatinine. Urinary fluoride concentrations fluctuate during the day in large part because fluctuations in an individual's hydration during the day result in fluctuations in urinary dilution (and therefore, urinary concentrations). Adjusting for urinary creatinine is particularly important because the resulting measure adjusts for urinary dilution. As a result, measures of fluoride in spot urine samples adjusted for creatinine have been found to have excellent agreement with 24-hour samples (Zohouri 2006). Timed spot samples also have an important advantage over 24-hour samples in that they are less imposing on study participants. This is an important consideration when designing cohort studies because the imposition of difficult tasks like collecting 24-hour urines serve to reduce participation, which, in turn, reduces the study's sample size and statistical power.[6]

33. Another limitation in our exposure measurements is that, for most of the mothers, we did not have urine samples for every trimester. In our age 4 IQ analysis, 49%, 42%, and 9% of the mother-offspring pairs had urine samples for one, two, and all three trimesters, respectively. In the age 6-12 analysis, the respective percentages were 56%, 39%, and 5%; while in the ADHD study, the respective numbers were 57%, 36.4%, and 6.5%. It is common for prospective cohort studies to only have one or two exposure measurements during the prenatal period, but this does not introduce undue imprecision in the exposure estimate, as exposures to a toxicant have limited variation during pregnancy.

34. Importantly, the imprecision in our exposure measurements does not explain the large and significant associations we observed between maternal urinary fluoride and neurodevelopmental

[6] To put it in simple terms, less people will volunteer to participate in a study if it requires them to collect all of their urine throughout the entire day, including while they are in public spaces, such as their work environment and restaurants, etc.

effects. Imprecision in exposure measurements (of the classical or random type, as noted above) is a type of non-differential error that introduces scatter into the analysis which has a generally expected effect of biasing the results towards the null hypothesis. To put it another way, imprecisions in exposure measurements make it *harder*, not easier, to detect an association between an exposure and outcome, much like background noise makes it harder to hear a sound or signal of interest. Imprecision in the exposure measurement is thus anticipated to *obscure* an association, rather than create spurious associations where none otherwise exist. Because of this, improvement in the measurement of a particular exposure tends to reveal and strengthen associations associated with that exposure, not eliminate them.

35. Another limitation with our studies is, as with most observational studies, we could not rule out the potential for uncontrolled confounding from factors that we did not measure. For example, we did not have data on arsenic which is a neurotoxicant that has been associated with fluoride in certain rural drinking water supplies. While it always preferable to have more data than less, it is unlikely that arsenic is a meaningful confounder in our cohort. To be a confounder, a covariate must be associated with *both* the outcome *and exposure*. In our cohort, the main source of fluoride is from *salt*, not water.[7] Accordingly, even if arsenic is correlated with fluoride in rural water supplies in Mexico, this association is unlikely to be materially associated with fluoride exposures in our cohort.

36. Finally, an additional limitation in our studies is that we did not have information on the iodine status of our cohort. Iodine has been theorized to be a potential effect-modifier for fluoride's nervous system effects, i.e., deficiencies of iodine may magnify fluoride's effects, and vice versa (NRC 2006). However, failure to control for an effect modifier is unlikely to produce an association between exposure and outcome that does not otherwise exist. Moreover, in Mexico, salt is required by law to be

[7] The water in Mexico City has low levels of fluoride (i.e., 0.16 mg/L) and thus does not present a meaningful exposure in our cohort (Cantoral et al. 2019).

iodized. Fluoride levels in our cohort are thus likely correlated with *increased* iodine. To the extent that iodine modifies the effect of fluoride in our population, it is more likely to be in the direction of *reducing* toxicity rather than magnifying it.

D. Implications of Our Findings to the General Population in Water-Fluoridated Areas

37. In 2016, we published the largest characterization to date of urinary and plasma fluoride levels throughout pregnancy (Thomas, et al. 2016). At the time we published this study, there had yet to be a population-based study of fluoride exposures among pregnant women in North America, although there were two small-scale studies available from Israel and Poland. The lack of data from North America prevented us, at that time, from comparing the urinary fluoride levels in our cohort with populations from Canada or the United States.

38. Urine and plasma fluoride are metrics of the total absorbed dose of fluoride, sometimes referred to as the "internalized" or "bioavailable" dose. These internalized doses do not currently permit one to directly estimate the amount of fluoride that is ingested (i.e., the "external" exposure), nor do they permit the determination of source apportionment of the fluoride exposures. Internalized doses, however, are more relevant than external intake in predicting toxic effects, since they reflect the concentration of toxics that are being delivered to target organs in the body.

39. Our 2016 study presented the urinary and plasma fluoride levels from 825 and 330 pregnant women from our cohort, respectively. The urine samples were collected and measured using the procedures discussed above for our neurodevelopmental papers (i.e., early morning 2nd voids that were adjusted for creatinine), and both the urine and plasma samples were tested under the direction of Dr. Angeles Martinez-Mier from Indiana University, a world leader in the measurement of fluoride in biological samples.

40. The average creatinine-adjusted urinary fluoride level across all three trimesters in the

ELEMENT cohort was 0.91 mg/L, with a standard deviation of 0.4 mg/L.[8] The average plasma fluoride level across all three trimesters was 0.0221 mg/L, with a standard deviation of 0.0164 mg/L.[9]

41. By the time we published our 2018 study on ADHD behaviors, general population data had become available on maternal urinary fluoride levels in pregnancy (Till 2018). As we noted in our 2018 study, the maternal fluoride levels in the Canadian study are similar to the levels in our cohort (Bashash 2018). The mean (creatinine-adjusted) maternal urinary fluoride level among pregnant women living in the water-fluoridated areas of Canada was 0.87 mg/L, with a standard deviation of 0.50 mg/L, which is clearly in the same range as our cohort (i.e., mean = 0.91 mg/L, SD = 0.4 mg/L). The urine samples in the Canadian study were tested by Dr. Martinez-Mier using the same creatinine-adjustment method, which increases the comparability of the data.

42. The similarity in maternal urinary fluoride levels between pregnant women in the ELEMENT cohort and water-fluoridated areas of the Canadian cohort is consistent with the fact that both populations are receiving so-called "optimal" levels of fluoride through fluoridation programs (i.e., salt fluoridation in Mexico, and water fluoridation in Canada). Since salt fluoridation programs are designed to replicate the doses provided by fluoridated water, it is a reasonable, first-order expectation that populations living in salt-fluoridated and water-fluoridated areas will receive similar doses of fluoride.

43. The maternal urinary fluoride data from the ELEMENT cohort and water-fluoridated areas of Canada support the conclusions that the two populations have essentially the same *internalized* doses of fluoride. The internalized doses in water-fluoridated areas are thus in the range that we have

[8] The 75th and 90th percentile values were 1.09 mg/L and 1.37 mg/L, respectively.

[9] We tested for and found no correlation between creatinine-adjusted urinary fluoride and sociodemographic variables, including maternal age, maternal education, child sex, smoking status, birth order, and cohort. Although we found a trend towards increasing urinary fluoride levels through the first 22-23 weeks of pregnancy, and a reduction thereafter, these trends were not statistically significant (Thomas 2016).

found to be associated with substantial and significant neurodevelopmental harms in the ELEMENT cohort.

44. Although direct comparisons of *external* fluoride intake cannot yet be made, such information is not necessary to generalize the neurodevelopmental results from the ELEMENT cohort to water-fluoridated areas.

45. There is no identified reason to believe that the neurodevelopmental effects of fluoride will differ by the source of exposure, be it fluoridated salt or fluoridated water; once inside the body the source of fluoride is immaterial.

46. For the reasons stated, it is my opinion to a reasonable degree of scientific certainty that the results of the ELEMENT studies support the conclusion that fluoride is a developmental neurotoxicant at levels of internalized exposure seen in water-fluoridated communities.

I declare under penalty of perjury, under the laws of the United States, that the foregoing is true and correct to the best of my knowledge and belief.

Executed on May 20, 2020, in Seattle Washington.

HOWARD HU, MD, MPH, ScD

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Liu Y, Téllez-Rojo M, Hu H, et al. Fluoride exposure and pubertal development in children living in Mexico City. *Environ Health* 2019;18(1):26.

Mullenix PJ, Denbesten PK, Schunior A, Kernan WJ. Neurotoxicity of sodium fluoride in rats. *Neurotoxicol Teratol* 1995, 17(2):169–177.

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Pal, S., Sarkar, C., Protective effect of resveratrol on fluoride induced alteration in protein and nucleic acid metabolism, DNA damage and biogenic amines in rat brain. *Environ. Toxicol. Pharmacol*. 2014, 38, 684–699.

Téllez-Rojo MM, Bellinger DC, Arroyo-Quiroz C, Lamadrid-Figueroa H, Mercado-Garcia M, Schnaas-Arrieta L, Wright RO, Hernández-Avila M, Hu H. Longitudinal associations between blood lead concentrations lower than 10 microg/dL and neurobehavioral development in environmentally exposed children in Mexico City. *Pediatrics* 2006;118(2):e323-e330.

Thomas DB, Basu N, Martinez-Mier EA, Sanchez BN, Zhang Z, Liu Y, Parajuli RP, Peterson K, Mercado-Garcia A, Bashash M et al: Urinary and plasma fluoride levels in pregnant women from Mexico City. *Environ Res* 2016, 150:489-495.

Thomas D, Sanchez B, Peterson K, Basu N, Martinez-Mier EA, Mercado-Garcia A, Hernandez-Avia M, Till C, Bashash M, Hu H, Tellez-Rojo M. Prenatal fluoride exposure and neurobehavior among children 1-3 years of age in Mexico. *British Medical Journal* 2018; 75(Suppl 1):A10.

Till C, Green R, Grundy JG, Hornung R, Neufeld R, Martinez-Mier EA, Ayotte P, Muckle G, Lanphear B: Community Water Fluoridation and Urinary Fluoride Concentrations in a National Sample of Pregnant Women in Canada. *Environ Health Perspect* 2018, 126(10):107001.

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Wechsler, D. (1999). Wechsler abbreviated scale of intelligence (WASI) manual. San Antonio, TX: Psychological Corporation.

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,

CURRICULUM VITAE OF
HOWARD HU, MD, MPH, ScD

CURRICULUM VITAE Date Prepared: May, 2019

NAME: Howard Hu

PRIMARY AFFILIATION: School of Public Health, University of Washington
SECONDARY AFFILIATION: School of Public Health, University of Michigan

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LINKS: https://deohs.washington.edu/faculty/hu_howard
https://www.linkedin.com/in/howard-hu-059703a/?trk=public-profile-join-page

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EDUCATION:

9/1973-6/1976	Biology	B.Sc.	Brown University
9/1977-6/1982	Medicine	M.D.	Albert Einstein College of Medicine
9/1979-6/1980 (degree in 6/1982*)		M.P.H. (Occ Hlth)	Harvard School of Public Health
9/1985-6/1986	Epidemiology	M.S.	Harvard School of Public Health
7/1986-6/1990	Epidemiology	Sc.D.	Harvard School of Public Health

* Awarding of the Harvard M.P.H. to medical students is delayed until the M.D. degree is conferred

POSTDOCTORAL TRAINING:

Research Fellowships

7/1987-6/1988 Occupational Health Research Fellow, Dept. of Environmental Health
Harvard School of Public Health

Internship and Residencies

7/1982-6/1983	Intern in Medicine	Boston City Hospital
7/1983-6/1984	Junior Assistant Resident, Internal Medicine	Boston City Hospital
7/1984-6/1985	Senior Assistant Resident, Internal Medicine	Boston City Hospital
7/1985-6/1987	Resident, Occupational Medicine	Harvard School of Public Health

CERTIFICATION AND LICENSURE:

1984	Massachusetts Medical License Registration
1985	American Board of Internal Medicine, Diplomate
1987	American Board of Preventive Medicine, Diplomate (Occupational Medicine)
2006	Michigan Medical License Registration
2013	College of Physicians & Surgeons of Ontario
2018	Washington State Medical License Registration

ACADEMIC APPOINTMENTS:

9/1988-6/1992	Instructor in Medicine Department of Medicine, Harvard Medical School
9/1988-6/2006	Associate Physician (Clinical and Research), Channing Laboratory, Department of Medicine, Brigham & Women's Hospital
9/1990-6/1994	Assistant Professor of Occupational Medicine Department of Environmental Health, Harvard School of Public Health

7/1992-6/1997	Assistant Professor of Medicine Department of Medicine, Harvard Medical School
7/1994-6/2002	Associate Professor of Occupational Medicine Department of Environmental Health, Harvard School of Public Health
7/1997-8/2006	Associate Professor of Medicine Department of Medicine, Harvard Medical School
7/2002-8/2006	Professor of Occupational and Environmental Medicine (tenured) Department of Environmental Health, Harvard School of Public Health
9/2006-6/2012	Chair and Professor of Environmental Health Sciences (tenured), Department of Environmental Health Sciences, University of Michigan School of Public Health
9/2006-8/2009	Adjunct Professor of Occupational and Environmental Medicine Department of Environmental Health, Harvard School of Public Health
9/2006-6/2012	Research Associate Physician, Channing Laboratory, Department of Medicine, Brigham & Women's Hospital
5/2007-2012	Professor of Epidemiology, University of Michigan School of Public Health
5/2007-2012	Professor of Internal Medicine, University of Michigan Medical School
1/2009-2012	NSF International Endowed Department Chair, University of Michigan School of Public Health, Department of Environmental Health Sciences
7/2012-2018	Professor of Environmental Health, Epidemiology and Global Health (tenured) Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada (on sabbatical/administrative leave, 2017-2018)
7/2012-2018	Professor, School of Medicine, University of Toronto, Toronto, Ontario, Canada
7/2012-	Adjunct Professor, Department of Environmental Health Sciences, University of Michigan School of Public Health
7/2012-2013	Director, Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada
7/2013-6/2017	Founding Dean, Dalla Lana School of Public Health, a Faculty of the University of Toronto, Toronto, Ontario, Canada
7/2017-	Affiliate Professor (started as Visiting Scholar until December, 2017), Department of Occupational and Environmental Health Sciences, University of Washington School of Public Health, Seattle, WA

ADMINISTRATIVE APPOINTMENTS:

7/1991-6/2006	(Founding) Director, Metals Epidemiology Research Group, Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, and Department of Environmental Health, Harvard School of Public Health
7/1992-6/1995	Director, Commission to Investigate the Health and Environmental Effects of Nuclear Weapons Production, International Physicians for the Prevention of Nuclear War
7/1996-6/2006	Director, Residency Program in Occupational and Environmental Medicine, Harvard School of Public Health
7/1996-8/2006	Director, Occupational and Environmental Medicine Core, National Institute for Occupational Safety and Health Educational Resource Center at the Harvard School of

Public Health
7/1998-6/2004 (Founding) Medical Editor, Environmental Health Perspectives (official journal of NIEHS)
7/2000-8/2006 Associate Director, the Harvard NIEHS Environmental Sciences Center, Harvard School of Public Health
7/2004-6/2009 (Founding) Principal Investigator and Director, Harvard Center for Children's Environmental Health and Disease Prevention Research (co-PI and co-Director after 9/1/08)
9/2006-6/2012 Chair, Department of Environmental Health Sciences, University of Michigan School of Public Health
9/2006-2012 Director, Occupational Epidemiology Core, NIOSH Education and Research Center, University of Michigan
9/2006-2012 Co-Director, Michigan-Harvard/Harvard-Michigan Metals Epidemiology Research Group
7/2009-2011 Director, NIA T32 Training Grant in Aging and Public Health, University of Michigan School of Public Health
1/2010-2012 Chair, Faculty Steering Committee on Global Health, University of Michigan School of Public Health
4/2011-2012 (Founding PI) and Director, University of Michigan NIEHS P30 Core Center.
7/2012-2013 Director, Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada
7/2013-6/2017 Founding Dean, Dalla Lana School of Public Health, a Faculty of the University of Toronto, Toronto, Ontario, Canada

CLINICAL APPOINTMENTS:

7/1985-6/1987 Attending Physician, Emergency Department, Whidden Memorial Hospital
7/1985-6/1988 Assistant Visiting Physician, Department of Medicine, Boston City Hospital
1/1985-6/2006 Consultant in Occupational and Environmental Medicine, Center for Occupational and Environmental Medicine, Northeast Specialty Hospital (formerly known as the Olympus Specialty Hospital, the Massachusetts Respiratory Hospital, and Norfolk County Hospital).
3/1987-9/1987 Attending Physician, Occupational Health Program, University Hospital/Boston University Medical Center
7/1988-9/2006 Associate Physician, Brigham and Women's Hospital
7/1990-6/1995 Occupational/Environmental Medicine Consultant, Brigham and Women's Hospital Employee Health Services
7/2007-2012 Associate Physician, Division of General Medicine, Department of Medicine, University of Michigan Health System
1/2019-present Staff Physician, RotaClinic-Lake City, Seattle, WA

OTHER ACADEMIC POSITIONS and MAJOR VISITING APPOINTMENTS:

7/1987-6/1990 Visiting Physician, South Cove Health Center, Boston (Chinatown)
7/1996-8/2006 Associate, Center for Health and the Global Environment, Harvard Medical School
2/1997 Alice Hamilton Visiting Professor, Division of Occupational and Environmental Medicine, Department of Medicine, University of California at San Francisco
11/2000- Visiting Scientist, Sri Ramachandra Medical College and Research Institute
7/2010- Senior Consultant, Tianjin Centers for Disease Control and Prevention, Tianjin, China
10/2012- Visiting Professor, Shanghai Key Laboratory of Children's Environmental Health, Xinhua Hospital, Shanghai Jiao-Tung University, China
7/2013-6/2016 Visiting Professor, Shanghai Jiao Tong School of Medicine, China
5/2015- Affiliate Scientist to the Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Canada

MAJOR RESEARCH INTERESTS:

1. Environmental and molecular epidemiologic research related to heavy metals, potential endocrine disruptors, other neurotoxicants, carcinogens, etc.
2. Gene-environment interactions; epigenetic dysregulation
3. Fetal/early life exposures and long-term effects
4. Aging-environment interactions
5. Environmental health, health inequities and health disparities, human rights
6. Health and the global environment
7. "Big Data" for population health
8. Environmental sensitivities/Multiple chemical sensitivities

GRANTS (as PI, Co-PI, or primary mentor only):

Past Funding:

1980 (summer) Montefiore Hospital, Bronx NY,PI; $2,000 (approx)
A study of rural and occupational health in Tulua, Colombia, South America
1982 (summer) Albert Einstein College of Medicine, PI; $3,000 (approx)
A study of occupational/environmental health in Shanghai, China
7/1987-6/1989 NIEHS Center Grant ES00002 Pilot Project, PI; $12,000
The Long-term Renal and Neurologic Effects of Childhood Plumbism
7/1989-6/1990 NIEHS subcontract 7083-1, PI; $50,000 (approx)
The Use of X-Ray Fluorescence to Measure Lead Burden and Childhood Lead Exposure
7/1990-6/1992 Agency for Toxic Substances and Disease Registry, PI; $150,000 (approx)
"Clinical Environmental/ Occupational Medicine Research Fellowship Award",
7/1990-6/1991 NIEHS Center Grant ES00002 Pilot Project, PI; $12,000
The Metabolic Effects of Pregnancy and Lactation on Lead Burden

7/1990-6/1991 Harvard School of Public Health Basic, PI
Research Support Grant; $10,000
K-X-Ray Fluorescence Measured Lead Burden

10/1991-11/1991 NIOSH Special Grants, PI; $50,000 (approx)
The Carpenters Lead Project

4/1991-3/1996 NIEHS/R01, PI; $2,200,000 (approx)
The Epidemiology of Lead, Diet and Blood Pressure

7/1991-6/1996 NIEHS/R01 supplement, PI; $240,000 (approx)
The Epidemiology of Lead, Diet and Blood Pressure--Research Supplement for Minority Investigator

7/1992-6/1995 NIEHS/R01 (Office of Research on Women), PI; $200,000 (approx)
Lead and Hypertension in Women

7/1993-6/1996 NIEHS/subcontract, PI; $150,000 (approx)
Exposure to Neurotoxins as Risk Factors for Amyotrophic Lateral Sclerosis

7/1995-6/1998 State of Washington, Department of Labor, PI; $350,000 (approx)
SPECT Imaging of the Brain in Patients with Multiple Chemical Sensitivity Syndrome and Controls

7/1996-6/1997 NIEHS Center Grant ES00002 Pilot Project, PI; $15,000
Electrocardiographic abnormalities in association with low-level lead exposure among middle-aged to elderly men: the Normative Aging Study

4/1995-3/2000 NIEHS Project PI (Program Project PI: Richard Monson); $1,800,000 (approx)
Lead Exposure, Accumulation in Bone, and Reproductive Toxicity Among Men and Women In Mexico

4/1995-3/2000 NIEHS Project PI (Program Project PI: Richard Monson); $1,900,000 (approx)
Lead Exposure, Accumulation in Bone, and Cognitive Toxicity Among Elderly Men and Women

6/1997-5/2002 NIEHS/R01 ES05257 PI; $2,312,274
Lead Biomarkers, Aging, and Chronic Disease

7/1997-6/1999 NIEHS Center Grant ES00002 Pilot Project, PI; $10,000
The effect of genetic polymorphisms of metallothionein-IIA on mRNA levels in middle-aged to elderly men: the Normative Aging Study

7/1998-6/2003 NIEHS/R01 PI (with no-cost extension; 5R01ES007821); $2,291,833
Lead Dose Biomarkers, Reproduction, and Infant Outcomes

7/1999-6/2000 NIEHS Center Grant ES00002 Pilot Project, co-PI; $14,000
Magnetic Resonance Spectroscopy in the Evaluation of Lead Neurotoxicity: the Normative Aging Study

7/2000-6/2001 MAVERIC (Massachusetts Area Veterans Epidemiology Resource and Institute Center) Pilot Project PI (with Dr. Robert Wright, co-PI); $10,000
The Use of Magnetic Resonance Spectroscopy in Lead Poisoning

7/2000-6/2001 NIOSH Center Grant Pilot Project, PI (with Dr. Robert Wright, co-PI); $12,000
Interaction between ApoE Genotype and Lead Exposure in the Development of Cognitive Impairment

7/2002-6/2004 The Rasmussen Foundation/Health Care Without Harm; $50,000

Medical Use of Phthalate Containing Products in the Neonatal Intensive Care Unit and Biomarkers of Neonatal Phthalate Metabolites

7/2002-6/2003 NIEHS Center Grant Pilot Project, PI; $8,000
Vitamin D Receptor Gene and Bone Lead in Reproduction

3/2004-2/2005 The Critelli Family Foundation; $10,000
Review of Environmental Cadmium Exposure and Toxicity

4/2000-3/2007 NIEHS Project Leader (Program Project PI: Richard Monson; 5P01ES05947); $2,472,677; Controlled Trial in Pregnancy of Dietary Supplements for the Suppression of Bone Resorption and Mobilization of Lead into Plasma (no cost extension)

4/2000-3/2007 NIEHS Project co-Leader (Program Project PI: Richard Monson; 5P01ES05947); $1,210,000 (approx); A Community-Based Study of Lead Exposure Pathways, Biomarkers of Dose, Health Effects, and Phytoremediation Strategies at the Tar Creek Superfund Site (no cst extension)

4/2002-9/2007 NIEHS/R01 PI (5R01ES010798); $3,011,295
Gene-Metal Interactions and Parkinson's Disease

10/2003-9/2007 NCMHI/P20 Project Leader (MD000501-01; Hughes Harris, PI); $828,781(Project)
"FAMU and Harvard Center for Health and Health Care Disparities"

8/2003-7/2008 NIEHS/R01 PI (2R01ES05257-11A2); $3,357,424 (bécame co-PI in 2007 after move to University of Michigan)
Lead-Gene Interactions and Cognition

6/2004-3/2009 NIEHS/P01 PI (5 P01ES012874-01); $6,662,670 (became co-PI in 2006 after move to University of Michigan)
Metals Mixtures and Children's Health (Center for Children's Environmental Health and Disease Prevention Research)

7/2002-12/2009 NIH/R03 PI (1R03TW005914; no cost ext through 2008); $192,000 (approx)
Lead, Genes, and Cognition in Children in Chennai, India

9/2006-7/2011 NIEHS/R01 PI (R01ES0007821); $3,116,831
Fetal Origins of Neurobehavior: Lead and Cholesterol Metabolism Interactions

7/2006-6/2011 NIEHS/R01 co-PI (R01ES013744; PI Wright), $3,200,000
Stress, Lead, Iron Deficiency and Neurodevelopment

7/2006-6/2011 NIEHS/R01 co-PI (RO1ES014930; PI Wright), $2,800,000
Metal Mixtures and Neurodevelopment

2/2008-2/2010 Michigan Institute for Clinical and Health Research (MICHR; home of the UM CTSA; UL1RR024986) Pilot Project PI; $26,000 (no cost extension)
Epigenetics of Early Life Events and Environmental Toxicants

4/2009-4/2010 Michigan Alzheimer's Disease Research Center Pilot Project PI, $25,000
Environment, Epigenetics and Alzheimer's Disease (no cost extension)

12/2009-12/2010 University of Michigan Center for Global Health Pilot Project PI, $25,000
Climate Variability and Impacts on Mortality and Morbidity in Chennai, India: A Pilot Project Stemming from the 2009 U.S.-India Workshop on Climate Change and Public Health, Goa India (no cost extension)

9/2009-9/2010 Michigan Institute for Clinical and Health Research (MICHR; home of the UM CTSA; UL1RR024986) Pilot Project PI; $26,000 (no cost extension)
Epigenetics and Epigenomics in the Etiology of Alzheimer Disease

7/2008-6/2011 NIA/T32 PI (T32AG027708); $450,000
Interdisciplinary Training Program in Aging and Public Health

4/2010-3/2015 NIEHS P42 Superfund Co-Inv, Project 2, Co-investigator (P42ES017198; PI: Alshawabkeh, Project 2 Leader: Meeker) Puerto Rico Testsite For Exploring Contaminant Threats, $12,000,000

4/1/2011-6/2015 NIEHS Core Environmental Health Sciences Center, Founding PI and Director (until 2012; now consultant; P30 ES017885), $ 4,620,100;
"Lifestage Exposures and Adult Disease"

4/2010-3/2014 NIEHS/EPA P20 Co-PI and Clin Health Specialist (P20 ES018171; PI Peterson)
Formative Children's Environmental Health and Disease Prevention Center, $1,959,960; "Perinatal Exposures, Epigenetics, Child Obesity & Sexual Maturation"

7/1/2013-6/30/2014 CIHR, Canadian Institute for Health Services and Policy Research; Planning Grants-Priority Announcement:Partnerships for Health System Improvement; PI, $24,992
"The Surviving Opioid Overdose with Naloxone (SOON) Project and Roundtable"

07/1/11-06/30/16 NIEHS K01 ES019909 (co-mentor; PI: Somers)
"Immune dysfunction associated with early life heavy metal exposure"

4/1/12-3/30/17 NIEHS R01ES013744 (consultant; PI: Wright; Mt Sinai School of Medicine)
"Stress-Lead Interactions and Child Development"

7/1/2012-7/1/2017 European Commission (EC), Funded under FP7-Health, Project 304925, co-Investigator; PI, epidemiologic studies, $6,000,000 E
"A novel micronutrient-based strategy to prevent hearing impairments: test and road to market for age-related hearing loss and preservation of residual hearing"

Current Funding

6/1/2012-7/1/2019 1R01ES021446-01, PI, $4,140,000 (parent + supplement awards);
"Prenatal and Childhood Exposure to Fluoride and Neurodevelopment"

5/15/2015-5/15/2019 Health Canada; PI, $200,000 (Phase 1); $1,400,000 (proposed Phase 2)
"A Community-based First Nation Study of Cancer and the Environment in Northern Ontario"

4/1/13-3/31/23 NIEHS/EPA P01ES022844 (co-inv; PI: Peterson at the University of Michigan)
"Lifecourse Exposures & Diet: Epigenetics, Maturation & Metabolic Syndrome."

7/1/16-6/30/21 CIHR (co-PI; Director; PI: Jeffrey Brook at the Dalla Lana School of Public Health) $4,700,000 CNDN
"CANadian Urban Environmental (CANUE) Health Research Consortium"

9/1/16-8/31/21 NIH 5R01ES026033-02, (consultant; PI: Arora at Mt. Sinai School of Medicine) $648,000 "Novel Biomarker to Identify Critical Windows of Susceptibility to Metal Mixture"

Applications Under Review

Wellcome Trust, co-investigator (PI: P Landrigan)
"Quantifying the Cognitive and Economic Benefits of Reducing Air Pollution to Achieve Climate Change Mitigation"

Competitive Renewal Application In Progress

R01ES021446-01, PI, $4,140,000
A Prospective Study of Early Life Exposure to Fluoride, Thyroid Function, and Neurobehavioral Outcomes

Amended Application In Progress

R01ES007821-11, PI, $4,800,000;
Early Life Toxicants and Cardiovascular Outcomes" (priority score 27 by CASE Study section; 25th percentile)

New Application in Progress

Wellcome Trust, xxx, multiple-PI
Addressing Two Critical Gaps in Understanding the Impacts of Lead Exposure on the Global Burden of Disease: (a) Impacts on Cardiovascular Disease; (b) Exposures and Sources in Low and Middle-Income Countries

HONORS AND AWARDS:

1978-1982 National Health Service Corps Scholarship
1985-1988 National Research Service Award
1990-1992 Agency for Toxic Substances and Disease Registry Clinical Environmental Medicine Award
1994 Will Solimene Award of Excellence, American Medical Writers Association, for: Chivian E, McCally M, Hu H, Haines H, eds. *Critical Condition: Human Health and the Environment*. Cambridge: The MIT Press, 1993.
1997 Alice Hamilton Lecturer, University of California at San Francisco
1998 First Prize for Best Infant Nutrition Research, Instituto Danone, Mexico (for González-Cossío T, Peterson KE, Sanín L, Fishbein SE, Palazuelos E, Aro A, Hernández-Avila M, Hu H. "Decrease in birth weight in relation to maternal bone lead burden." Published in *Pediatrics*)
1999 National Institute for Environmental Health Sciences "Progress and Achievement of the

Year Award", 1998-1999
1999 True Memorial Lecturer, Maine Medical Center, Portland ME.
2000-2001 Faculty Sabbatical Award, Harvard School of Public Health
2000-2001 Senior Fulbright Scholar in India
2001 Hoopes Prize, Faculty Mentorship (for Senior Thesis of Charles Lin, "More than Black and White: Lead Poisoning as an Environmental Justice Issue in Boston")
2003 Best Paper in Preventive Medicine by a Medical Student (for Senior Thesis of Vanitha Janakiraman; Janakiraman V, Hu H, Mercado-Garcia A, Hernandez-Avila M. A randomized crossover trial of nocturnal calcium supplements to suppress bone resorption during pregnancy. Am J Prev Med 2003;24:260-4.). American College of Preventive Medicine, Ulrich and Ruth Frank Foundation for International Health.
2004 Das Travel Grant Award, The South Asia Initiative, Harvard University (for Travel in India)
2005 Adolph G. Kammer Merit in Authorship Award, the American College of Occupational and Environmental Medicine (for Rhodes D, Spiro A, Aro A, Hu H "Relationship of Bone and Blood Lead Levels to Psychiatric Symptoms: The Normative Aging Study", Published in the *Journal of Occupational and Environmental Medicine*)
2006 Teacher of the Year Award, Occupational/Environmental Medicine Residents, Harvard School of Public Health
2006 Harriett Hardy Award, the New England College of Occupational and Environmental Medicine
2009 Linus Pauling Award for Lifetime Achievements, American College for the Advancement of Medicine
2011 Award for Excellence, American Public Health Association
2015 John R. Goldsmith Award for Outstanding Contributions to Environmental Epidemiology, International Society for Environmental Epidemiology
2016 Election to Fellowship, Canadian Academy of Health Sciences

MEMBERSHIPS IN PROFESSIONAL SOCIETIES

Memberships

1981- American Public Health Association (APHA)
1982-2006 Massachusetts Coalition for Occupational Safety and Health
1983-1989 American College of Physicians
1985- Physicians for Social Responsibility
1987- Physicians for Human Rights
1990- International Society for Environmental Epidemiology (ISEE)
1990-2000 American Association for the Advancement of Science
1990-2006 Association of Occupational and Environmental Clinics (AOEC)
1991- International Physicians for the Prevention of Nuclear War (IPPNW)

1994-1996 Society for Occupational and Environmental Health (SOEH)
2000-2012 American College of Occupational and Environmental Medicine (ACOEM)
2009-2012 Society of Toxicology
2012- Canadian Public Health Association (CPHA)

Committee Assignments

1981-1982 Program Committee, Occupational Safety and Health Section, APHA
1987-1988 Program Committee, Asian-American Caucus, APHA
1992-1998 Membership Committee, ISEE
1995-1998 Quality Assurance Committee, AOEC
1997-1998 Program Committee, 1998 Superfund Basic Research Program, Annual National Meeting
2001-2006 Program Committee, New England College of Occupational and Environmental Medicine Annual Meetings

EDITORIAL POSITIONS AND BOARDS:

1977-1982 Einstein Community Health Newsletter
1988-1992 Bookreview Co-Editor, Section on Occupational Safety and Health, Am Public Health Assoc.
1993- Journal of Health and Human Rights
1998- Environmental Health Perspectives (Founding Medical Editor, 1998-2004; Associated Editor, 2004-)
2004- American Journal of Industrial Medicine
2007-2009 Faculty of 1000 Medicine
2017- Current Environmental Health Reports
2017- Faculty of 1000 Medicine

PEER REVIEW SERVICE

American Journal of Epidemiology
American Journal of Industrial Medicine
Archives of Environmental and Occupational Health
Biomed Central
Circulation
Environmental Health
Environmental Health Perspectives
Environment International
Environmental Research
Epidemiology

Indian Journal of Medical Research
Journal of Health and Human Rights
Journal of the American Medical Association
Kidney International
Lancet
New England Journal of Medicine
Pediatrics
PLOS One
Science of the Total Environment

TEACHING:

1. LOCAL CONTRIBUTIONS (at the Harvard School of Public Health, 1985-2006)

1985-	"Toxicology of the Kidney and Urinary Tract" Guest Lecturer for TOX204a,b
1988-	"Occupational Health" Guest Lecturer for EH201a,b
1989-1992	"Lead Toxicology" Guest Lecturer for TOX204a,b
1990-	Grand Rounds in Occupational/Environmental Medicine Director
1990-2000	Introduction to Occupational and Environmental Medicine (EH232c,d) Course director, lecturer
1990-	"The Epidemiology of Lead Exposure, Dose, and Toxicity" Guest Lecturer for EPE215c,d and EPE215t
1990-	"Solvent toxicity" Fundamentals of Industrial Hygiene, Continuing Education Department
1992	"Current Research on Lead", Metals Epidemiology Research Group Seminar Presenter
1992	"Lead Poisoning Without a Known Source in a Hyperthyroid Patient" Case discussant, Grand Rounds in Occupational and Environmental Medicine
1992-	"Biological Markers of Lead Dose" Guest Lecturer, EHE280c,d
1994-	"Screening for Lead Toxicity" Guest lecturer, EPI227d
1994-	"Lead Exposure and Biological Monitoring" Guest Lecturer, ID263b
1994-	"Case Study: Lead" Guest Lecturer and Case Discussant, EH202d
1996-	Introduction to Environmental Health (EH201b)

Course director and lecturer

1997- Human Health and Global Environment Change (EH278a,b)
Course Co-developer, Co-director, and lecturer

Hospital courses and Invited Teaching Presentations (Harvard-affiliated Hospitals)

1990 Guest Lecturer on Occupational Medicine
Residency Program, Department of Medicine, Brigham and Women's Hospital

1994 Speaker, Grand Rounds; "Is Lead a Ticking Time Bomb?"
Department of Obstetrics and Gynecology, Brigham and Women's Hospital

1994 Speaker, Grand Rounds; "Is Lead a Ticking Time Bomb?"
Department of Medicine, Brockton V.A. Hospital

1994 Speaker, Symposium on Preventive Medicine and Clinical Epidemiology,; "Is Lead a Ticking Time Bomb"; Brigham and Women's Hospital

1995 Discussant, "Multiple Chemical Sensitivity", Occupational/Environmental Medicine Grand Rounds, Occupational Health Program, Harvard School of Public Health

1996 Guest lecturer, "Lead Toxicity as a Paradigm for a Regional and Global Health Hazard", Environmental Health Student Group, Holmes Society, Harvard Medical School

1997 Speaker, "Mobilization of maternal bone lead as a hazard to the fetus", Grand Rounds, Dept. of Neonatology, Beth Israel Hospital, Boston, MA

2000 Guest lecturer, “Update on Lead Toxicity Research”, Program in Pediatric Toxicology, Children’s Hospital

2000 Discussant, “Adult Lead Toxicity”, Weekly Case Round, Department of Medicine, Brigham and Women’s Hospital, Boston.

2000 Lecturer, “Update on Lead Toxicity, Hypertension, and Chronic Renal Failure”, Renal Rounds, Division of Nephrology, Department of Medicine, Brigham and Women’s Hospital, Boston.

2002 Lecturer, “Maternal Bone Lead as a Threat to Fetal Development”, Program in Neonatology, Beth Israel-Deaconness Hospital, Boston, MA

Doctoral student committees

Chair and member:

Dr. Rokho Kim	Dr.P.H. Occupational Health and Epidemiology, ‘96
Dr. Yawen Cheng	Sc.D. Epidemiology, ‘98
Dr. Sharon Tsaih	Sc.D. Epidemiology, ‘99
Dr. Hung Yi Chuang	Sc.D. Occupational Health, ‘99
Dr. Adrienne Ettinger	Sc.D. Environmental Health, ‘03
Dr. Florence Wang	Sc.D. Environmental Health, ‘05
Dr. Sung K. Park	Sc.D. Environmental Health, ‘05
Dr. Pradeep Rajan,	Sc.D. Occupational Health, ‘06

Member/Advisor:

Dr. How Ran Guo	Sc.D. Occupational Health, '94
Dr. Joshua Cohen	Sc.D. Health Policy and Management, '94
Dr. Jane Hoppin	Sc.D. Environmental Health, '95
Dr. Salma Elreedy	Sc.D. Environmental Health, '97
Dr. Mary Jean Brown	Sc.D. Maternal and Child Health, '00
Dr. Brisa Sanchez	Sc.D. Biostatistics, '06
Dr. Ami Zota	Sc.D. Environmental Health, '07
Dr. Ananya Roy	Sc.D. Environmental Health, '08
Dr. Elissa Wilker	Sc.D. Environmental Health, '09

Post-doctoral fellow mentor:
Dr. Marinelle Payton (Channing Lab), Dr. Susan Korrick (Channing Lab), Dr. Rokho Kim (Channing Lab), Dr. Viji Potula (HSPH Research Fellow), Dr. Barbara Nowak (Visiting Scientist from Silesian University School of Medicine, Poland), Dr. Robert Wright (Channing Lab), Dr. Ming Tsuang Wu (HSPH Research Fellow), Dr. Yawen Cheng (Channing Lab), Dr. Geeta Mathur (neonatology fellow at the Brigham and Women's Hospital), Dr. Sri Hari Bojja (HSPH Research Fellow), Dr. Hae-Kwan Cheong (Visiting Scientist from Dongguk University School of Medicine, S. Korea), Dr. Sahar Elmarsafawy (HSPH Research Fellow), Dr. Jing Lu (Visiting Scientist from the Chinese Academy of Preventive Medicine), Dr. Dieter Affeln (Occ/Env Med Fellow), Dr. Ahmed Gomaa (Occ/Env Med Fellow), Dr. Chris Leffler (Occ/Env Med Fellow), Dr. Ronald Dykeman (Occ/Env Med Fellow), Dr. Uma Dhanabalan (Occ/Env Med Fellow), Dr. Hsien-Wen Hsu (Occ/Env Med Fellow), Dr. Betty Ann Cohen (Occ/Env Med Fellow), Dr. Arvin Chin (Occ/Env Med Fellow), Dr. Daniel Rhodes (Occ/Env Med Fellow), Dr. Richard Wittman (Occ/Env Med Fellow), Dr. Sun-Dong Lee (Visiting Scientist from Sangji University, Korea), Dr. Ronald Green (Occ/Env Med Fellow), Dr. Erma Lawson (Environmental Health Fellow), Dr. Marc Weisskopf (Environmental Health Fellow), Dr. Bridget Bagert (Occ/Env Med Fellow), Dr. John Jarrell (Visiting Scientist from University of Calgary), Dr. Jennifer Weuve (Environmental Health Fellow), Dr. Karen Chou (Visiting Scientist from Michigan State), Dr. Nitin Jain (Channing Laboratory Fellow), Dr. Adrienne Ettinger (Children's Center Scientist), Dr. Sam Myers (Fellow in Alternative and Complementary Medicine), Dr. Marcelo Targino (Occ/Env Med Fellow), Dr. Manish Arora (Post-doctoral fellow from University of Sydney), Dr. Huiling Nie (Post-doctoral fellow from McMaster University).

Other faculty mentorship:
Elizabeth Rubinstein (HMS Summer research), Alicia Marier (HMS Summer research), Vanitha Janakiraman (HMS Summer research), Young-Sook Lim (Harvard College Summer research), Charles Lin (Harvard College Senior thesis research), Ed Hsieh (Harvard College Summer research), Naveen Thomas (Emory University Medical School Senior thesis research). Shreekrishna Akilesh (Harvard Dental School summer research), Christine Pace (HMS Summer research)

Advisory and supervisory responsibilities

1985-1987	Attending Physician, outpatient general medicine clinic, Boston City Hospital; weekly precepting for housestaff and medical students

1990-2006	Preceptor, Residency in Occupational and Environmental Medicine, Harvard School of Public Health at the Mass Respiratory Hospital
1990-2006	Advisor to general M.P.H. students, Harvard School of Public Health.

2. LOCAL CONTRIBUTIONS (at the University of Michigan, 2006-2012)

2006-	Principles of Environmental Health (EHS-500) Course director and lecturer
2006-	Environmental Epidemiology (EHS-608) Guest lecturer on birth cohorts and environmental epidemiology
2006-	Occupational and Environmental Disease (EHS-501) Guest lecturer on metals exposure and health effects; Course Director (2009-)
2007-	Metals Exposure, Biomarkers and Toxicity: A Multi-disciplinary Environmental Epidemiology Approach (EHS-698 reading course) Course director and lecturer
2008-2009, 2010-2011	Topics in Environmental Health Sciences (EHS-688) Course director and lecturer
2009	Occupational and Environmental Disease (EHS-501) Course director and lecturer
2009-	On-line (Long-distance Foundations in Public Health Certificate Program): Principles of Environmental Health (EHS-500-801) Course director and lecturer
2009	Introduction to Public Health (HMP-200) Guest lecturer on environmental health
2009-	Seminars in Aging and Public Health (EPID 813) Course director and lecturer
2011	Seminar on Public Health in China (HMP-xxx) Guest lecturer on "Environmental Health in China"

Post-doctoral fellow mentor:

Dr. Sung Kyun Park (Environmental Health Sciences Fellow, now Research Assistant Professor), Dr. Brisa Sanchez (Biostats Research Assistant Professor, now Assistant Professor), Dr. Richard Pilsner (Robert Wood Johnson Health & Society Fellow), Dr. Aimin Zhang (Environmental Health Sciences Fellow, Toxicology Training Grant), Dr. Ananya Roy (Environmental Health Sciences Fellow), Dr. David Cantonwine (Reproductive Sciences Fellow).

Doctoral Student Advisor (principal)

David Cantonwine	Ph.D.	Environmental Health Sciences (2009)
Myriam Afeiche	Ph.D.	Environmental Health Sciences (co-mentor with Karen Peterson; 2010)
Yoon-Hyeong Choi	Ph.D.	Environmental Health Sciences (co-mentor with Sung Kyun Park; 2011)

Katie F. Bush	Ph.D.	Environmental Health Sciences (co-mentor with Marie O'Neill; 2011)
Kelly Bakulski	Ph.D.	Environmental Health Sciences (2012)
Gamola Fortenberry	Ph.D.	Environmental Health Sciences (co-mentor with John Meeker; 2013)
Siying Huang	Ph.D.	Environmental Health Sciences (2013)
Deena Thomas	Ph.D.	Environmental Health Sciences (2014)
Rebecca Tutino	Ph.D.	Environmental Health Sciences (2015)
Zishaan Farooqui	Ph.D.	MD-PhD Medical Scientist Training Program (2015)

Masters Student Thesis Advisor

Bradley Lampe (OEE), Troy Meissner (OEE), Pheba Alexander (OEE), Brian Davis (OEE & HBHE), Aaron Leftwich (OJOC program), Suengwon Lee (Nutrition), Allen Zhong (OEE), Graham Newman (OEE), Jacqueline Barkoski (OEE)

Undergraduate Thesis Advisor

Lauren Schwartz (Neuroscience, LSA)

3. LOCAL CONTRIBUTIONS (at the University of Toronto, 2012-present)

2012	Determinants of Community Health (Faculty of Medicine) Guest lecturer on 'The Future of Medicine & Public Health in a Crowded, Diverse, Aging, Stratified, Urbanized, Polluted, Hot, Thirsty, Hungry, Debt-Ridden World".
2012-	CHL5004H Introduction to Public Health Guest lecturer on "The Future of Public Health (and Your Role !) in a Hot, Flat, Crowded…and Diverse, Aging, Stratified, Urbanized, Polluted, Thirsty, Hungry, Debt-Ridden World". "What is Public Health?", "Climate Change and Health"
2012-	CHL 5912F Industrial Toxicology. Guest lecturer on the "Toxicology of Metals".
2013-2014	Department of Family & Community Medicine "Building Blocks" (short course for International post-graduate primary care trainees); Guest lecturer on "Public Health & Primary Care"
2013-	CHL5701H Doctoral Seminar, Collaborative Doctoral Program in Global Health Guest lecturer on "The Challenges of Environmental Health in a Rapidly-Changing World, from the Molecular to the Global".
2014	JCR1000 "Interdisciplinary Approach to Global Challenges" Guest lecturer on "Global Environmental Health"
2014-	PHS100H1 "Grand Opportunities in Global Health"; Guest lecturer on "Urban Environments"
2015	Public Health & Preventive Medicine Residency Rounds "Physicians, Climate, and other Global Environmental Changes: Our Role"
2016	CHL5004H Introduction to Public Health, Course Co-Director (with Professor Erica

DiRuggierro)

2016 CHL 7001H F6 Environmental-Molecular Epidemiology, Course Co-Moderator (with Professor Morteza Bashash)

2016 CHL5701H Doctoral Seminar, Collaborative Doctoral Program in Global Health, Course Co-Director (with Professors Erica DiRuggierro and Abdallah Daar)

2016 Joint Seminar, "The Impact on Intelligence, Behaviour, and Society of Lead Exposure: A Case Study of a Global Pollutant and On-going Research"; Collaborative Program in Neurosciences and Collaborative Global Health Doctoral Program, University of Toronto

2016 CHL5420H "Global Health Research Methods"
Guest lecturer on "The Early Life Exposures in Mexico to Environmental Toxicants Project (ELEMENT): A Global Health Collaboration Case Study"

Masters student research advisor
Maelle Marchand

Doctoral student advisor
Adele Carty

Doctoral student thesis committee member
Laura Bogaert

Doctoral student thesis examination committee member
Claudie CY Wong (doctoral student in epidemiology, Jockey School of Public Health and Primary Care, Chinese University of Hong Kong)
Zilong Zhang (doctoral student in epidemiology, Jockey School of Public Health and Primary Care, Chinese University of Hong Kong)

Post-doctoral fellow mentor:
Siying Huang, Ph.D.; Morteza Bashash, Ph.D.; Roman Pabayo, Sc.D. (Harvard School of Public Health); Tripler Pell, M.D., M.P.H.

4. LOCAL CONTRIBUTIONS (at the University of Washington, 2017-present)

Doctoral student thesis research mentor
Megan Suter

Doctoral student special projects advisor
Rachel Shaffer
Joey Frostad
Rebecca De Buen

5. NIH K-grant mentorship:

Robert Wright, M.D., M.P.H. (K-23 ES000381, "*Neurochemical and Genetic Markers of Lead Toxicity"*), 2000-2005; Dr. Wright is now Prof of Pediatrics, Mt. Sinai School of Medicine
Marc Weisskopf, Ph.D. (K-01 ES012653, "*New Biomarkers of Neurotoxicity*"), 2004-2009; Dr. Weisskopf is now Associate Prof of Occup Health, Harvard Sch Public Health
Sung Kyun Park, Sc.D. (K-01 ES016587; "*Environment, Novel Aging Outcomes, and Genetics*"), 2009-2014; Dr. Park is now Assistant Prof, Department of Epidemiology, University of Michigan Sch Public Health
Emily Somers, Ph.D. (K-01 ES019909; *"Immune Dysfunction Associated with Early Life Heavy Metals Exposure"*), 2011-2016; Dr. Somers is now Associate Prof, Division of Rheumatology, Department of Internal Medicine, University of Michigan Medical School

COMMITTEE, ORGANIZATIONAL, AND VOLUNTEER SERVICE

National/International

1978-1982 Taskforce on Occupational and Environmental Health, Co-coordinator, Am Med Stu Assoc
1989 Ad Hoc Study Committee, National Institute for Environmental Health Sciences Council
1989-2006 Association of Occupational and Environmental Medicine Clinics (AOEC)-- (through the Northeast Specialty Hospital Center for Occupational and Environmental Medicine)
1989-1990 Member, Relative Risk Reduction Strategies Committee, Science Advisory Board, U.S. Environmental Protection Agency
1989-1992 Member, Board of Directors, Physicians for Human Rights, Boston, MA
1991 National Institutes of Health, General Clinical Research Center Program, Site Visit Team
1992- Member, National Advisory Committee, Physicians for Human Rights, Boston, MA
1992 Special Study Section member (R3/S1/B3), National Institutes of Health
1994 Ad Hoc Reviewer, National Institutes of Health, General Dental Research Center Program
1994- Advisory Board, Institute for Energy and Environmental Research
1994-1996 Associate, Project on Global Environmental Change and Health, Physicians for Social Responsibility
1995 Ad Hoc Reviewer, National Institutes of Health, Diagnostic Radiology Study Section
1996- Membor, Editorial Board, Health and Human Rights—an International Journal
1995-1998 Advisory Committee, Consortium for Environmental Education in Medicine, Cambridge, MA.
1996-1997 Reviewer, Agency for Toxic Substances and Disease Registry
1997-1998 Program Committee, Annual Mtg, NIEHS Superfund Basic Research Group Centers
1998-2013 (Founding) Medical Editor (1998-2004); Associated Medical Editor (2004-), Environmental Health Perspectives (official journal of NIEHS)
2001 Ad Hoc Reviewer, National Institutes of Health, R-13 applications

2002-2006 External Advisory Committee, Program Project on Lead and Osteoporosis, University of Rochester
2003-2005 Member, Ad-Hoc Expert Panel to Form Medical Management Guidelines for Lead-Exposed Adults, (supported by NIOSH and AOEC)
2003-2009 Member, Working Group on Lead and Pregnancy, Advisory Committee on Childhood Lead Poisoning Prevention, U.S. Centers for Disease Control and Prevention
2004 Ad Hoc Reviewer, National Institutes of Health, K-23 applications
2004 Ad Hoc Reviewer, Draft of "Immunization Safety Review: Vaccines and Autism" Immunization Safety Review Committee, Institute of Medicine, National Academies of Science
2004 Finalist (one of 8), Search for Director, National Institute for Environmental Health Sciences, U.S. National Institutes of Health
2005 Member, Strategic Planning Conference, National Institute for Environmental Health Sciences, Research Triangle Park, NC
2006 Ad Hoc Reviewer, Draft of "Preterm Birth: Causes, Consequence, and Prevention" Committee on Understanding Premature Birth and Assuring Health Outcomes, Institute of Medicine, National Academies of Science
2006 Member, External Advisory Committee, NIEHS Center, University of Rochester
2007 Member, Ad Hoc Study Section, Special Emphasis Panel/Scientific Review Group 2007/05 ZES1 JAB-C (DI) (NIEHS Discover Centers)
2007-2010 Member, Board on Population Health and Public Health Practice, Institute of Medicine, National Academies, Washington DC.
2007 Member, Ad Hoc Review Panel, Centers of Excellence Program, Swedish Council for Working Life and Social Research.
2007-2008 Member, Search Committee for Director of Extramural Research, NIEHS
2007 Special Consultant, Ad Hoc Study Section, Special Emphasis Panel/Scientific Review Group 2008/01 ZAR1 CHW-G (NIAMS Arthritis Centers)
2008 Report Reviewer, Draft National Research Council Report, "The National Children's Study Research Plan: A Review", National Academies
2008 Report Reviewer, Draft National Research Council Report, "Gulf War and Health: Updated Literature Review of Depleted Uranium", Institute of Medicine, National Academies
2008-2009 Data Safety Monitoring Board, "d-Penicillamine Chelation in lead-poisoned Children—A Phase II/III Trial" (R01FD003361; PI: Michael Shannon)
2008 Subcommittee to review Draft Report on Bisphenol A, Science Board, Food and Drug Administration
2008 Planning Committee, International Symposium on the Environmental and Health Consequences of Metal Mining and Smelting
2008-2009 Co-Chair, Planning Committee, "Climate Change Impacts on Public Health in India", Workshop that took place in Goa, India in Aug-Sept 2009 co-sponsored by UM Center for Global Health, the US Centers for Disease Control and Prevention and the Indian Council for Medical Research

2008 Finalist (one of 2), Search for Director, National Institute for Environmental Health Sciences, U.S. National Institutes of Health
2009-2012 Member, Board on Environmental Studies and Toxicology, National Research Council
2009 Reviewer, NIH Challenge Grants, Special Emphasis Panel/Scientific Review Group 2009/10 ZRG1 GGG-F
2009-2010 External Member, Academic Program Review Site Visit Committee, Department of Environmental and Occupational Health Sciences, University of Washington School of Public Health
2010-2012 Member, External Advisory Committee, University of Rochester NIEHS P30 Core Center
2010 Member, Ad-hoc review committee, National Health Research Institutes of Taiwan, Special Emphasis Panel—NHRI-Kaoshiung Medical College Program Project on ": "Gene Environment Interaction in the Genesis of Asthma and Allergic Diseases"
2010-2012 Member, Advisory Board, Institute of Public Health, Florida Agricultural & Mechanical University, Tallahassee, FL
2011 Reviewer, NIEHS Career Development Awards, Special Emphasis Panel/Scientific Review Group 2011/05 ZES1 LKB-J (K9)
2011-2016 Member, NIEHS National Advisory Environmental Health Sciences Council
2012 Member, Editorial Board, Journal of Alzheimer's Disease
2015 Member and External Reviewer, School of Population and Public Health Review Committee, University of British Columbia, Vancouver, B.C.
2016- Chair, Board of Directors, Canadian Urban Environmental Health Research Consortium, (National Consortium based out of the Dalla Lana School of Public Health)
2017- Member, Energy Research Committee, Health Effects Institute, Boston, MA
2017-2018 Executive Co-Chair, Workshop on the Global Burden of Disease-Pollution and Health Initiative, March 1-2, 2018, Institute for Health Metrics and Evaluation, Seattle, WA
2017- Executive Co-Leader, Global Burden of Disease-Pollution and Health Initiative
2019- Member, Research Advisory Committee, Centre of Environmental Health, The Public Health Foundation of India and the Tata Institute of Social Sciences, New Delhi, India
2019- Reviewer, draft report on trace metals levels in pregnancy women, Agency for Toxic Substances and Disease Registry, Centers for Disease Control and Prevention, Atlanta

Regional

1988-1990 Health Facilities Appeals Board, Member, Dept. Public Health, Comm. Of Mass.
1988-2006 Advisory Board, Massachusetts Department of Public Health, Sentinel Event Notification System for Occupational Risks (SENSOR) Project
1989-1995 Advisory Board, Massachusetts Division of Occupational Hygiene, Lead Registry Project
1990-1992 Board of Directors, Member, Health Care for All, Boston, Massachussetts
1993-1995 Faculty Council, Member, Harvard School of Public Health
1995-2006 Faculty Advisory Committee, Public Health Practice Program, Harvard School of Public Health

1996-2006 Advisory Board, Boston VA Environmental Hazards Center, Boston
1997-2001 Faculty Steering Committee, Center for Children's Health, Harvard School of Public Health
1996-2006 Senior Epidemiology Consultant, Massachusetts Veterans Epidemiology Research and Information Center, Boston.
1996-2006 Associate, Center for Health and the Global Environment, Harvard Medical School
1997-2002 Faculty Advisory Committee on Continuing Professional Education, Harvard School of Public Health
1998-2006 Faculty Steering Committee, Masters of Public Health program, Harvard School of Public Health
2001-2003 Board of Directors, New England College of Occupational and Environmental Medicine
2001-2006 Associate Director, Harvard NIEHS Environmental Sciences Center, Harvard School of Public Health
2001-2006 Senior Advisory Council Member, Lowell Center for Sustainable Production, University of Massachusetts, Lowell, MA
2003-2006 Member, Human Subjects Committee, Harvard School of Public Health
2003-2006 Advisory Committee, Occupational Health Services Research Program, Harvard School of Public Health
2006 Study Section Review Committee, Pilot Project Program, Graham Environmental Sustainability Institute, School of Natural Resources and Environment, University of Michigan
2006-2007 Chair, Planning Committee, Health Sector, May 8-10, 2007 National Summit on Coping with Climate Change, University of Michigan
2007-2009 Member, Advisory Committee, SPH Practice Committee, University of Michigan School of Public Health
2007-2012 Member, Residency Advisory Committee, General Preventive Medicine Residency, University of Michigan School of Public Health
2008-2009 Member, Steering Committee, NIA T32 Training Grant on Aging Research (PI: Mary Haan), University of Michigan School of Public Health
2008-2013 Member, Advisory Committee, Outstanding New Environmental Scientist Awardee (Marie O'Neill), NIEHS
2008-2009 Member, Search Committee for Director of the Risk Science Center, University of Michigan School of Public Health
2009 Co-Chair, Planning Committee, Workshop on Predicting and Preventing Climate Change Impacts on Public Health, Goa, India (Collaboration with the UM Center for Global Health, the US Centers for Disease Control and Prevention, and the Indian Council for Medical Research)
2009-2011 Director and PI, NIA T32 Training Grant on Aging Research, University of Michigan School of Public Health
2009-2010 Member, Planning Committee, University Research Corridor (U of M, Michigan State, Wayne State) symposium on environmental health sciences in January 2010

2009-2012 Faculty Associate, Center for Global Health, University of Michigan
2009-2012 Member, Internal Advisory Board, Cancer Epidemiology Education in Special Populations Program, University of Michigan School of Public Health
2009-2011 Chair, Steering Committee on Global Health, University of Michigan School of Public Health
2010-2012 Member, Executive Committee, Graham Environmental Sustainability Institute, University Of Michigan
2010-2012 Member, Committee on Diversity, University of Michigan School of Public Health
2012-2017 Chair, Executive Committee, Dalla Lana School of Public Health, University of Toronto
2012-2017 Chair, Tenure Committee, Dalla Lana School of Public Health, University of Toronto
2012-2017 Chair, Decanal Promotions Committee, Dalla Lana School of Public Health, University of Toronto
2012-2017 Chair, Executive Advisory Committee, Institute for Global Health Equity & Innovation, Dalla Lana School of Public Health, University of Toronto
2013-2015 Interim Director, Institute for Global Health Equity & Innovation, Dalla Lana School of Public Health, University of Toronto
2013-2014 Co-Chair, Research Committee, Dalla Lana School of Public Health, University of Toronto
2014-2017 Chair, Executive Advisory Committee, Institute for Health Policy Management and Evaluation, University of Toronto
2014 Chair, Ad-hoc Committee to create an Institute for Indigenous Health (based on a $10 million endowment gift made to DLSPH), Dalla Lana School of Public Health, University of Toronto; Chair, Executive Advisory Committee beginning 2015
2015-2017 Chair, Executive Advisory Committee, Joint Centre for Bioethics, University of Toronto
2015- Chair (2015-2017); Member (2017-present), Taskforce on Environmental Health, Ministry of Health and Longterm Care, Province of Ontario
2016-2017 Chair, Executive Advisory Committee, Centre for Critical Qualitative Health Research, University of Toronto
2017-2018 Executive Co-Chair, Workshop on the Global Burden of Disease-Pollution and Health Initiative (a collaboration between the Global Alliance on Health and Pollution and the Institute for Health Metrics), Seattle, WA

Hospital

1982-1985 Occupational Safety and Health Committee, Member, Boston City Hospital, Boston
1983-1984 House Officers Association, Treasurer, Boston City Hospital
1984-1985 House Officers Association, Co-President, Boston City Hospital

OTHER PUBLIC SERVICE

1987 Member, Fact-finding tour on "The Health Effects of Massive Exposure to Tear Gas",

Seoul, South Korea, July 11-18 (Sponsored by Physicians for Human Rights, American College of Physicians)

1988 Member, Fact-finding tour on "Chemical Weapons and the Iraqi Kurdish refugees", Turkey Oct 6-16 (Sponsored by Physician for Human Rights and the MacArthur Foundation)

1990 Leader, Fact-finding tour on "Health and Human Rights in Burma (Myanmar)", Thailand-Burma Dec. 26-Jan 6 (Sponsored by Physician for Human Rights and the MacArthur Foundation)

2009 Consultant and senior advisor, Fact-finding tour on “Mining and Potential Exposures and Health Effects in Guatemala”, August 2009 (Sponsored by Physicians for Human Rights)

CONSULTING POSITIONS

1987-1989 Consultant, "In-Vivo Total Body Lead Analysis by X-Ray Fluorescence", NIH/SBIR Grant 2R44ES03918-02

1988-1989 Consultant, "Boston Area Health Coalition Demonstration Project", DHHS/MP000003-A1

1993-1995 Consultant, Employee Health Services, Brigham and Women’s Hospital

1994 Consultant, Public Welfare Foundation, Washington, DC (review of Environmental Programs)

1997-2006 Consultant, Pediatric Environmental Health Center, Children’s Hospital, Boston, MA

2000 Consultant, Doris Duke Foundation, New York, NY (review of potential Environment and Medicine programs)

2009-2010 Consultant and Member, Academic Program Review Site Visit Committee, Department of Environmental and Occupationa Health Sciences, University of Washington School of Public Health, Seattle, WA

2011 Consultant, JPB Foundation, New York, NY (review of Environmental Health programs)

2014- Advisor, Hearing Health Sciences, Ann Arbor MI and Amsterdam, Netherlands

VISITING PROFESSORSHIPS

1997 Alice Hamilton Visiting Professor, University of California at San Francisco

2000-2001 Visiting Professor, Sri Ramachandra Medical College & Research Institute, Chennai, India

2004 Visiting Professor, Department of Environmental Medicine, University of Rochester

2013 Visiting Professor, Shanghai Key Laboratory, Shanghai Jiao-Tung University

SEMINARS AND EXTRAMURAL INVITED PRESENTATIONS (last 15 years, since 2003; prior presentations upon request)

2003 Guest lecturer, "Lead as a trans-generational toxin", Seminar series, Department of OB/GYN, Brigham and Women's Hospital
2003 Plenary speaker, "Clinical opportunities in environmental health", Annual Leadership Retreat, National Institute for Environmental Health Sciences, Greensboro, NC.
2003 Discussant, "Uncontrolled Hypertension in a Painter", Grand Rounds in Occupational/Environmental Medicine, Harvard School of Public Health
2003 Discussant, "A 53-Year Old Teacher with Chemical Sensitivities", Grand Rounds in Occupational/Environmental Medicine, Harvard School of Public Health
2003 Lecturer, "Pestilence and Progress: The Future of Public Health through the Lens of Blood", Center for Blood Research Symposium, Museum of Science, Boston, MA.
2003 Speaker, "Bones, Genes, Plasma, and Lead: New Frontiers in Understanding the Toxicity of an Old Hazard", Distinguished Lecture Series. National Center for Environmental Health/Agency for Toxic Substances and Disease Registry, Centers for Disease Control and Prevention, Atlanta GA.
2003 Plenary speaker, "Biomarkers, Genes, Interactions and Lead: New Insights from Research on an Old Hazard", Superfund Basic Research Program Annual Meeting, Dartmouth University, Hanover, NH.
2003 Special Lecturer, "Lead Exposure and Chronic Disease: Recent Research on Susceptible Sub-populations", Florida Agricultural and Mechanical University, Tallahassee, FL.
2004 Speaker, "New Frontiers in Understanding the Toxicity of Lead", Department of Environmental Medicine, University of Rochester, Rochester, NY.
2004 Presenter, "Lead Exposure During Pregnancy: Mobilization of Maternal Bone Lead Stores and Their Threat to the Fetus", Semi-annual meeting of the Childhood Lead Poisoning Prevention Branch, Centers for Disease Control and Prevention, Baltimore, MD
2004 Presenter, "Environmental Medicine", Annual meeting of the Editorial Board, *Environmental Health Perspectives*, Baltimore MD
2004 Plenary speaker, "Metals, Genes, and Neurodegeneration: the Approach of the Metals Epidemiology Research Group at the Harvard School of Public Health", National Institute for Environmental Health Sciences Conference on Neurodegeneration.
2004 Discussant, "Suspected Lead Toxicity" Grand Rounds in Occupational/Environmental Medicine, Harvard School of Public Health
2004 Discussant, "Mercury Exposure in a Metal Worker", Grand Rounds in Occupational/Environmental Medicine, Harvard School of Public Health
2004 Presenter, "Effects of Our Environment on Intellect, Behavior, Life and Death," Leadership Council meeting, Harvard School of Public Health
2004 Guest Speaker, "Biomarkers, Genes, Interactions and Lead: New Insights from Research on an Old Hazard", Department of Environmental Health, University of Michigan School of Public Health
2004 Guest Speaker, "Medicine, Public Health, and the Great American Melting Pot: A Second-Generation Chinese-American Reflects on His Personal Odyssey", Sponsored by the Asian Student Association, Harvard School of Public Health
2004 Speaker, "Aging, the Environment and Genetics: Recent Insights from

Epidemiologic Studies of Environmental Lead Exposure", Annual Leadership Retreat, National Institute for Environmental Health Sciences, Pinehurst, NC.

2004 Plenary Speaker, "Guidelines for the Management of Lead-Exposed Adults: Recommendations by a National Expert Panel Based on Recent Research", New England College of Occupational and Environmental Medicine Annual Meeting

2005 Lecturer, "Biomarkers, Genes, Interactions and Lead: New Insights from Research on an Old Hazard", Sri Ramachandra Medical College and Research Institute, Chennai, Tamil Nadu, India

2005 Lecturer, "Your Child's IQ, Behavior and Neuropathology: Genes or Environment?", the Harvard Club of Boston, Boston, MA

2005 Guest Speaker, "Metals, Neurodevelopment, and Neurodegeneration: The Work of the Metals Epidemiology Research Group at HSPH", Neurostatistics Working Group, Harvard School of Public Health, Boston, MA.

2005 Plenary Speaker, "Aging, the Environment and Genetics: Recent Insights from Epidemiologic Cohort Studies of Environmental Lead Exposure", NIEHS Symposium on Aging and the Environment, Duke University, Durham, NC.

2005 Plenary Speaker, "SPECT Imaging and Chemical Intolerance", NIEHS/NIAA symposium on "Chemical Intolerance and Addiction: a Shared Etiology?", Research Triangle Park, NC

2005 Workshop Presenter, "Social and Environmental Threats: the Unnecessary Epidemics", Harvard School of Public Health Leadership Council Annual Conference, Boston, MA

2005 Keynote Speaker, "Our Food, Our Water, Our Homes: Toxic Metals", The Boston Foundation, Boston, MA.

2006 Invited Speaker (invited by David Schwartz, NIEHS Director), "Goal IV: Improve and Expand Community-Linked Research", Roundtable on Environmental Health Sciences, Research, and Medicine; Institute of Medicine, National Academy of Sciences, Wash DC.

2006 Speaker, "The Future of Environmental Health Sciences at the University of Michigan", Dean's Advisory Board, University of Michigan School of Public Health, Ann Arbor, MI

2006 Keynote Speaker and Harriett Hardy Annual Lecturer, "The 'E' in Occupational/ Environmental Medicine: the Present and the Future", New England College of Occupational Medicine Annual Meeting, New Bedford, MA

2007 Speaker, "The Future of Environmental Health Sciences at the University of Michigan", Meetings of the UMSPH Alumni Council and the EHS Emeritus Faculty, Ann Arbor, MI

2007 Moderator and Speaker, "The Normative Aging Study: Health Effects of Lead", Symposium on the Health Effects of Lead, 2007 Annual Meeting of the International Society for Environmental Epidemiology, Mexico City, Sept 8, 2007

2007 Guest Lecture, "Uncovering the Impact of the Environment on Disease: Big Opportunities for Physician-Scientists", Medical Scientist Training Program, University of Michigan Medical School

2007 Guest Lecture, "Industrialization, Pollution and Public Health in India: Can India Survive Modernization?", Osher Institute, Ann Arbor, MI

2007 Plenary Speaker, "Environmental Equity: Local and Global Challenges and the Balance Between Research and Advocacy", Michigan's Premier Public Health Conference,

October 16, 2007, Dearborn, MI

2007 Board Member Lecture, "Metals, Genes, Health and Human Rights: from the Molecular to the Global", Fall Meeting of the Board of Population Health and Public Health Practice, Institute of Medicine, National Academies of Science, Washington DC, Dec 13, 2007.

2008 Speaker, "MDs as Leaders for Change in Environmentalism", 2008 Annual Regional Political Leadership Institute, American Medical Student Association, University of Michigan Medical School, February 16, 2008

2008 Speaker, Grand Rounds, "The Impact of Environmental Pollutants on Disease: New Insights and Implications for Research and Medical Practice" Department of Medicine, University of Michigan Health System.

2008 Guest Lecture, "Emerging Insights into the Pervasive Influence of Environment Toxicants on Reproductive Outcomes and Offspring Development: Lead as a Case Study", Reproductive Sciences Program, University of Michigan

2008 Panelist, "Environmental Health in China", Public Health Grand Rounds, Division of Health Practice, University of Michigan School of Public Health

2008 Keynote Speaker, "Human Health and the Role of Water", Symposium on Water, Health & The Environment, Graham Environmental Sustainability Institute, University of Michigan

2008 Guest Speaker, "Lead Exposure and Toxicity: New Insights Using Molecular Epidemiology" Wadswoth Laboratories and SUNY-Albany

2008 Speaker: "Impact of Climate Change on Human Health: Vulnerability" 5th AKKA World Kannada Conference, Chicago IL

2008 Speaker, "The 'E' in Occupational/Environmental Medicine: the Present and the Future", Michigan Occupational/Environmental Medicine Annual Meeting, Mackinac Island, MI

2008 Speaker, "Impact of Climate Change on Human Health", University of Michigan Chapter of the American Medical Student Association, Ann Arbor, MI

2008 Speaker, "Early Life Origins of Adult Chronic Disease: Environmental Health and Toxicology at a Crossroads" Michigan Chapter fo the Society for Toxicology, Ann Arbor, MI

2009 Speaker, "Evidence for Lead as an Environmental Stressor of Alzheimer's Disease and the Role of Epigenetics", Symposium Panel, Annual Meeting of the Society for Toxicology, Baltimore, MD

2009 Keynote Speaker, "Lead, Late-Life and Early Life Effects, and the Emerging Field of Environmental Epigenetics: Looking Ahead", Annual Meeting of the American College for the Advancement of Medicine, San Diego, CA

2009 Speaker, "Lead Toxicity and Mechanistically-Oriented Molecular Epidemiology: Targeting the Epigenetics of Alzheimer's Disease", Seminar Series, Institute for Environmental Health Sciences, Wayne State University, Detroit, MI

2009 Speaker, "Climate Change Impacts on Health in the Developing World", Research Discussion Series, University of Michigan Center for Global Health

2009 Speaker, "Autism, Aggressive Behavior, Anxiety, and Alzheimer's: are Environmental Toxicants Playing a Major Etiologic Role?", Department of Psychology, University of Michigan

2009 Speaker, "Early Life Exposures and Endocrine Disruption: Evidence from Molecular

Epidemiology", Pediatric Endocrine Seminar, University of Michigan Medical School

2009 Distinguished Speaker, "Lead Toxicity: Twenty Years of Research On The Poison That Keeps on Poisoning" 10th Anniversary of the Department of Microbiology and Environmental Toxicology, University of California at Santa Cruz

2010 Speaker, "The Centers for Disease Control and Prevention & the Environmental Protection Agency: Potential Funding Opportunities for Regional Collaboration in Michigan", University Research Corridor Symposium on Environmental Health, Detroit, MI.

2010 Speaker, "The Future of Public Health", University of Washington School of Public Health

2010 Speaker, "The Environment Meets the Epigenome: Is This Where Autoimmunity Begins?" Symposium on Autoimmunity and Epigenetics, University of Michigan

2010 Keynote Speaker, "A New Twist to an Old Story: The Evidence for Early Life Lead Exposure as a Risk Factor for Alzheimer's Disease through Epigenetic Programming", NIEHS Environmental Health Sciences Center and Toxicology Training Program Retreat, University of Rochester, NY

2010 Speaker, "Lead Toxicity: Twenty Years of Research on The Poison That Keeps on Poisoning" and "Environmental Health Sciences at the University of Michigan", Tianjin Centers for Disease Control, Tianjin, China

2010 Speaker, "Pediatric Lead Toxicity", Xinhua Hospital and the Shanghai Jiao-Tung Medical University Department of Pediatrics, Shanghai, China

2010 Speaker, "Environmental Health Sciences at the University of Michigan", Fudan University, Shanghai, China

2010 Speaker, "Alzheimer's Disease, Epigenetics and the Environment", Symposium Update, Alzheimer's Disease Association, Ann Arbor, MI

2010 Speaker, "Environmental Justice, Progress (and the Lack Thereof) and the Role of Research", Roundtable on Environmental Health Sciences, Research and Medicine, Institute of Medicine, National Academies, Washington DC.

2010 Speaker, "White Coats, Population Science and Poison Gas: A Life Spent at the Intersection of Academic Medicine, Global Health & Human Rights", Robert Wood Johnson Clinical Fellows Program, University of Michigan Medical School, Ann Arbor, MI

2011 Speaker, "The Three Most Difficult Challenges to Molecular Epidemiologic Research on Gene-Environment Interactions: Lead Toxicity as a Case Study." Department of Human Genetics, University of Michigan Medical School, Ann Arbor, MI

2011 Speaker, "The Integration of Data on Environmental Carcinogens with Population and Genetic Resources", "Opportunities & Challenges for Translational Research on Cancer Prevention", Translational Cancer Prevention & Biomarkers Workshop, Mazamdur-Shaw Cancer Center, Bangalore, India.

2011 Speaker, "Success in the Academy", Faculty Panel, Students of Color of Rackham, Rackham Graduate School, University of Michigan

2011 Speaker, "White Coats, Population Science and Poison Gas: Fact-Finding Missions by Health Professionals for Human Rights" , Sujal Parikh Memorial Symposium, University of Michigan Medical School.

2011 Speaker, "The Analysis of Biomarker Data to Ascertain the Contribution of Environmental

Exposures to the Etiology of Disease: Lead Exposure and Toxicity as a Case Study", Department of Computational Medicine and Bioinformatics, University of Michigan Medical School.

2012 Speaker, "Research and Analysis Linking Upstream and Downstream Disparities Work", Webinar hosted by the Health & Environmental Funders Network, Bethesda, MD, with 52 Foundations related Health.

2012 Keynote Speaker, "The Future of Public Health & Medicine in a Crowded, Diverse, Stratified, Hot, Urbanized, Polluted, Thirsty, Hungry and Debt-Ridden World". E.J. Van Liere Memorial Convocation and Health Sciences Center Research Day, West Virginia University, Morgantown, West Virginia

2012 Plenary Speaker, "Transgenerational Impacts of Pollutants on Offspring: Recent Insights and Case Studies", Connaught Global Challenge International Symposium, University of Toronto.

2012 Speaker, "Environmental Impacts on Aging (+ an update on the Dalla Lana School of Public Health)", Community Medicine Rounds, University of Toronto

2012 Speaker, "The Environment & Public Health in a Research-Intensive University: Opportunities for Scholarship in a Crowded, Diverse, Stratified, Hot, Urbanized, Polluted, Thirsty, Hungry and Debt-Ridden World", School for the Environment, University of Toronto

2012 Speaker, "Big Public Health Challenges (& Opportunities) in a Crowded, Diverse, Aging, Stratified, Urbanized, Polluted, Hot, Thirsty, Hungry, Debt-Ridden World", External Advisory Meeting, Public Health Ontario, Toronto

2012 Speaker, "Canadian Public Health Schools (in a Crowded, Diverse, Aging, Stratified, Urbanized, Polluted, Hot, Thirsty, Hungry, Debt-Ridden World): The View from Toronto, External Advisory Board Meeting, Institute for Population and Public Health, Canadian Institutes for Health Research, Toronto

2012 Speaker, "Sustainable Development and Health: The Global Mining Industry", Canadian Society for International Health Annual Meeting, Ottawa

2012 Speaker, "Big Public Health Challenges (& Opportunities) in a Crowded, Diverse, Aging, Stratified, Urbanized, Polluted, Hot, Thirsty, Hungry, Debt-Ridden World", Xinhua Hospital/Shanghai Jiao-Tung University, Shanghai, China.

2012 Speaker, "The Impact of Population-Wide Lead Exposure and Gene-Lead Interactions on Chronic Disease", Genetic Grand Rounds, Sick Kids Hospital, Toronto.

2012 Speaker, "Looking behind the curtain: Lead Toxicity as a Case Study of Methodologic Challenges in Gene-Environment Interactions Research", Strategic Training in Advanced Genetic Epidemiology (STAGE), Dalla Lana School of Public Health, University of Toronto.

2012 Keynote speaker: "Public Health—the Next Frontier in Health Professions Education". Council of Health Sciences annual retreat, University of Toronto.

2013 Speaker, "White Coats, Population Science and Poison Gas: Lessons from a Life Spent at the Intersection of Academic Medicine, Global Health & Human Rights", Joint Center for Bioethics, University of Toronto

2013 Speaker, "Gauging environmental impact on the development of chronic inflammation",

Connaught Global Challenge Workshop, University of Toronto.

2013 Speaker, "The Future of Public Health & Medicine in a Crowded, Diverse, Aging, Stratified, Urbanized, Polluted, Hot, Thirsty, Hungry, Debt-Ridden World", Grand Rounds, Department of Medicine, University of Toronto.

2013 Speaker, "Metals, Mega-trends, and Me: Reflections on Research and the Vision for the Dalla Lana SPH", Occupational and Environmental Medicine Grand Rounds, St. Michael's Hospital, Toronto, ON.

2013 Speaker, "Air pollution and Cardiovascular Disease: Health Impacts, Mechanisms, and Research Opportunities", UniversityofToronto & FMUSP-InCor SymposiumonCardiology, Sao Paolo, Brazil.

2013 Speaker: "Lead Exposure's Impact on Health and Policy: A History of Neglect and Missed Opportunities", Public Health Policy Rounds, CIHR Strategic Training Program in Public Health Policy, University of Toronto.

2013 Speaker: "Lead Toxicity: The Long Tail of Health Impacts (and On-going Research Opportunities!) From an Historical Environmental Air Pollutant", Southern Ontario Centre for Air Pollution and Aerosol Research, University of Toronto.

2013 Speaker: "Water and Sanitation", Water, Sanitation and Hygiene (WASH) Canada, Toronto, Ontario, Canada

2014 Speaker: "Conflict and Public Health", Ontario Medical Association, Toronto, Canada

2014 Panelist: "Judging Evidence: Finding a Place for Variation in an Evidence-Based World", Health Quality Ontario, Toronto, Canada

2014 Speaker: "The Grand Convergence: Creating Health in a Globalized World", Special meeting of the Canadian Chamber of Commerce in Shanghai

2014 Speaker: "The Grand Convergence: Creating Health in a Globalized World", Jockey School of Public Health and Primary Care, Chinese University of Hong Kong, Hong Kong, China

2015 Speaker: "The Grand Convergence: Creating Health in a Globalized World", School of Public Health and the ASEAN Institute, Mahidol University, Bangkok, Thailand

2015 Speaker: "Gene-environment Interactions and the Role of Big Data in Environmental Health" Seminar series, School of the Environment, University of Toronto, Toronto, Canada

2015 Speaker: "Global Health Security", Ill with Illness—Economic, Social & Security Barriers to the Provision of Global Health, Munk School of Global Affairs, University of Toronto, Toronto, Canada

2015 Speaker: "The Dalla Lana School of Public Health: Big Ideas and Initiatives for Creating Health in a Globalized World", Speaker Series, University of Toronto Alumni of Toronto.

2015 Speaker: "Unique Scientific Opportunities for the Precision Medicine Initiative National Research Cohort: Exposomics, Data Linkage, and Global Collaborations". Working group on President Obama's Precision Medicine Initiative (Chaired by Francis Collins, Director, NIH)

2015 Speaker: "What is the Role of Schools of Public Health in the 21st Century?" 50th Anniversary Celebration of the Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec.

2015 Welcoming Address: "Global Public Health and Mental Health", Going Glo-cal for Mental Health conference, Centre for Addictions and Mental Health/Department of Psychiatry/Dalla

Lana School of Public Health, Toronto, ON

2015 John Goldsmith Memorial Lecture: "Big Data, Environmental (and Social) Epidemiology, Power and Politics", Opening Plenary Session, International Society for Environmental Epidemiology Annual Meeting, Sao Paulo, Brazil

2015 Inaugural Speaker: "The Future of Public Health and Medicine in a Crowded and Complex World", Global Health Leadership Series, PSG Medical School & the Shanti Ashram Foundation, Coimbature, Tamil Nadu, India

2016 Speaker "The Future of Public Health & Medicine in a Crowded, Diverse, Aging, Stratified, Urbanized, Polluted, Hot, Thirsty, Hungry, Debt-Ridden World", Indian Institutes of Public Health—Hyderabad, Hyderabad, India

2016 Speaker: "Integration of Public Health & Health Care: The Unmet Agenda for a Truly Sustainable Health System", Board of Directors Retreat, Toronto East General Hospital, Toronto

2016 Plenary speaker: "Health Promotion, Prevention and Health Protection: Innovative Initiatives", 6th Asia-Pacific Conference on Public Health | 1st ASEAN Health Promotion Conference Bangkok, August

2016 Speaker: "Big Data, Environmental (and Social) Epidemiology, Power and Politics", Mount Sinai School of Medicine, New York, NY

2016 Plenary Speaker: "The Impact of Environmental Toxicants on Health: Recent Epidemiologic Approaches & Advances", International College of Integrative Medicine Annual Meeting, Toronto, ON

2016 Plenary Speaker: "Big Data and Implications for Environmental Health", 15th Anniversary Conference, Jockey Club School of Public Health & Primary Care, Chinese University of Hong Kong, Hong Kong

2016 Plenary Speaker: "Innovations in Assessing Lead Poisoning and Child Health: Policy & Clinical Implications", Chinese University of Hong Kong-Fudan-Oxford International Symposium on Health Impacts of Environmental Exposures", Hong Kong

2016 Speaker: "Addressing a Changing Environment (and Impacts on Health, AKA Can India Survive Modernization?", Indian Institutes of Technology Alumni, Canada, International Conference 2016, Toronto.

2016 Plenary Speaker, "Hidradenitis Suppurativa: Research Directions from a Population Health Perspective", Symposium on Hidradenitis Suppurativa Advances, Toronto.

2016 Plenary Speaker, "Children's Environmental Health", The 2016 Annual National Conference on Children's Healthcare, Shanghai, China

2016 Special Guest Speaker, "Big Data, Environmental (and Social) Epidemiology, Power and Politics", Shanghai Municipal Center for Disease Control, Shanghai, China

2016 Lecturer, "Lead and Human Health: Recent Research and Associated Lessons for Science & Policy", Fudan University School of Public Health, Shanghai, China

2017 Lecturer, "The Impact of Environmental Toxicants on Health: Recent Epidemiologic Approaches & Advances", Saw Swee Hock School of Public Health, National University of Singapore, Singapore

2017 Lecturer, "The Future of Academic Public Health", Saw Swee Hock School of Public Health,

National University of Singapore, Singapore

2017 Lecturer, "Recent Advances in Understanding, Preventing, and Reversing the Impact of Environmental Factors on Health", Society of Chinese Bioscientists in America, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, ON

2017 Lecturer, "Environmental Epidemiology in the Era of Exposomics, Lifecourse Epidemiology, Big Data and Big Science", Department of Environmental Health, Harvard School of Public Health, Boston, MA

2017 Speaker, "The Role of a Re-emergent Canadian School of Public Health in a Hot, Hungry, Polluted, Aging, Polarized World Prone to Pandemics, Chronic Disease, and Unsustainable Health Systems", Royal Canadian Institute for Science, Toronto, ON

2017 Speaker, "The Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) Birth Cohort Study: Current Research on Fluoride and Neurodevelopment", Seminar Series in Environmental Epidemiology, University of Washington School of Public Health, Seattle, WA

2017 Plenary Speaker: "New realities arising from the extractive industries and agri-business: the Pollution and health perspective," Hong Kong Summit of Global Health Leaders. University of Hong Kong, Hong Kong

2018 Plenary Speaker: "The GBD-Pollution and Health Initiative: Challenges & Opportunities", Workshop on the Global Burden of Disease-Pollution and Health Initiative, Institute for Health Metrics, University of Washington, Seattle, WA

2018 Guest Lecturer: "Partnerships, Local Responsiveness, National and Global Impacts", University of Iowa College of Public Health, Iowa City, IA

2018 Plenary Speaker: "Current Research on Fluoride and Neurodevelopment: The Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) Birth Cohort Study", Annual meeting of the International Academy of Oral Medicine and Toxicology, Denver, CO

2018 Speaker, "Recent Epidemiologic Research on Lead Toxicity: New Surprises regarding an Old Global Pollutant", Department of Environmental and Occupational Health Sciences Seminar Series, University of Washington School of Public Health, Seattle, WA

2018 Speaker: "The Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) Birth Cohort Study: Current Research on Fluoride and Neurodevelopment", Symposium on Fluoride research, Annual meeting of the International Society for Environmental Epidemiology/International Society for Exposure Science, Ottawa, ON

2018 Panelist, "The Fluoridation Decision: Considering the Evidence for Benefits, Possible Risks as well as Ethical World Views", Annual meeting of the International Society for Environmental Epidemiology/International Society for Exposure Science, Ottawa, ON

2018 Speaker: "Grand Opportunities", The UC-Irvine School of Population Health and the Samueli College of Health Sciences, Irvine, CA

2018 Speaker, "The Global Burden of Disease-Pollution and Health Initiative", Office of the Director and the Global Environmental Health Program, U.S. National Institute for Environmental Health Sciences, Research Triangle Park, NC

2019 Speaker, "Evaluating, treating and managing disabilities of patients with chemical intolerance", Symposium on Chemical Intolerance—A Way Forward, Marilyn Brachman

Hoffman Foundation and the Hoffman Program on Chemicals and Health at the Harvard T.H. Chan School of Public Health, Dallas, TX

2019 Guest Lecturer: "The Global Burden of Disease-Pollution and Health Initiative", Center for Population Health Sciences, Stanford University, Palo Alto, CA

INVENTIONS/PATENTS: n/a

BIBLIOGRAPHY: (H-index, as of April, 2019, Google Scholar: 83)

Peer-reviewed journals

1. Hu H, Markowitz SB. A case-study of industrial bladder cancer. Einstein Quarterly Review of Biology and Medicine 1982;1:29-35.

2. Hu H. Benzene and myelofibrosis. Annals of Internal Medicine 1987;106:171-172

3. Hu H, Milder FL, Burger DE. X-Ray Fluorescence: Issues surrounding the application of a new tool for measuring burden of lead. Environmental Research 1989;49:295-317.

4. Hu H, Fine J, Epstein P, Kelsey K, Reynolds P, Walker B. Tear Gas: Harrassing agent or toxic chemical weapon? JAMA 1989;262:660-663.

5. Hu H, Cook-Deegan R, Shukri A. The use of chemical weapons: Conducting an investigation using survey epidemiology. JAMA 1989;262:640-643.

6. Hu H, Tosteson T, Aufderheide AC, Wittmers L, Burger DE, Milder FL, Schidlovsky G, Jones KW. Distribution of lead in human bone: I. Atomic absorption measurements. Basic Life Sci 1990;55:267-274.

7. Burger DE, Milder FL, Morsillo PR, Adams BB, Hu H. Automated bone lead analysis by k-x-ray fluorescence for the clinical environment. Basic Life Sci 1990;55:287-292.

8. Schidlovsky G, Jones KW, Burger DE, Milder FL, Hu H. Distribution of lead in human bone: II. Proton microprobe measurements. Basic Life Sci 1990;55:275-280.

9. Jones KW, Schidlovsky G, Burger DE, Milder FL, Hu H. Distribution of lead in human bone: III. Synchrotron x-ray microscope measurements. Basic Life Sci 1990;55:281-286.

10. Hu H, Milder FL, Burger DE. X-ray fluorescence measurements of lead burden in subjects with low-level community lead exposure. Arch Environ Health 1990;45:335-341.

11. Hu H, Win KU, W, Arnison ND. Burma: Health and human rights. Lancet 1991;337:1335.

12. Hu H. A 50-year follow-up of childhood plumbism: hypertension, renal function, and hemoglobin levels among survivors. Am J Dis Child 1991;145:681-687.

13. Hu H. Knowledge of diagnosis and reproductive history among survivors of childhood plumbism. Am J Publ Health 1991;81:1070-1072.

14. Hu H, Milder FL, Burger DE. The use of K-X-Ray Fluorescence for measuring lead burden in epidemiological studies: high and low lead burdens and measurement uncertainty. Environ Health Perspect 1991;94:107-110.

15. Hu H, Pepper L, Goldman R. Effect of repeated occupational exposure to lead, cessation of exposure, and chelation on levels of lead in bone. Am J Ind Med 1991;20:723-735.

16. Hu H. Toxic weapons, epidemiology, and human rights. Polit Politics and Life Sci 1992;February:3-4.

17. Hu H, Sparrow D, Weiss S. Association of serum albumin with blood pressure in the Normative Aging Study. Am J Epidemiol 1992;136:1465-1473.

18. Hu H, Christiani D. Reactive airways dysfunction after exposure to tear gas. Lancet 1992;339:1535.

19. Hu H. Physicians, IPPNW, and the Environment. PSR Quarterly 1993;3:79-87.

20. White RF, Diamond R, Proctor S, Morey C, Hu H. Residual cognitive deficits 50 years after lead poisoning during childhood. Br J Industr Med 1993;50:613-622.

21. Hu H, Beckett L, Kelsey K, Christiani D. The left-sided predominance of asbestos-related pleural disease. Am Rev Resp Dis 1993;148:981-984.

22. Payton M, Hu H, Sparrow D, Young JB, Landsberg L, Weiss ST. Relation between blood lead and urinary biogenic amines in community-exposed men. Am J Epidemiol 1993;138:815-825.

23. Hu H, Kotha S. Ethics and epidemiology: International Guidelines. Polit Life Sci 1993;February:29-30.

24. Goldman RH, White R, Kales SN, Hu H. Lead poisoning from mobilization of bone stores during thyrotoxicosis. Am J Industr Med 1994;25:417-424.

25. Bellinger D, Hu H, Titlebaum L, Needleman HL. Attentional correlates of dentin and bone lead levels in adolescents. Arch Environ Health 1994;49:98-105.

26. Watanabe H, Hu H, Rotnitzky A. Correlates of bone and blood lead levels in carpenters. Am J Industr Med 1994;26:255-264.

27. Hu, H. Decision-making in human health impact assessments: a clinician's perspective. Environ Impact Assess Rev 1994;14:439-450.

28. Hu H, Watanabe H, Payton M, Korrick S, Rotnitzky A. The relationship between bone lead and hemoglobin. JAMA 1994;272:1512-1517.

29. Payton M, Hu H, Sparrow D, Weiss ST. Low-level lead exposure and renal function in the Normative Aging Study. Am J Epidemiol 1994;140:821-829.

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31. Guo H-R, Chiang H-S, Hu H, Lipsitz SR, Monson RR. Arsenic in drinking water and urinary cancers: a preliminary report. Environ Geochem Health 1994;s16:119-128.

32. Hoppin JA, Aro ACA, Williams PL, Hu H, Ryan PB. Validation of K-xrf bone lead measurements in young adults. Environ Health Perspect 1995;103:78-83.

33. Smith CM, Wang X, Hu H, Kelsey KT. A polymorphism in the δ-Aminolevulinic acid dehydratase gene may modify the pharmacokinetics and toxicity of lead. Environ Health Perspect 1995;103:248-253.

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37. Hu H, Kotha S, Brennan T. The role of nutrition in mitigating environmental insults: policy and ethical issues. Environ Health Perspect 1995;103(Suppl 6):185-190.

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levels of lead. Medicine Lavoro 1995;86:229-235.

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40. Potula V, Hu H. Occupational and lifestyle determinants of blood lead levels among men in Madras, India. Int J Occup Environ Health 1996;2:1-4.

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46. Hu H, Payton M, Korrick S, Aro A, Sparrow D, Weiss ST, Rotnitzky A. Determinants of bone and blood lead levels among community-exposed middle-aged to elderly men: the Normative Aging Study. Am J Epidemiol 1996;144:749-759.

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53. González-Cossío T, Peterson KE, Sanín L, Fishbein SE, Palazuelos E, Aro A, Hernández-Avila M, Hu H. Decrease in birth weight in relation to maternal bone lead burden. Pediatrics 1997;100:856-862.

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Salud Pública Mex [Public Health in Mexico] 40:119-126, 1998.

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Abstracts of Work (Upon request)

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UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF CALIFORNIA
AT SAN FRANCISCO

FOOD & WATER WATCH, et al., Plaintiffs, vs. U.S. ENVIRONMENTAL PROTECTION AGENCY, et al. Defendants.	Civ. No. 17-CV-02162-EMC **DECLARATION OF BRUCE LANPHEAR, MD, MPH**

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I, Bruce Lanphear, MD, MPH, declare that:

1. I am a Clinical Investigator at the BC Children's Hospital Research Institute, BC Children's Hospital, and Professor in the Faculty of Health Sciences at Simon Fraser University in Vancouver, British Columbia.

2. I am also the Co-Principal Investigator of an ongoing study to examine the impact of early-life fluoride exposures on intellectual abilities in a cohort of mothers and offspring from Canada known as the MIREC Study. Our study of fluoride and IQ in the MIREC cohort was funded by a grant from the U.S. National Institutes of Health (NIH).

I. SUMMARY OF QUALIFICATIONS

3. A complete summary of my qualifications and publications can be found in my Curriculum Vitae, which has been marked as Plaintiffs' Exhibit 6 and attached herein.

4. I have studied the impact of toxic chemicals, including lead and pesticides, on children's brain development for over 20 years. My research has been almost exclusively funded by federal agencies, including the Environmental Protection Agency (EPA), Centers for Disease Control and Prevention, the Department of Housing and Urban Development, Health Canada, National Institute of Allergy and Infectious Diseases, National Institute for Child Health and Human Development, National Institute of Environmental Health Sciences, National Institute of Neurologic Diseases, and the National Heart, Lung and Blood Institute.

5. My research has been published in leading medical and scientific journals, including *Journal of the American Medical Association*, *New England Journal of Medicine*, and *Pediatrics*, and has been extensively relied upon by environmental and public health agencies, including the EPA. My pooled analysis of blood lead and IQ (Lanphear 2005) was cited by the EPA as the critical study upon which the Agency based the current national air standard for lead.

6. I have served on the editorial boards of seven academic journals, including *Public Health Reports* (the official journal of the U.S. Surgeon General), *PLoS Medicine* (a peer-reviewed medical journal published by the Public Library of Science), and *Environmental Health Perspectives* (a journal funded by the National Institutes of Environmental Health Sciences).

7. I have served on numerous scientific committees on environmental health issues impacting children, including multiple scientific advisory boards for the EPA and the Executive Council on Environmental Health for the American Academy of Pediatrics. My work with the EPA has included invited expert advisory roles on EPA's (i) Science and Research Work Group of the Children's Health Protection Advisory Committee (1998-2001); (ii) Workshop on Assessing Environmental Exposures to Children (2000-2002); (iii) Clean Air Scientific Advisory Committee (2006-2008); (iv) Science Advisory Board for Evaluating Dust Lead Standards (2010-2012); and (v) Science Advisory Board for Evaluating Hazards of Partial Water Line Replacement (2011-2012).

8. My research has earned various awards and honors, including the Research Integrity Award from the International Society for Environmental Epidemiology in 2012, the Public Policy and Advocacy Award from the Academic Pediatric Association in 2013, and the Research Award from the Academic Pediatric Association in 2015.

9. I have been involved with the MIREC Study for over 10 years. I was a Co-Principal Investigator for the neurobehavioral assessments conducted when the children were 3 to 4 years old and I oversaw the neurodevelopmental assessments in Vancouver. I have been a coauthor of twelve publications from the MIREC Study, including three publications on fluoride described below.

10. In light of the consistent association between elevated fluoride and IQ reported in cross-sectional studies (Choi, et al. 2012), we received a grant from the NIH to study the association between prenatal and early-life measures of fluoride and IQ in children in the MIREC cohort. To date, we have

published three peer-reviewed studies, including the most extensive assessment of fluoride exposure during pregnancy ever conducted and prospective studies on early life fluoride exposure on IQ. These studies have been published in *Environmental Health Perspectives*, *JAMA Pediatrics*, and *Environment International* (Till 2018, Green 2019, Till 2020). Our study on prenatal fluoride and IQ was the highest scoring study in *JAMA Pediatrics* in 2019 (Christakis 2020).

11. I agreed to participate as a non-retained expert in this case because I believe it is a public duty to present the results of studies that suggest substantial risk to public health. I have asked *not* to be compensated for this work.

II. SUMMARY OF OPINIONS

12. Our study of prenatal fluoride and IQ in the MIREC cohort (Green 2019) further enhances the quality of data related to the neurotoxicity of fluoride. As with the ELEMENT cohort, we employed a prospective cohort design, had extensive control for potential confounders, and had multiple measures of fluoride exposure during pregnancy, including three types of urinary fluoride measurements for each trimester of pregnancy.

13. The maternal urinary fluoride levels in the MIREC cohort were significantly associated with lower intellectual abilities in 3-4-year-old children. These associations remain large and significant when controlling for relevant covariates.

14. Converging results from the MIREC and ELEMENT cohorts indicate that exposure to "optimal" levels of fluoride during fetal development is associated with diminished intelligence in childhood.

15. In the MIREC cohort, exposure to fluoridated water in infancy, particularly among formula-fed infants, was also associated with diminished intelligence (Till 2020). This association remains significant after controlling for fetal fluoride exposure and other relevant covariates, suggesting that

susceptibility to fluoride's adverse neurological effects may extend into infancy.

III. BASIS FOR OPINIONS

A. The Growing Problem with Brain-Based Disorders

16. As I have discussed elsewhere, the causes of death and disability in children have shifted over the past century (Lanphear 2015). Concerted public health efforts to control tuberculosis, cholera, typhoid, and other infectious agents in the early twentieth century led to a dramatic reduction in child mortality, followed by a rise in life expectancy. By the end of the twentieth century, the 'new morbidities of childhood' had emerged: attention deficit hyperactivity disorder (ADHD), autism, asthma, obesity, and preterm birth. Learning disabilities and neurodevelopmental disorders are now two of the most prevalent morbidities in children. About 7.6% of US children are estimated to have a learning disability, and 13% are estimated to have a neurodevelopmental disorder, including anxiety, autism, conduct disorder, depression, or ADHD (Lanphear 2015). These data indicate that we are in the midst of an epidemic of brain-based disorders.

17. Neurotoxicants can have a lifelong impact on brain function. Children who have higher blood lead concentrations, for example, may never meet the same peak cognitive ability in adulthood as that in less exposed children. At the other end of the age spectrum, cognitive decline is accelerated in adults who have higher bone lead concentrations and some evidence has shown that lead exposure is a risk factor for the development of late-onset Alzheimer's disease. Few birth cohorts have been studied into adulthood; however, it would be surprising if the effects of other neurotoxicants observed in school-aged children do not persist into adulthood (Lanphear 2015). The cumulative impact of exposures to various toxins that only modestly impact intellectual abilities can be substantial (Lanphear 2015).

18. The high reported prevalence of learning disabilities and neurodevelopmental disorders has fueled research to better understand the role of environmental chemicals, including the use of prospective

cohort studies that collect individualized biomarkers of exposure to environmental toxins. Biologic markers, or biomarkers, of exposure, which can enhance our ability to quantify an individual's internal dose of a contaminant, are revolutionizing the study of environmental toxins in the same way genetic tests are revolutionizing the study of heritability (Lanphear 2015).

B. The MIREC Cohort Is a Comprehensively Characterized Birth Cohort

19. The MIREC[1] cohort in Canada was developed to obtain biomonitoring data for pregnant women and their infants to examine potential adverse health effects of early-life exposure to environmental chemicals.

20. The MIREC cohort is a geographically diverse and comprehensively characterized birth cohort. Women were recruited during the first trimester of pregnancy from 10 cities across Canada, including cities that add fluoride to water for caries prevention purposes (e.g., Toronto), and cities that do not (e.g., Vancouver). Women were followed through delivery and their offspring have undergone periodic neurodevelopmental tests, including IQ testing.

21. We administered questionnaires during pregnancy and early childhood to collect information on demographics, occupation, lifestyle, medical history, environmental exposures and diet. Dietary questions included whether the mother drank tap water during pregnancy, how many glasses of water and other beverages she consumed, and duration of breastfeeding.

22. Information on the pregnancy and the infant was abstracted from medical charts. Maternal urine was collected at multiple points throughout pregnancy, as was blood, urine, hair, breast milk, cord blood and infant meconium. These samples have been archived in a biobank.

23. Study staff from each participating study site completed a 3-day training session that was

[1] MIREC stands for Maternal-Infant Research on Environmental Chemicals. It is an interdisciplinary collaboration between Health Canada scientists and clinical and academic researchers, and was funded by Health Canada, the Ontario Ministry of the Environment, and a grant from the Canadian Institutes of Health Research.

led by a PhD-level psychologist and focused on specialized training of the neurodevelopmental tests. The training emphasized the importance of providing an ideal and standardized environment in the home by ensuring that the test area was well-lit, quiet, and free from distractions and interruptions.

C. Urinary Fluoride Study (Till 2018)

24. In 2018, we published the most comprehensive study of urinary fluoride during pregnancy that has ever been conducted (Till 2018). Our study included 1,566 pregnant women from the MIREC cohort who had urine samples for each trimester of pregnancy. It was the first study of its kind in water-fluoridated areas of North America. A similar study has recently been published of a smaller pregnancy cohort in California (Uyghurturk 2020), but our study remains the largest and most thorough.

1. Methodological Strengths

25. Our study of urinary fluoride was conducted in accordance with sound and objective science practices. Important strengths of the study include: (1) a large study size, with over 1,500 women and over 5,000 urine samples; (2) collection of urine samples from each trimester for each mother; (3) empirical data on the actual measured water fluoride levels for each mother's water treatment plant boundary (WTP) during the course of the pregnancy; (4) control for other factors that have potential to influence urinary fluoride excretion, including tea consumption, alcohol use, pre-pregnancy BMI, maternal age, maternal education, annual household income, and race; (5) control for fluctuations that can occur in urine fluoride during the day by adjusting for dilution using two methods (specific gravity and creatinine) and controlling for time of void and time since last void; and (6) measurement of fluoride in urine using the same scientist (Dr. Martinez-Mier), method (microdiffusion), and laboratory (University of Indiana) as the ELEMENT cohort, thereby enhancing the comparability of the data.

26. Dr. Martinez-Mier's lab at the University of Indiana is considered a gold-standard lab for the testing of fluoride in urine and blood. EPA appears to recognize Dr. Martinez-Mier's expertise as she

was approached by EPA to serve as an expert in this case.

2. Fluoridated Water Has a Large and Significant Effect on Urinary Fluoride

27. In our study, fluoride in water had the strongest correlation with urine fluoride of all the factors that we measured, thus confirming that fluoridated water remains a major source of fluoride intake (Till, 2018).

28. The average urinary fluoride level among pregnant women in fluoridated areas is almost two times higher than the average levels in nonfluoridated areas (Till 2018).

29. The average creatinine-adjusted[2] maternal urinary fluoride level in the fluoridated areas is 0.87 mg/L, versus 0.46 mg/L in the non-fluoridated areas.[3]

30. Our data suggests that, for every 0.5 mg/L increase in water fluoride level, urinary fluoride levels will increase by 74-82%.

31. Our findings are consistent with prior studies showing that, among adults, fluoride levels in urine are closely correlated with the concentration of fluoride in water.

32. As part of our study, we attached a table showing the full distribution of urinary fluoride levels, including the 75th and 95th percentile exposures for each trimester (Till et al. 2018, Table S4). At the second trimester, 95th percentile values in the fluoridated areas were 2 mg/L (adjusted for creatinine), and 1.63 mg/L (adjusted for specific gravity).

[2] Creatinine-adjustment of spot urine samples adjusts for dilution and has been found to have good agreement with 24-hour fluoride values (WHO 2014, Zohouri 2006). We used the same method for creatinine adjustment as Bashash (2017). We also adjusted for dilution by correcting for specific gravity. Our adjustments for creatinine and specific gravity produced results that were highly correlated ($r = 0.91$) and interchangeable in our analyses of the factors that increase urinary fluoride.

[3] The average specific gravity-adjusted concentration in the fluoridated areas was 0.71 mg/L (SD 0.38 mg/L), with a range of 0.10 to 3.12 mg/L.

3. Pregnant Women in Water-Fluoridated Areas of the MIREC Cohort Have Similar Urinary Fluoride Levels as the ELEMENT Cohort

33. One of the key findings from our 2018 study is that pregnant women who live in water-fluoridated areas of Canada have urinary fluoride levels that are essentially the same as the urinary fluoride levels documented in the ELEMENT cohort.

34. The similarity in maternal urinary fluoride levels between the MIREC and ELEMENT cohorts can be appreciated when comparing the respective mean values (0.87 vs. 0.91 mg/L), standard deviations (0.50 vs. 0.40 mg/L), and ranges (0.14-3.80 vs. 0.02-3.67 mg/L) of the study participants in the water fluoridated areas of the MIREC cohort vs. the ELEMENT cohort.

35. The similarity in maternal urinary fluoride levels between the MIREC and ELEMENT cohorts is of scientific and public health relevance given the findings of Bashash (2017) showing an inverse association between maternal urinary fluoride and offspring IQ.

D. Prenatal Fluoride/IQ Study (Green 2019)

36. In 2019, we published our findings on the relationship between prenatal fluoride exposure and IQ in the MIREC cohort. The study, which was published in *JAMA Pediatrics*, provides reliable and unbiased results and was conducted in accordance with sound and objective science practices.

1. Methodological Strengths

37. ***Prospective Birth Cohort Study Design***: A key strength with our study is that we used a prospective cohort study design, also known as a longitudinal study. Prospective studies are the best available method for investigating the impact of environmental chemicals and, as noted earlier, have helped to revolutionize our understanding of how chemicals impact childhood health.

38. ***Extensive Control for Potential Confounders***: The MIREC cohort is one of the most comprehensively characterized birth cohorts, with abundant individualized data on factors that may influence neurodevelopment. We took full advantage of this data. We excluded study participants if there

was a known fetal abnormality, if they had any medical complications (i.e., cancer, renal disease, cardiovascular disease), or if there was known maternal alcohol or drug abuse during pregnancy. For analyses using water fluoride, we excluded women if they did not drink tap water during their pregnancy. For those not excluded, we controlled for the following factors: maternal education; maternal age; quality of the child's home environment (HOME); child sex; mother's race; city of residence; secondhand smoke; maternal blood or urinary concentrations of other neurotoxicants, such as lead, arsenic, mercury, manganese, and PFOA. Additionally, we controlled for the diurnal fluctuations that may occur in urinary fluoride levels by including time of day that the urine sample was collected and time since last void.

39. ***Individualized Measures of Fluoride Exposure***: Another important strength of our study is that we had multiple individualized measures of prenatal fluoride exposure, including: (1) urinary fluoride samples averaged across each trimester of pregnancy and corrected for urinary dilution; (2) measured water fluoride levels from within each participant's water treatment plant boundary during the course of their pregnancy;[4] and (3) questionnaire data about how much water each woman drank from tap water and water-based beverages.

40. ***Large, Multi-Center Cohort***: Our study included 512 mother-offspring pairs which is a robust sample size for statistical analyses. Further, the mother-offspring pairs came from 6 cities across Canada, some of which fluoridate their water (average F = 0.59 mg/L), and some of which do not (average F = 0.13 mg/L).[5] Our study thus permitted us to examine the impact of fluoride exposures on IQ in communities with water fluoridation, thus addressing what some have perceived to be a limitation of prior

[4] Water treatment plants measured fluoride levels daily if fluoride was added to municipal drinking water and weekly or monthly if fluoride was not added to water. We matched participants' postal codes with water treatment plant zones, allowing an estimation of water fluoride concentration for each woman by averaging water fluoride concentrations (in milligrams per liter) during the duration of pregnancy.

[5] Pregnant women in the fluoridated areas tended to have higher incomes and more education, which may help explain the lack of difference in average *unadjusted* IQs between fluoridated and non-fluoridated areas (Green 2019, Table 1).

studies of fluoride neurotoxicity.

41. ***Reliable and Objective IQ Test***: We assessed children's intellectual abilities with the Wechsler Preschool and Primary Scale of Intelligence, Third Edition (WPPSI-III). This is a validated IQ test with excellent internal reliability (r = 0.96), and good test-retest reliability (r = 0.86). We used Full Scale IQ (FSIQ), which is a measure of global intellectual functioning, as the primary outcome. The FSIQ score is comprised of two composite scores: Verbal IQ (VIQ)—representing verbal reasoning and comprehension—and Performance IQ (PIQ)—representing nonverbal reasoning, spatial processing, and visual-motor skills.

42. ***Blinded Assessments***: As with the ELEMENT cohort, our study was "blinded," meaning the examiners were not aware of the mother's fluoride exposure status at the time of the examination. This eliminates the potential for examiner bias.

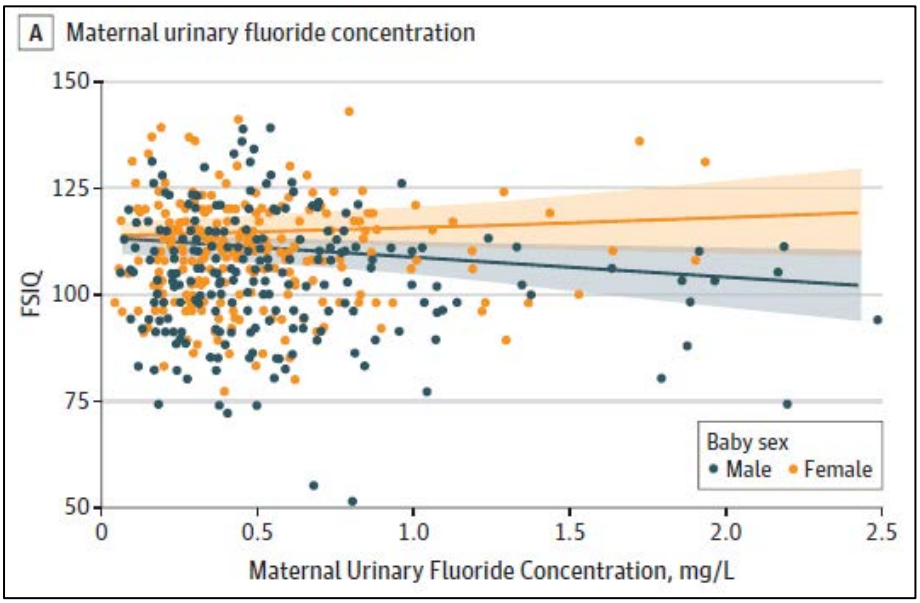
43. ***Statistical Analyses that Did Not Assume Linearity***: We conducted sound, objective, and rigorous statistical analyses that: (i) controlled for the impact of the large number of measured covariates; (ii) examined the data for collinearity, outliers, and influential points; and (iii) scrutinized the shape of the relationship between fluoride and IQ. With respect to linearity and possible threshold effects, we conducted sensitivity analyses that used quadratic and natural log effect models as well as ran spline analyses that examined the relationship below 0.5 mg/L, 0.8 mg/L, and 1.0 mg/L in urine (and below 0.4 mg/day and 0.8 mg/day in fluoride intake). We did *not* assume that statistical associations between fluoride and IQ were linear and without threshold.

44. Short of intentionally dosing pregnant mothers with fluoride, we maximized the power of environmental epidemiology to investigate whether prenatal fluoride exposure is associated with neurocognitive deficits in a prospective, observational cohort study.

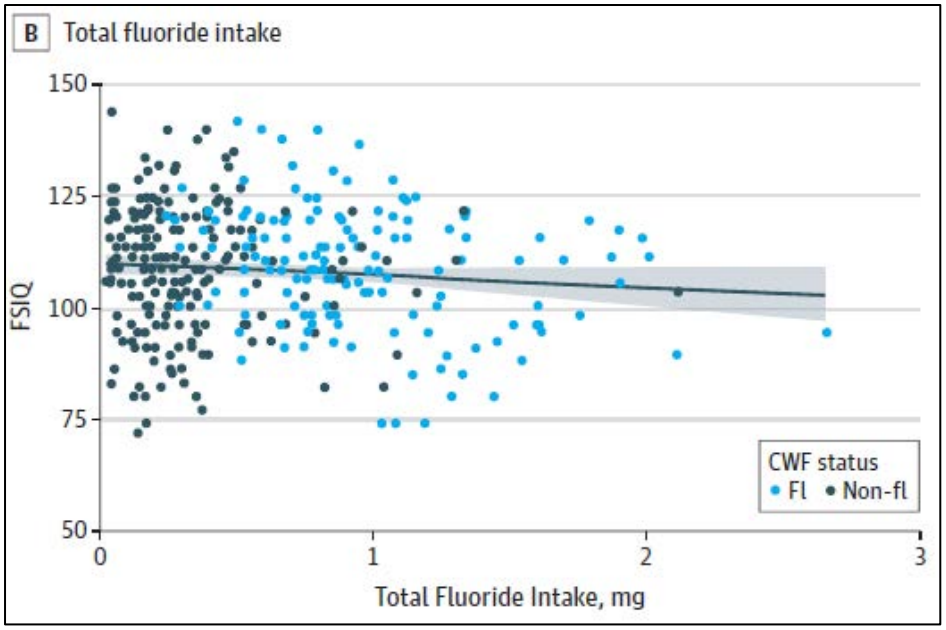
2. Prenatal Fluoride Exposure Is Associated with Large and Significant Reductions in IQ in the MIREC Cohort

45. All three measures of prenatal fluoride exposure—(i) maternal urinary fluoride, (ii) maternal fluoride intake from beverages, and (iii) water fluoride concentration during pregnancy—were associated with large, statistically significant decreases in IQ among the 3 to 4-year old children in the MIREC cohort.

46. After controlling for covariates, a 1-mg/L increase in maternal urinary fluoride[6] was associated with a **4.49 lower IQ** score (in boys); a 1-mg higher daily intake of fluoride from beverages was associated with a **3.66 lower IQ** score (in boys and girls); and a 1 mg/L higher water fluoride concentration was associated with a **5.29 lower IQ** score (in boys and girls). These fluoride-associated reductions in IQ that we found showed a linear, dose-response relationship with no apparent indication of a threshold (see figures below).



[6] We used specific gravity (SG) as the primary adjustment method for this study. The average SG-adjusted concentration among women from the fluoridated areas was 0.69 mg/L (SD = 0.42), which is consistent with the concentration in fluoridated areas from the larger cohort (0.71 mg/L, SD = 0.38) (Till 2018). Sensitivity analyses using the creatinine-adjusted urinary fluoride values did not change the results between fluoride and IQ (Green 2019, eTable 2).



47. The effect sizes that we found are large and rival the impact of a population blood lead concentration of 5 µg/dL.[7] Fourteen percent of the women had urinary fluoride concentrations exceeding 1.0 mg/L, and thus the impact for some children may exceed the ranges identified above.

48. Although maternal urinary fluoride was associated with significant reduction in full-scale IQ in boys, it was not associated with diminished full-scale IQ in girls. As is often the case, the reason for this discrepancy is not currently known. It is known, however, that boys have a higher prevalence of neurodevelopmental disorders such as ADHD, learning disabilities, and intellectual disabilities than girls. It is also known that boys and girls may respond differently to some neurotoxicants. In our studies of the MIREC cohort, for example, we found that low levels of blood lead correlate with a loss of IQ in boys, but not girls (Desrochers-Couture 2018).

49. The possibility that boys are more sensitive to prenatal fluoride exposure than girls is

[7] My pooled analysis of blood lead and IQ found that an increase in childhood blood lead from <1 to 10 µg/dL was associated with a 6.9 IQ point decrement (Lanphear 2015, p. 814). General population exposures to lead today are now on the low-to-mid range of this spectrum, with relatively few children having blood lead levels as high as 10 µg/dL.

supported by at least one animal study, in which males had greater deficits from prenatal exposure and females had greater deficits from postnatal exposure (Mullenix et al 1995). While we did not find sex-specific differences with our other two exposure measures (water F concentration and water F intake), these other measures may better correlate with chronic or postnatal exposure and thereby reflect distinct risks**.**

3. Convergent Findings of ELEMENT and MIREC Cohorts.

50. The significant associations we observed between prenatal fluoride and IQ in the MIREC cohort are consistent with the findings from the ELEMENT cohort (Bashash, 2017).

51. In the ELEMENT study, an increase of 1 mg/L in creatinine-adjusted maternal urine was associated with a loss of 6.3 IQ points among 4-year olds, as measured by General Cognitive Index (GCI) of the McCarthy Scales of Children's Abilities. In our analysis, an increase of 1 mg/L in creatinine-adjusted maternal urine was associated with a loss of 4.96 IQ points among 3- to 4-year old boys, as measured by the WPPSI-III test (Green 2019, eTable 2). These effect sizes are generally consistent with each other.

52. The consistency of results in both population cohorts adds further confidence that the association is real, particularly when viewed in the context of other studies that have reported inverse associations between fluoride and IQ in many different locations in other countries, as well as general knowledge about the vulnerability of the developing brain.

E. Infant Fluoride/IQ Study (Till 2020)

53. We recently completed and published a study that examined whether fluoride exposures during infancy have an influence on IQ at 3-4 years (Till 2020).

54. Concerns have been raised about the use of fluoridated water in baby formula due to the high intake of water by bodyweight during infancy. These high intakes have been associated with

significant increases in dental fluorosis, including in the permanent teeth.

55. In our study, we obtained information about fluoride intake of infants through questionnaires that the mothers completed when the children were 30 to 48 months of age.[8] The questionnaire included the question, "How old was your baby when you ceased breastfeeding exclusively?" Women who breastfed exclusively for six months or longer were included in the breastfeeding (BF) group; those who reported introducing formula within the first six months (never breastfed or partial breastfeeding) were included in the formula-feeding (FF) group.

56. As a separate measure of infant fluoride exposure, we estimated fluoride intake by obtaining the measured water fluoride levels within the water treatment plant boundary during infancy. We took the average of these levels, multiplied by the amount of time that that the infant was not exclusively breast-fed during the first year,[9] and divided it by the estimated average water intake among Canadian formula-fed infants (0.8 L). We excluded any mother-offspring pair if the mother reported not drinking tap water.

1. Methodological Strengths

57. Our study of infants shares many of the same methodological strengths as our prenatal study, including: (i) prospective cohort design; (2) extensive control for potential confounders (discussed below); (3) blinded assessment; (4) relatively large cohort (398 mother-offspring pairs) from both fluoridated and non-fluoridated areas; (5) the same validated and standardized IQ test that we used for the prenatal study (i.e., Wechsler Primary and Preschool Scale of Intelligence-III); and (6) rigorous statistical

[8] The answers to these questions correlated well with the contemporaneous infant feeding practices that were reported among 11% of the cohort. Among women with breastfeeding questionnaire data and infant feeding observation data, the median difference for when breast-feeding ceased was 0 months, with two-thirds being within 1.5 months of each other.

[9] The mean duration of exclusive breastfeeding was 4.98 months; 13.6% of women reported never breastfeeding, 8% reported discontinuing breastfeeding after the first three months, and 50.2% reported continuing to breastfeed at six months or longer. Average water fluoride concentration did not significantly differ between the BF (mean=0.32 mg/L) and FF groups (mean=0.29 mg/L; p=.18).

analyses that tested for sex-specific effects and scrutinized the impact of outliers and influential points.

58. We adjusted for potential confounding by selecting covariates *a priori* that have been associated with fluoride, breastfeeding, and children's intellectual abilities. Final covariates[10] included child's sex and age at testing, maternal education, maternal race, second-hand smoke in the home, and quality of the child's home environment (measured at time of testing using the Home Observation for Measurement of the Environment (HOME). We also controlled for fetal fluoride exposure, using the previously measured maternal urinary fluoride concentrations averaged across each trimester of pregnancy.

2. Fluoride Exposure During Infancy Is Associated with Significant Reductions in Non-Verbal IQ in the MIREC Cohort

59. We found that fluoride exposure during infancy is associated with significant reductions in non-verbal IQ in the MIREC cohort.

60. For each 0.5 mg/L increase in water fluoride concentration, we found a decrease of 4.4 Full-Scale IQ (FSIQ) points among preschool children who were formula-fed in the first six months of life; 0.5 mg/L is the approximate difference in mean water fluoride level between fluoridated (0.59 mg/L) and non-fluoridated (0.13 mg/L) regions. In contrast, we did not find a significant association between water fluoride concentration and FSIQ among children who were exclusively breastfed in the first 6 months.

61. The association between water fluoride concentration and FSIQ must be interpreted with caution, however, because the association became nonsignificant when two outliers were removed.

62. We observed an even stronger association between water fluoride and PIQ (non-verbal intelligence). A 0.5 mg/L increase in water fluoride level predicted a decrement in non-verbal IQ in both

[10] For each analysis, a covariate was retained in the final model if its p-value was <0.20 or its inclusion changed the regression coefficient of water fluoride concentration or fluoride intake from formula by more than 10%.

the formula-fed (**9.3-points**) and the breastfed groups (**6.2-points**). Adjusting for fetal exposure or removing two extreme scores did not appreciably alter these results.

63. We observed converging results using fluoride intake from formula feeding, which is a continuous, time-weighted exposure estimate. For each 0.5 mg/day of fluoride intake, we found an **8.8-point** decrement in non-verbal IQ; adjusting for fetal exposure attenuated the association only slightly (**7.6-point** decrement).

64. The time-weighted fluoride intake estimate may reflect a more refined measure of exposure in infancy because it captures differences in both water fluoride level and the proportion of time each child was given formula over the first year of life. Yet, our binary classification of whether a child was exclusively breastfed for the first 6 months may distinguish infants who are exposed to higher amounts of fluoride during the early infancy period when the brain undergoes significant development because breast milk contains minutes amounts of fluoride.

65. Taken together, these findings suggest that using "optimally" fluoridated water (0.7 mg/L) to reconstitute infant formula may diminish the development of intellectual abilities in young children, particularly non-verbal abilities. The findings also suggest that both prenatal and early childhood fluoride exposure affect the development of non-verbal intelligence to a greater extent than verbal intelligence. Prior studies examining prenatal exposure to fluoride and IQ showed a similar pattern.

F. The Limitations of Our Studies Do Not Provide a Likely Explanation for the Results

66. As with all epidemiological studies, our fluoride studies have limitations. These limitations, however, are unlikely to explain the large and significant associations that we have found between early-life exposures and IQ.

67. Most of the limitations in our studies involve fluoride measurement. These limitations

include: (1) use of spot urine samples instead of 24-hour samples;[11] (2) lack of water fluoride measurements from the participant's home; (3) reliance on questionnaire data as to water consumption and breast-feeding; (4) lack of information on the fluoride content of the infant formula concentrate and other sources of fluoride exposure; and (5) use of non-validated methods[12] for estimating total beverage-based intake of fluoride by mothers and water fluoride intake by infants.

68. The limitations in our exposure estimates are non-differential, meaning they apply equally to study participants with low fluoride exposure and high fluoride exposure. Non-differential errors in exposure measurement will generally bias the results towards the null (i.e., attenuate, rather than inflate, an association between exposure and outcome). Because of this, the limitations in our exposure estimates do not provide a likely explanation for the significant IQ decrements we observed with fluoride exposures. If anything, these limitations likely attenuated the relationship.

69. Another limitation of our studies is that the MIREC cohort tends to be more affluent, more educated, and less ethnically diverse than the general population. Our results may thus not be representative of how fluoride may affect IQ in more disadvantaged populations. On the other hand. affluent populations tend to have less confounders (e.g., less exposure to other stressors and toxicants that can negatively affect neurodevelopment) (Lanphear 2015). We thus worry less about the role of confounders in the MIREC cohort than we would in other cohorts.

70. Finally, despite our comprehensive array of covariates included, our studies could not address the possibility of unmeasured residual confounding. This is a limitation in all observational

[11] A 24-hour sample of urine is considered the optimal dosimeter for measuring chronic fluoride exposure (WHO 2014). While we did not have 24-hour samples available to test, we partially controlled for this by adjusting samples by creatinine. Creatine-adjusted urine fluoride measurements have been found to have a strong correlation with 24-hour samples (Villa 2010; Zohouri 2006).

[12] These methods were not validated in the sense that they have not yet been replicated by other authors in other studies. Our method for assessing fluoride intake from beverages did show internal validity, however, by predicting maternal urinary fluoride levels. This can be seen in the highly significant correlations that we found ($p < 0.0001$) between maternal urinary fluoride and number of glasses of water consumed per day and black tea consumption (see Till 2018).

studies, and thus inherent to the field. One of the potential confounders for which we lacked data was maternal IQ. We did, however, control for maternal education which is highly correlated with maternal IQ. Moreover, a greater proportion of women living in fluoridated communities (76%) had a university-level degree compared with women living in nonfluoridated communities (66%), and thus it seems unlikely that controlling for maternal IQ would affect our results, particularly since there is no reason to believe that maternal IQ would be correlated with maternal urinary fluoride.

71. I understand that the EPA has suggested that the location of our study in Canada somehow reduces the relevance of our findings to populations in the US. I disagree. From a biologic standpoint, there is no credible basis to believe that people in the U.S. will respond differently to fluoride than people in Canada. Nor am I aware of any credible reason to conclude, let alone suspect, that people in water-fluoridated areas of the U.S. are exposed to materially less fluoride than people in water-fluoridated cities of Canada.

IV. CONCLUSION

72. The collective evidence from prospective cohort studies supports the conclusion that fluoride exposure during early brain development diminishes the intellectual abilities in young children, including at the purportedly "optimal" levels of exposure for caries prevention.

I declare under penalty of perjury, under the laws of the United States, that the foregoing is true and correct to the best of my knowledge and belief.

Executed on May 20, 2020, in Vancouver, British Columbia, Canada.

BRUCE LANPHEAR, MD, MPH

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1984-1986	Paramedic, Jackson County Jail, Kansas City, Missouri
1988-1989	Physician, International Travel Clinic, University of Cincinnati, Cincinnati, Ohio
1988-1989	Staff Physician, Sexually Transmitted Disease Clinic, Cincinnati Public Health Department, Cincinnati, Ohio
1989-1992	Assistant Professor of Environmental Health, Associate Director, Medical Center Health Services, University of Cincinnati
1992-1997	Senior Instructor, Departments of Pediatrics and of Community & Preventive Medicine, University of Rochester School of Medicine.
1992-1994	National Research Scholar Award in General Pediatric Research, University of Rochester School of Medicine and Dentistry.
1992-1997	Assistant Professor, Department of Pediatrics and of Community & Preventive Medicine, University of Rochester School of Medicine.
1997-2002	Associate Professor, Department of Pediatrics, Children's Hospital Medical Center and the University of Cincinnati, Cincinnati, Ohio.
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1997-2006	Associate Professor (Adjunct), Departments of Pediatrics and of Environmental Medicine, University of Rochester School of Medicine & Dentistry, Rochester, NY.
1998-2003	Associate Director for Research, Division of General & Community Pediatrics, Children's Hospital Medical Center.
2001-2002	Associate Professor (tenured), Department of Pediatrics, University of Cincinnati, Cincinnati, Ohio.
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2008-	Clinician Scientist, Child & Family Research Institute, BC Children's Hospital, University of British Columbia

Education

1980-1985	Bachelor of Arts in Biology
1980-1986	University of Missouri at Kansas City, Medical Degree (1986)
1986-1987	Internship, University of Arkansas for Medical Sciences, Little Rock, Arkansas
1987-1988	Tulane School of Public Health & Tropical Medicine Masters in Public Health & Tropical Medicine
1987-1989	General Preventive Medicine and Public Health Residency Tulane School of Public Health & Tropical Medicine
1992-1995	Postdoctoral Fellowship in General Academic Pediatric Research University of Rochester School of Medicine, Rochester, NY

Awards and Honors

2011	Sterling Prize in Controversy, Simon Fraser University
2012	Research Integrity Award, International Society for Environmental Epidemiology
2013	Public Policy and Advocacy Award, Academic Pediatric Association
2015	Research Award, Academic Pediatric Association
2015	Confederation of Union Faculty Associations of British Columbia (CUFA-BC) Academic of the Year Award
2018	Lumina Award from the Women for Healthy Environmental Health, Pittsburgh, PA

Teaching Experience

1992-1997	Course Instructor, "Public Health & the Environment", Department of Community & Preventive Medicine, The University of Rochester School of Medicine and Dentistry. A required course for MPH students taught annually.
1997-2008	Founding Director, NIH-funded, General Academic and Community Pediatric Research Fellowship Training Program, Cincinnati Children's Hospital Medical Center. This interdisciplinary, research training program, which included pediatricians, psychologists and epidemiologists, was the first training program in Children's Environmental Health.
1998-2008	Course Co-Instructor, "Children's Health & the Environment", Department of Environmental Health, The University of Cincinnati School of Medicine. A course taught every other year to MPH, PhD and postdoctoral trainees in medical subspecialties.
2008-	Course Instructor, "Children's Health and the Environment". A 2-week intensive course taught annually to 4th year undergraduate students at Simon Fraser University.
2011-	Course Instructor, "Plagues, Pollutants and Poverty: The Origins and Evolution of Public Health". An undergraduate course at Simon Fraser University.

Committee and Community Involvement

1993-1997	Lead Poisoning Prevention Task Force, Monroe County Health Department.
1994-1997	Investigational Review Board, Rochester General Hospital
1995-	Scientific Consultant, National Center for Healthy Housing, Columbia, Maryland.
1996-1997	Member, New York State Task Force on Environmental Neurotoxins, University of Rochester School of Medicine
1996-2001	Member, National Institute for Environmental Health Sciences Grant Review Committee for Community-Based Interventions (FG)
1996-1998	Chairman, U.S. Department of Housing and Urban Development Committee on Lead-Contaminated House Dust
1998	Member, Review Group for National Research Service Awards, Health Resources and Services Administration
1998-2000	Member, Cincinnati Board of Health, Cincinnati, Ohio.
1998-2001	Member, Science and Research Work Group, Office of Children's Health Protection Advisory Committee, U.S. EPA
1998-2000	Member, Cincinnati Lead Poisoning Prevention Advisory Task Force, Cincinnati, Ohio.
1999	Member, K23 Grant Review Committee, National Institute for Environmental Health Sciences, August 1999
1999	Member, Expert Panel on Soil Pica Behavior, Agency for Toxic Substance Disease Registry, June 7th-8th, Atlanta, Georgia
2000	Member, Panel on Health Disparities: Linking Biological and Behavioral Mechanisms with Social and Physical Environments, National Institute for Environmental Health Sciences, July 14-15th
2000-2002	Member, Workshop on Assessing Environmental Exposures to Children, U.S. Environmental Protection Agency, July 26-27th
2000-2004	Member, Children's Environmental Health Project, AAP's Child Health Research Center, Rochester, NY.
2001	Senate Testimony, "Ensuring that Children with Dangerous Levels of Lead in their Blood Receive Care as Early as Possible". Subcommittee on Housing and Transportation of the Committee on Banking, Housing and Urban Affairs, 107th U.S. Congress, November 13th, 2001.
2001	Reviewer, National Research Council, National Academy of Science Update of the 1999 Arsenic in Drinking Water Report
2001-2003	Member, Expert Panel on Children's Health and the Environment, North American Commission for Environmental Cooperation
2002-	Member, Scientific Advisory Board, Scientist Communication Network.
2003	Member, "Herculaneum Health Study Workshop" Agency for Toxic Substance Diseases Registry, May 22nd to 23rd, 2003
2003-2004	Panel Member, "Lead Poisoning in Pregnant Women", Mt. Sinai for Children's Health and the Environment, New York, NY
2003	Member, "Invitational Workshop on a proposed American Family Study" National Human Genome Research Institute, December 1st to 3rd, 2003.

2004-2006	Member, Committee on "Ethical Consideration for Research on Housing-Related Health-Hazards involving Children", National Research Council and the Institute of Medicine, The National Academies
2004	Congressional Testimony, "Tapped Out? Lead in the District of Columbia and the Providing of Safe Drinking Water", Subcommittee on Environment and Hazardous Materials of the Committee on Energy and Commerce, U.S. House of Representatives, 108th Congress, July 22nd, 2004
2005	Reviewer, "Superfund and Mining Megasites – Lessons from the Couer d" Alene River Basin", National Research Council, The National Academies.
2005	Ad Hoc Member, NIEHS Board of Scientific Counselors Review of the Epidemiology Branch, April 3rd to April 5th, 2005
2005	Senate Briefing, "The Connection of Environmental Chemicals and Learning Disabilities", U.S. Senate, May 10th, 2005
2006	Invited Participant, NIEHS Strategic Planning Forum, National Institute for Environmental Health Sciences, Chapel Hill, North Carolina, October 17-18th, 2006.
2006-2008	Member, U.S. EPA's Clean Air Scientific Advisory Committee Lead Review Panel.
2006-2008	Member, National Children's Study Steering Committee, NICHD
2006	Invited Participant, "How Does Housing Affect Health Outcomes of Children?", MacArthur Foundation, Chicago, Illinois, June 21st-22nd, 2006.
2006- 2010	Member, External Scientific Advisory Committee, Richmond Center for Excellence in Tobacco Research, American Academy of Pediatrics.
2007	Testimony, Vermont State Legislature, "The Lingering Legacy of Lead Toxicity", Montpelier, Vermont, February 1st, 2007
2007	Testimony, Connecticut State Legislature, "The Legacy of Lead Toxicity", Hartford, Connecticut, March 14th, 2007. (PG)
2007	Invited Testimony, United States Senate Hearing, "Lead and Children's Health". Committee on Environmental and Public Works, October 18th, 2007
2007-2008	Member, Committee on "Committee on Contaminated Drinking Water at Camp Lejeune", National Research Council, The National Academies.
2008	Member, Expert Panel on Health and the Environment, Statistics Canada, Ottawa,
2008-	Member, Alliance for the Global Elimination of Lead Paint, Intergovernmental Forum on Chemical Safety (IFCS), World Health Organization
2008-2009	Reviewer, Toxicological Review and Recommended Toxicological Reference Values for Environmental Lead Exposure in Canada, Health Canada
2009-2013	Scientific Advisor, Canada Lead Study funded by Health Canada (Patrick Levallois, Principal Investigator).
2009-2014	Board Member, Barro Sin Plomo
2009-2010	Member, Health and Environment Experts Advisory Group of the Canadian Longitudinal Study on Aging, Canadian Institutes of Health Research
2010-2012	Member, US Environmental Protection Agency Science Advisory Board for Evaluating Dust Lead Standards
2010-2013	Advisor, Canada Environmental Health Law and Canadian Partnership for Children's Health and Environment Retrofit Project
2010-2012	Member, Physicians Advisory Panel, Canada Health Measures Survey
2010	Invited Testimony, United States Senate Hearing, "Research on Environmental Health Factors with Autism and Neurodevelopmental Disorders", August 3rd, 2010
2010	Member, Joint FAO/WHO Expert Panel for Toxicological and Health Review of Bisphenol A
2010-2015	Board Member, Global Community Monitoring, Oakland, California
2010-	Chairman, Scientific Advisory Committee for Dartmouth University's Program in Children's Health and the Environment

2011-2016 Member, American Academy of Pediatrics Executive Council on Environmental Health
2011-2012 Member, US Environmental Protection Agency Science Advisory Board for Evaluating Hazards of Partial Water Line Replacement
2011 Invited Testimony, Special Committee on Cosmetic Pesticides, Legislative Assembly, Province of British Columbia, October 7th, 2011
2011-2012 Member, Panel on Health Effects of Low-level Lead, Office of Health Effects, National Toxicology Program of the National Institutes of Environmental Health Sciences,
2012- Member, Expert Advisory Committee, Canada Health Measures Survey
2012- Member, Environmental Defence Fund Science Advisory Committee on Toxics
2015 Reviewer, Review of Clinical Guidance for the Care of Health Conditions Identified by the Camp Lejune Legislation, Institute of Medicine, The National Academies
2016- Member, The Lancet Commission on Pollution, Health & Development
2016- Member, Targeting Environmental Neuro-Developmental Risks (TENDR)
2016 Member, Steering Committee, The National Lead Summit, United States
2017 Rockefeller Foundation Academic Writing Retreat, Bellagio, Italy
2017- Member, Advisory Committee for the Flint (MI) Cohort Study
2017- Pure Earth Leadership Council
2018- Member Project TENDR Advisory Board
2018- Member, Mercury Disability Board Committee, Health Canada

Editorial Boards

2000-2015 Assistant Editor, *Environmental Research*
2000-2008 Deputy Editor, *Public Health Reports*
2004 Associate Editor, *Pediatrics* supplement on Children's Environmental Health
2004-2017 Editorial Board Member, *PLoS Medicine*
2005-2014 Editorial Board Member, *Breastfeeding Medicine*
2007- Editorial Board Member, *Environmental Health*
2008-2012 Editorial Review Board Member, *Environmental Health Perspectives*
2012-2015 Associate Editor, *Environmental Health Perspectives*
2016- Advisor, *Environmental Health Perspectives* News Section

Societies and Organizations

1989-2008 American Public Health Association
1996-2015 Academic Pediatric Association
1997-2012 American Association for the Advancement of Science
2000-2008 Society for Pediatric Research
2001-2008 American Pediatric Society
2001-2016 Specialty Fellow, American Academy of Pediatrics
2006- Fellow, Collegium Ramazzini
2006- Member, International Society for Environmental Epidemiology
2008- Founding Member, International Society for Children's Health & the Environment
2011-2017 Secretary and Treasurer, International Society for Children's Health & the Environment
2012- Member, International Society for Exposure Science
2017-2018 Vice-President, International Society for Children's Health & the Environment
2019-2020 President, International Society for Children's Health & the Environment

Video and Website Production – www.littlethingsmatter.ca

1. Canadian Environmental Health Atlas: A Portal to Discover the Promise of Environmental Health.
2. Shifting the Curve: The Impact of Toxins on ADHD in U.S. Children (video)
3. Little Things Matter: The Impact of Toxins on the Developing Brain (video)
4. Little Things Matter: The Impact of Toxins on Preterm Birth (video)
5. Prevention Paradox: Why We are Failing to Prevent Disease (video)
6. Little Things Matter: The Deadly Impact of Airborne Particles (video)
7. Cause or Cure: A Plea for Prevention (video)
8. Crime of the Century: The Failure to Prevent the Lead Pandemic (video)

Original Research

1. Lanphear BP. Deaths in Custody. American Journal Forensic Medicine & Pathology 1987;8:299-301.
2. Lanphear BP, Snider DE. Myths of Tuberculosis. J Occ Med 1991;33:501-504.
3. Linnemann CC Jr, Cannon C, DeRonde M, Lanphear BP. Effect of educational programs, rigid sharps containers, and universal precautions on reported needle-stick injuries in healthcare workers. Infection Control Hospital Epidemiology 1991;12:214-20.
4. Lanphear BP, Buncher CR. Latent period for malignant mesothelioma of occupational origin. Journal Occupational Med 1992;34:718-721.
5. Lanphear BP, Linnemann CC Jr, Cannon CG, DeRonde MM. Decline of clinical hepatitis B in workers at a general hospital. Clinical Infectious Disease 1993:11:10-14.
6. Lanphear BP, Linnemann CC Jr, Cannon C, DeRonde MM, Pendy L, Kerly L. Hepatitis C virus infection in health care workers. Infection Control Hospital Epidemiology 1994;15:745-750.
7. Lanphear BP, Emond M, Jacobs DE, Weitzman M, Winter NL, Tanner M, Yakir B, Eberly S. A side-by-side comparison of dust collection methods for sampling lead-contaminated house-dust. Environmental Research 1995;68:114-123.
8. Lanphear BP, Winter NL, Apetz L, Eberly S, Weitzman M. A randomized trial of the effect of dust control on children's blood lead levels. Pediatrics 1996;98:35-40.
9. Christy C, Pulcino M, Lanphear BP, McConnochie K. Screening for tuberculosis infection in urban children. Arch Pediatrics Adolescent Med 1996;150:722-726.
10. Lanphear BP, Weitzman M, Eberly S. Racial differences in environmental exposures to lead. American Journal of Public Health 1996;86:1460-1463.
11. Lanphear BP, Weitzman M, Winter NL, Tanner M, Yakir B, Eberly S, Emond M, Matte TD. Lead-contaminated house dust and urban children's blood lead levels. American Journal of Public Health 1996;86:1416-1421.

12. Lanphear BP, Byrd RS, Auinger P, Hall CB. Increasing prevalence of recurrent otitis media among children in the United States. Pediatrics 1997. http//www.pediatrics.org/cgi/contents/full99/3/e1.
13. Emond MJ, Lanphear BP, Watts A, Eberly S for the Rochester Lead-in-Dust Study Group. Measurement error and its impact on the estimated relationship between dust lead and children's blood lead. Environmental Research 1997;72:82-92.
14. Lanphear BP, le Cessie S, Atkinson WL, Watelet L. Association of live births and the resurgence of measles. International Journal Epidemiology 1997;26:204-211.
15. Rust SW, Burgoon DA, Lanphear BP, Eberly S. Log-additive versus log-linear analysis of lead-contaminated house dust and children's blood lead levels: Implications for residential dust-lead standard. Environmental Research 1997;72:173-184.
16. Lanphear BP, Roghmann KJ. Pathways of lead exposure in urban children. Environmental Research 1997;74:67-73.
17. Lanphear BP, Byrd RS, Auinger P, Schaffer S. Community characteristics associated with elevated blood lead levels in children. Pediatrics 1998;101:264-271.
18. Lanphear BP, Rust SW, Burgoon DA, Eberly S, Galke W. Environmental exposures to lead and urban children's blood lead levels. Environmental Research 1998;76:120-130.
19. Lanphear BP. The paradox of lead poisoning prevention. Science 1998;281:1617-1618.
20. Lanphear BP, Hall CB, Black J, Auinger P. Risk factors for the early acquisition of HHV-6 and HHV-7 infection in children. Pediatric Infectious Disease Journal 1998;17:792-795.
21. Lanphear BP, Matte TD, Rogers J, Clickner R, Dietz B, Bornschein RL, Succop P, Mahaffey KR, Dixon S, Galke W, Rabinowitz M, Farfel M, Rohde C, Schwartz J, Ashley P and Jacobs DE. The contribution of lead-contaminated house dust and residential soil to children's blood lead levels: A pooled analysis of 12 epidemiologic studies. Environmental Research 1998;79:51-68.
22. Marron R, Lanphear BP, Kouides R, Dudman L, Manchester R, Christy C. Efficacy of informational letters on Hepatitis B immunization rates in university students. J Am College Health 1998;47:123-127.
23. Howard CR, Howard FM, Lanphear BP, deBlieck EA, Eberly S, Lawrence RA. Effect of early pacifier use on breastfeeding duration. Pediatrics 1999;103. http//www.pediatrics.org/cgi/contents/full103/3/e33.
24. Lanphear BP, Howard CR, Eberly S, Auinger P, Kolassa J, Weitzman M, Alexander K, Schaffer S. Primary prevention of childhood lead exposure: A randomized trial of dust control. Pediatrics 1999;103:772-777.

25. Moss ME, Lanphear BP, Auinger P. Association of dental caries and blood lead levels among the U.S. population. JAMA 1999;281:2294-2298.
26. Howard CR, de Blieck EA, ten Hoopen C, Howard F, Lanphear BP, Lawrence RA. Physiologic stability of newborns during cup and bottle-feeding. Pediatrics 1999;104:1204-1207.
27. Steiner JF, Curtis P, Lanphear BP, Vu KO, Reid A. Federally-funded fellowship training in primary care research: perspectives of program directors. Academic Medicine 2000;75:74-80.
28. Stone KE, Lanphear BP, Pomerantz WJ, Khoury J. Injuries and deaths in children due to window-falls. Journal of Urban Health 2000;77:26-33.
29. Mansour M, Lanphear BP, DeWitt TG. Barriers to asthma care among underserved, urban children. Pediatrics 2000;106:512-519.
30. Lanphear BP, Eberly S, Howard CR. Long-term effect of dust control on children's blood lead levels. Pediatrics 2000 http//www.pediatrics.org/cgi/contents/full106/4/e48.
31. Lanphear BP, Dietrich KN, Auinger P, Cox C. Cognitive deficits associated with blood lead levels <10 μg/dl in U.S. children and adolescents. Public Health Reports 2000;115:521-529.
32. Lanphear BP, Aligne C, Auinger P, Byrd R, Weitzman M. Residential exposures associated with asthma in U.S. children. Pediatrics 2001;107:505-511.
33. Lanphear BP, Kahn RS, Berger O, Auinger P, Bortnick S, Naahas R. Contribution of residential exposures to asthma in US children and adolescents. Pediatrics 2001. http://www.pediatrics.org/cgi/content/full/107/6/e98.
34. Phelan KJ, Kalkwarf H, Khoury J, Lanphear BP. Trends and patterns of playground injuries in U.S. children and adolescents. Ambulatory Pediatrics 2001;1:227-233.
35. Mansour M, Lanphear BP, Hornung R, Khoury J, Bernstein DI, Menrath W, Decolongon J. A side-by-side comparison of sampling methods for settled indoor allergens. Environ Res 2001;87:37-46.
36. Haynes E, Lanphear BP, Tohn E, Farr N, Rhoads GG. The effect of dust control on children's blood lead concentrations: A systematic review. Env Health Perspect 2002;110:103-107.
37. Lanphear BP, Hornung R, Ho M, Howard CR, Eberly S, Knauf K. Environmental lead exposure during early childhood. Journal of Pediatrics 2002;140:40-47.
38. Steiner JF, Lanphear BP, Curtis P, Vu KO. The training and career paths of fellows in the National Research Service Award (NRSA) program for research in primary medical care. Acad Med 2002;77:712-718.
39. Steiner JF, Lanphear BP, Curtis P, Vu KO. Indicators of early research productivity among primary care fellows. J Gen Intern Med 2002;17:845-851.

40. Kalkwarf HJ, Khoury JC, Lanphear BP. Milk intake in childhood and adolescence, adult bone density and osteoporotic fractures in U.S. women. Am J Clin Nut 2003;77:257-265.
41. Howard CR, Howard FM, Lanphear BP, Eberly S, deBlieck EA, Oakes D, Lawrence RA. A randomized trial of pacifier use and bottle-feeding and their effect on breastfeeding. Pediatrics 2003;111:511-518.
42. Curtis P, Dickinson P, Steiner J, Lanphear BP, Vu K. Building capacity for research in family medicine: Is the blueprint faulty? Family Medicine 2003;35:124-130.
43. Lanphear BP, Succop P, Roda S, Henningsen G. The effect of soil abatement on blood lead levels in children living near a former smelting and milling operation. Public Health Reports 2003;118:83-90.
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45. Kahn RS, Khoury JC, Nichols WC, Lanphear BP. Role of dopamine transporter genotype and maternal prenatal smoking in childhood hyperactivity-impulsivity, inattentive and oppositional behaviors. Journal of Pediatrics 2003:143: 104-110.
46. Auinger P, Kalkwarf HJ, Mansour M, Lanphear BP. Trends in otitis media in US children. Pediatrics 2003:112:514-520.
47. Haynes E, Kalkwarf H, Hornung R, Wenstrup R, Dietrich K, Lanphear B. Vitamin D Fok1 polymorphism and blood lead levels in children. Environ Health Persp 2003;111:1665-1669.
48. Steiner JF, Curtis P, Lanphear BP, Vu KO, Main DS. Assessing the role of influential mentors in the research development of primary care fellows. Academic Medicine 2004:79:865-872.
49. Yolton K, Auinger P, Dietrich KN, Lanphear BP, Hornung R. Exposure to environmental tobacco smoke and cognitive abilities among US children and adolescents. Environ Health Persp 2005:113:98-103.
50. Phelan KJ, Khoury J, Kalkwarf H, Lanphear BP. Residential injuries in US children and adolescents. Public Health Reports 2005;120:63-70.
51. Wilson SE, Kahn RS, Khoury J, Lanphear BP. Racial differences in exposure to environmental tobacco smoke among children. Environ Health Perspect 2005;113:362-367.
52. Lanphear BP, Hornung R, Ho M. Screening housing to prevent lead toxicity in children. Pub Health Rep 2005;120:305-310.
53. Rosner D, Markowitz G, Lanphear BP. J. Lockhart Gibson and the discovery of the impact of lead pigments on children's health: A review of a century of knowledge. Pub Health Rep 2005;120:296-300.

54. Lanphear BP, Hornung R, Khoury J, Yolton K, Baghurst P, Bellinger DC, Canfield RL, Dietrich KN, Bornschein R, Greene T, Rothenberg SJ, Needleman HL, Schnaas L, Wasserman G, Graziano J. Low-level environmental lead exposure and children's intellectual function: An international pooled analysis. Environ Health Perspect 2005;113:894-899.
55. Nagaraja J, Menkedick J, Phelan KJ, Ashley PJ, Zhang J, Lanphear BP. Deaths from residential injuries in US children and adolescents, 1985 to 1997. Pediatrics 2005;116:454-61.
56. Eskenazi B, Gladstone EA, Berkowitz GS, Drew CH, Faustman EM, Holland NT, Lanphear BP, Meisel SJ, Perera FP, Rauh VA, Sweeney A, Whyatt RM, Yolton K. Methodologic and logistic issues in conducting longitudinal birth cohort studies: Lessons learned from the Centers for Children's Environmental Health and Disease Prevention Research. Environ Health Persp 2005;113:1419-1429.
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58. Spanier AJ, Hornung R, Lierl M, Lanphear BP. Environmental exposures and exhaled nitric oxide in children with asthma. J Pediatrics 2006;149:220-226.
59. Yuan W, Holland S, Cecil K, Dietrich K, Wessel SD, Altaye M, Hornung R, Ris M, Egelhoff J, Lanphear B. The impact of early childhood lead exposure on brain organization: A functional magnetic resonance imaging study of language function. Pediatrics 2006;118:971-977.
60. Howard CR, Lanphear N, Lanphear BP, Eberly S, Lawrence RA. Parental responses to infant crying and colic: the effect on breastfeeding duration. Breastfeeding Med 2006;1:146-155.
61. Brinkman W, Geraghty S, Lanphear B, Khoury J, Gonzalez-Del-Rey J, DeWitt T, Britto M. Evaluation of resident communication skills and professionalism: A matter of perspective? Pediatrics 2006;118:1371-1379.
62. Braun JM, Kahn RS, Froehlich T, Auinger P, Lanphear BP. Exposures to environmental toxicants and attention deficit hyperactivity disorder in U.S. children. Environ Health Perspect 2006;114:1904-1909.
63. Brinkman WB, Geraghty SR, Lanphear BP, Khoury JC, Gonzalez-Del-Rey JA, DeWitt TG, Britto MT. Effect of multisource feedback on resident communication skills and professionalism: a randomized controlled trial. Arch Pediatr Adolesc Med 2007;161:44-49.
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65. Froehlich T, Lanphear BP, Dietrich KN, Cory-Slechta D, Wang N, Kahn RS. Interactive effects of a DRD4 polymorphism, lead, and sex on executive functions in children. Biol Psychiatry 2007:62:243-249.

66. Froehlich TE, Lanphear BP, Epstein JN, Barbaresi WJ, Katusic SK, Kahn RS. Prevalence, recognition and treatment of attention-deficit/hyperactivity disorder in a national sample of US children. Arch Pediatr Adolesc Med 2007;161:857-864.

67. Landrigan PJ, Woolf AD, Gitterman B, Lanphear B, Forman J, Karr C, Moshier EL, Godbold J, Crain E. The Ambulatory Pediatric Association Fellowship in Pediatric Environmental Health: A five-year assessment. EHP 2007;115:1383-1387.

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69. Cecil KM, Brubaker CJ, Adler CM, Dietrich KN, Altaye M, Egelhoff JC, Wessel S, Elangovan I, Hornung R, Jarvis K, Lanphear BP. Decreased brain volume in adults with childhood lead exposure. PLoS Med 2008;5:e112.

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71. Spanier AJ, Hornung RW, Kahn RS, Lierl MB, Lanphear BP. Seasonal variation and environmental predictors of exhaled nitric oxide in children with asthma. Pediatr Pulmonol 2008;43:576-583.

72. Braun JM, Froehlich TE, Daniels JL, Dietrich KN, Hornung R, Auinger P, Lanphear BP. Association of environmental toxicants and conduct disorder in U.S. children: NHANES 2001-2004. Environ Health Perspect 2008;116:956-962.

73. Yolton K, Khoury J, Hornung R, Dietrich KN, Succop P, Lanphear BP. Environmental tobacco smoke exposure and child behaviors. J Dev Behav Pediatr 2008;29:456-463.

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75. Geraghty SR, Khoury JC, Morrow AL, Lanphear BP. Reporting individual test results of environmental chemicals in breastmilk: potential for premature weaning. Breastfeed Med. 2008;3:207-213.

76. Spanier AJ, Kahn RS, Hornung RW, Wang N, Sun G, Lierl MB, Lanphear BP. Environmental exposures, nitric oxide synthase genes, and exhaled nitric oxide in asthmatic children. Pediatr Pulmonol. 2009;44:812-819.
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79. Braun J, Yolton K, Dietrich K, Hornung R, Ye X, Calafat AM, Lanphear BP. Prenatal Bisphenol A exposure and early childhood behavior. Environ Health Persp 2009;117:1945-1952.
80. Yolton K, Khoury J, Xu Y, Succop P, Lanphear B, Bernert JT, Lester B. Low-level prenatal exposure to nicotine and infant neurobehavior. Neurotoxicol Teratol. 2009;31:356-363.
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84. Brubaker CJ, Dietrich KN, Lanphear BP, Cecil KM. The influence of age of lead exposure on adult gray matter volume. Neurotoxicology 2010;31:259-266.
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89. Braun JM, Kalkbrenner AE, Calafat AM, Bernert JT, Ye X, Barr DB, Sathyanarayana S, Lanphear BP. Variability and predictors of urinary Bisphenol A concentrations during pregnancy. Environ Health Perspect 2011;119:131-137.
90. Wilson SE, Talaska G, Kahn RS, Schumann B, Khoury J, Leonard AC, Lanphear BP. White blood cell DNA adducts in a cohort of asthmatic children exposed to environmental tobacco smoke. Int Arch Occup Environ Health 2011;84:19-27.
91. Lanphear BP, Hornung RW, Khoury J, Yolton K, Lierl M, Kalkbrenner AE. Effects of HEPA air cleaners on unscheduled asthma visits and asthma symptoms in children exposed to second hand tobacco smoke. Pediatrics 2011;127:93-101.
92. Phelan KJ, Khoury J, Xu Y, Liddy S, Hornung R, Lanphear BP. A randomized, controlled trial of home injury hazard reduction: The HOME Study. Arch Pediatrics Adolesc Medicine 2011;165:339-345.
93. Cecil KM, Dietrich KN, Altaye M, Egelhoff JC, Lindquist DM, Brubaker CJ, Lanphear BP. Proton magnetic resonance spectroscopy in adults with childhood lead exposure. Environ Health Perspect 2011;119:403-408.
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96. Sathyanarayana S, Braun JM, Yolton K, Liddy S, Lanphear BP. Case Report: High prenatal Bisphenol A exposure and infant behavior. Environ Health Perspect 2011;119:1170-1175.
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Presentations

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2. “Common Misconceptions about Tuberculosis”. American Lung Association, St. Elizabeth’s Hospital, Belleville, IL, March 19, 1991.
3. “Prevention and Control of Infectious Disease in Health Care Workers”. Miami Valley Hospital, Dayton, OH, September 5, 1991.

4. “Transmission of Hepatitis B Virus Infection in Health Care Workers”. Ohio University, Athens, Ohio, March 21, 1992.
5. “Universal Immunization Against Hepatitis B Virus”. Grand Rounds, Dayton Children’s Hospital, May 1992, Dayton, Ohio.
6. "Correlation of Blood Lead Levels and Dust Lead Levels Using Three Dust Collection Methods. Environmental Protection Agency, Research Triangle, N.C., January 20,1994.
7. "Relation of Lead-Contaminated House Dust and Blood Lead Levels in Urban Children" Environmental Protection Agency, Washington, D.C., February, 1994.
8. "Lead-Contaminated House Dust and Blood Lead Concentrations in Children", Society for Pediatric Research, Seattle, Washington May 5, 1994.
9. "EPA Health-Based Standards for Soil and Dust". Alliance to End Childhood Lead Poisoning, Washington, D.C., May 17, 1994.
10. "Epidemiology of Tuberculosis in Health Care Settings". University of Cincinnati, Cincinnati, OH, August 19, 1994.
11. "A Side-by-Side Comparison of Sampling Methods for Lead-Contaminated House Dust". American Public Health Association, Washington, D.C., November 1, 1994.
12. “Trends in Childhood Exposure to Lead: Implications for Prevention”. University of Rochester, Pediatric Grand Rounds, February 15, 1995.
13. “Childhood Exposure to Lead”. Visiting Professor, Nazareth College, Rochester, New York, March 24, 1995.
14. “Transmission and Control of Infections in Health Care Workers”. (Moderator & Speaker) American College of Occupational Environmental Medicine, Las Vegas, Nevada, May 4, 1995.
15. “Lead Exposure Prevention Research at the University of Rochester”. New England Lead Conference, Kennebunkport, Maine, August 3, 1995.
16. “Prevention of Childhood Lead Exposure”. 1st Annual Midwest Conference on Childhood Lead Poisoning Prevention, Kansas City, MO, September 10-11, 1995.
17. “Childhood Lead Exposure: Implications for Occupational Health”. National Institute for Occupational Safety and Health, Cincinnati, OH, May 10, 1996.
18. “Community Characteristics and Children’s Blood Lead Concentrations”. American Public Health Association, New York City, NY, November 19, 1996.
19. “Evolution of a Disease: The Science of Childhood Lead Exposure Prevention.” American Public Health Association, New York City, NY, November 18, 1996.
20. “Childhood Lead Exposure: A Local and National Perspective.” Occupational Medicine Grand Rounds, University of Rochester, January 2, 1997.

21. "Prevention of Childhood Lead Exposure: The U.S. Experience". (Keynote) University of the West Indies and Pan American Health Organization, Kingston, Jamaica, January 23, 1997
22. "Lead-Contaminated House Dust and Children's Blood Lead Levels". (Keynote Presentation) Look Out for Lead Conference, Madison, WI, May 22, 1997.
23. "Primary Prevention of Childhood Lead Exposure: A Randomized Trial of Dust Control". American Public Health Association, Indianapolis, November 13, 1997.
24. "Evolution of a Disease: Prevention of Childhood Lead Exposure." Pediatric Grand Rounds, Medical University of South Carolina, Charleston, SC, March 20, 1998.
25. "The Science of Childhood Lead Exposure Prevention." Tulane/Xavier Center for Bioenvironmental Research, New Orleans, May 4-5th, 1998.
26. "Lead Hazard Control Research" Conference on Linking Health, Housing & Environment, Centers for Disease Control, Department of Housing and Urban Development, National Institutes of Health, Phoenix, Arizona, June 21-24, 1998.
27. "A Randomized Trial of Dust Control to Prevent Childhood Lead Exposure." Presenter and Co-chairman, Section on Heavy Metals, 1st International Conference on Children's Environmental Health, Amsterdam, The Netherlands, August 11-13th, 1998.
28. "Prevention of Childhood Lead Exposure: A Critique of the EPA's Proposed Residential Lead Standard". Office of Children's Health Protection, U.S. Environmental Protection Agency, Washington, D.C., November 5, 1998.
29. "Science and Policy of Lead Poisoning Prevention in the United States". Nicholas School of the Environment, Duke University, Durham, North Carolina, February 22, 1999.
30. "Behaviors in Early Childhood and Exposure to Environmental Toxins". (invited) Pediatric Environmental Health Conference, San Francisco, CA May 4, 1999.
31. "Patterns of Lead Exposure in Early Childhood". International Conference on Lead Exposure, Reproductive Toxicity and Carcinogenicity, Gargnano, Italy, May 7, 1999.
32. "Adverse Effects of Blood Lead Concentrations <10 μg/dL" (Invited), 17th International Conference Neurotoxicology Conference, Little Rock, Arkansas, October 17-20, 1999.
33. "Emerging Research and Implications for Prevention of Childhood Lead Exposure" (Invited), 2nd Annual Syracuse Lead Conference, Syracuse, New York October 27th, 1999.
34. "Prevention of Lead Poisoning in Children" Sierra Club, Omaha, NE, November 16th, 1999.
35. "Children's Environmental Health: A Focus on Residential Hazards" Department of Pediatrics, University of Nebraska Hospital, November 17th, 1999.
36. "Effectiveness of Lead Hazard Controls", New England Lead Conference, New Hampshire, Tufts University School of Medicine, April 25, 2000.

37. "Subclinical Lead Toxicity in U.S. Children and Adolescents", Pediatric Academic Societies, Boston, MA, May 15, 2000.
38. "Contribution of Residential Exposures to Asthma in U.S. Children and Adolescents", Pediatric Academic Societies, Boston, MA, May 16, 2000.
39. "The Effect of Soil Abatement on Blood Lead Concentration in Children living near a former Smelter and Milling Operation" (invited). Coeur d'Alene, Idaho, May 24, 2000.
40. "The Paradox of Lead Poisoning Prevention" (invited). National Institute of Justice, Washington, D.C., July 18th, 2000.
41. "Evolution of a Disease: Prevention of Childhood Lead Exposure." Pediatric Grand Rounds, Children's Hospital Medical Center, Cincinnati, Ohio, August 22, 2000.
42. "Children's Environmental Health: A Focus on Residential Hazards" Pediatric Grand Rounds, Department of Pediatrics, University of Rochester School of Medicine, Rochester, NY, September 20th, 2000.
43. "Prevention of Lead Poisoning in Childhood" 7th Annual Childhood New York State Lead Poisoning Prevention Conference, Purchase College, NY, September 29, 2000.
44. "Excavating the Enigmas of Childhood Lead Exposure". Department of Environmental and Occupational Medicine, Harvard University School of Public Health, Boston, MA, October 16th, 2000.
45. "Contribution of Residential Exposures to Asthma". Eliminating Childhood Lead Poisoning: Our Challenge for the Decade, Centers for Disease Control and the U.S. Department of Housing & Urban Development, December 11th, 2000.
46. "Setting Research Priorities for the Decade". (Moderator & Speaker) Eliminating Childhood Lead Poisoning: Our Challenge for the Decade, Centers for Disease Control and the U.S. Department of Housing & Urban Development, December 13th, 2000.
47. "Evolution of a Disease: Prevention of Childhood Lead Exposure." (Keynote Presentation) Look Out for Lead Conference, Madison, WI, April 12, 2001.
48. "Environmental Lead Exposure and Children's Intelligence at Blood Lead Concentrations below 10 μg/dl." APA Presidential Plenary Session, Pediatric Academic Society Meeting, Baltimore, MD, April 30, 2001.
49. "Elimination of Childhood Lead Exposure: Obstacles & Opportunities" (Plenary). National Housing Conference and Exposition, New Orleans, LA, May 16th, 2001.
50. "Prevention of Childhood Lead Exposure: A Public Health Perspective" (Keynote Presentation). Philadelphia Health Department, Philadelphia, PA, May 23rd, 2001.

51. "Evolution of a Disease: Prevention of Childhood Lead Exposure." (Keynote Presentation), Charles Drew University, Los Angeles, California, October 22nd, 2001.
52. "Primary Prevention of Childhood Lead Exposure" (Keynote Presentation), Midwest Regional Lead Conference, Pittsburgh PA, October 29th, 2001.
53. "Prevention of Childhood Lead Exposure: Shifting to Primary Prevention" (Keynote Presentation), Indiana Department of Health, Lead-Safe Conference, November 7th, 2001.
54. "A Strategy for Primary Prevention of Childhood Lead Exposure" A testimony to Housing and Transportation Subcommittee, U.S. Senate, Washington, D.C., November 13, 2001.
55. "Ethical issues of Environmental Research involving Children" (moderator and speaker). Panelists were Jeffrey Kahn, Ph.D., and Leonard Glantz, J.D., Raleigh-Durham, North Carolina, NIEHS Conference of Children's Environmental Health Centers, January 23, 2001.
56. "Evolution of a Disease: Science and Prevention of Childhood Lead Exposure." Grand Rounds, Omaha Children's Hospital, Omaha, Nebraska, March 1, 2002.
57. "Racial Disparities in Children due to Environmental Hazards" Ohio Commission on Minority Health, Columbus, Ohio March 27, 2002.
58. "Prevention of Childhood Lead Exposure in a Former Mining Community" Tar Creek, Oklahoma, April 4, 2002.
59. "Evolution of a Disease: Science and Prevention of Childhood Lead Exposure." Grand Rounds, Hasbro Children's Hospital, Brown University, Providence Rhode Island, May 17, 2002.
60. "Evolution of a Disease: Science and Prevention of Childhood Lead Exposure." Grand Rounds, Dayton Children's Hospital, Wright University, Dayton, Ohio May 22, 2002.
61. "Evolution of a Disease: Science and Prevention of Childhood Lead Exposure." International Lead Congress, Washington, DC, June 3rd, 2002.
62. "Residential Hazards: A Neglected Health Problem" Agency for Toxic Substances Disease Registry, Centers for Disease Control and Prevention, Atlanta, Georgia, August 19th, 2002.
63. "Control of Residential Exposures to Environmental Neurotoxins" National Center for Healthy Homes (Moderator and Speaker), Annapolis, VA, November 7th, 2003.
64. "The Promises and Potential Pitfalls of Primary Lead Poisoning Prevention" Purchase College, 9th Annual Childhood New York State Lead Poisoning Prevention Conference, Purchase College, New York,, October 4th, 2002.
65. "Evolution of a Disease: the Science and Prevention of Childhood Lead Exposure." Pediatric Grand Rounds, Syracuse, NY, October 9th, 2002.
66. "Evolution of a Disease: the Science and Prevention of Childhood Lead Exposure." University of Texas at El Paso, El Paso, Texas January 29th, 2003.

67. "Childhood Lead Poisoning" Introduction to Children's Environmental Health, Seattle, Washington, Pediatric Academic Society, May 3rd, 2003.
68. "The Legacy of Lead: Childhood Lead Poisoning in the 21st Century". Chicago Lead Summit, Chicago, Illinois, May 28th, 2003.
69. "The Legacy of Lead: Childhood Lead Poisoning in the 21st Century". Case Western Reserve University, Cleveland, Ohio, June 3rd, 2003.
70. "Housing and Children's Health", Sprawl: The impact on vulnerable populations, University of Cincinnati College of Medicine, Cincinnati, Ohio, July 8th, 2003.
71. "Trials and Tribulations of Protecting Children from Environmental Toxins". Duke University, Nicholas School of the Environment, Durham, NC, November 6th, 2003.
72. "Adverse Effects of Fetal and Childhood Exposures to Prevalent Toxins" Midwest Critical Regional Neonatology Conference, Covington, KY, November 14th, 2003.
73. "Control of Residential Hazards in Children" American Public Health Association, San Francisco, CA, November 18th, 2003.
74. "Low-Level Exposure to Environmental Lead Exposure and Children's Intellectual Function: An International Pooled Analysis". 21st International Neurotoxicology Conference, Honolulu, Hawaii, February 11th, 2004.
75. "Trials and Tribulations of Protecting Children from Environmental Hazards" Workshop on Ethical Issues on Children's Environmental Health, Children's Environmental Health Network, Washington, D.C. March 5, 2004.
76. "Low-Level Exposure to Environmental Lead Exposure and Children's Intellectual Function: An International Pooled Analysis", Pediatric Academic Societies Annual Meeting. Pediatric Research 2004;55:163A.
77. "The Impact of the Environment on Children's Health" Bob Smith Endowed Lecture, Department of Pediatrics, First Gulf Coast Children's Environmental Health Symposium, Baylor University, Houston, Texas.
78. "The Search for Environmental Causes of Learning Disabilities, Learning Disabilities Initiative, Baltimore, MD, May 18th, 2004.
79. "Residential Hazards in Children: A Neglected Public Health Problem", Pediatric Grand Rounds, Boston Medical Center, Department of Pediatrics, Boston University Medical Center, Boston, MA, May 20th, 2004.
80. "Residential Hazards in Children" "Healthier Homes, Stronger Families: Public Policy Approaches to Healthy Housing", National Center for Healthy Housing, Washington, D.C., June 2nd, 2004.

81. "Fetal and Early Childhood Exposures to Prevalent Toxins" Pediatric Grand Rounds, Ste. Justine Children's Hospital, University of Montréal, Montreal, Canada, June 16th, 2004.
82. "Childhood Exposure to Lead-Contaminated Soil: A Problem of the Past or a Problem from the Past?" National Academy of Science Committee on Superfund Site Assessment and Remediation in Coeur d'Alene River Basin", June 17th, 2004, Coeur d'Alene, Idaho.
83. "The Legacy of Lead" (Keynote Speaker). Chicago Lead Summit, Region V EPA Headquarters, September 15th, 2004.
84. "A Tale of Two Toxins: Children's Exposure to Tobacco and Lead" (with Michael Weitzman), The American Academy of Pediatrics, San Francisco, CA, October 10th, 2004.
85. "A Legacy of Childhood Lead Poisoning" University of Washington, Seattle, Washington, October 30, 2004.
86. "Protecting Children from Environmental Toxins", Pediatric Grand Rounds, Seattle Children's Hospital, Seattle Washington, March 10th, 2005.
87. "The Science and Politics of Childhood Lead Poisoning", Northwest Pediatric Environmental Health Conference, University of Washington, Seattle, Washington, March 11th, 2005.
88. "The Effects of Low-level Exposure to Environmental Toxins during Fetal Development and Early Childhood", Children's' Hospital of Fudan University, Shanghai International Pediatric Forum, Shanghai, China, June 16th to 18th, 2005.
89. "The Role of Biomarkers in Revealing Genetic and Environmental Influences of Disease and Disability" Psychiatry Grand Rounds, University of Cincinnati, February 8th, 2006.
90. "Trials and Tribulations of Protecting Children from Environmental Hazards: Ethical Issues", Johns Hopkins University of Medicine, March 17th, 2006.
91. "Key Elements of a Primary Prevention Strategy for Lead Poisoning", Albany Law School, Union University, Albany, New York, March 16th, 2006.
92. "Low-Level Lead Toxicity: The Ongoing Search for a Threshold"", Case Western Reserve University, City Club of Cleveland, Cleveland, OH March 4th, 2006.
93. Integrating Genetic and Environmental Influences in Pediatric Research" (Moderator and Speaker), Pediatric Academic Societies, San Francisco, CA, April 30th 2006.

94. "Ethical Issues in Housing Health Hazard Research Involving Children" (Topic Symposia) Pediatric Academic Societies, San Francisco, CA, May 2nd 2006.
95. "Low-Level Lead Toxicity: The Ongoing Search for a Threshold"", International Workshop on Neurotoxic metals: from Research to Prevention, University of Brescia, Italy, June 17th, 2006.
96. "Efficacy of HEPA-CPZ Air Cleaners on Unscheduled Asthma Visits and Asthma Symptoms", International Society for Environmental Epidemiology, Paris France, September 6th, 2006.
97. "Protecting Children from Environmental Toxins", Region VIII Children's Environmental Health Summit, Vail, Colorado September 20th, 2006.
98. "Integrating Genetic and Environmental Biomarkers in Pediatric Epidemiology", Visiting Professor, Simon Fraser University and University of British Columbia, Vancouver, British Columbia, October 19th-20th, 2006.
99. "The Legacy of Lead", Indiana Lead Conference, Indianapolis, Indiana, October 24, 2006.
100. "Ethical dilemmas in Children's Environmental Health", Seminar Series in Ethics of Toxicology, University of Champagne-Urbana, Champagne, Illinois, November 19th, 2006.
101. "Low-Level Lead Toxicity: Implications for Prevention"", WHO Informal Workshop on Lead, University of Munich, Germany, November 30th, 2006.
102. "Low-Level Lead Toxicity: The Ongoing Search for a Threshold"", National Environmental Public Health Conference, National Centers for Disease Control, Atlanta, Georgia, December 4th, 2006.
103. "The Epidemiologic Conquest of Childhood Lead Toxicity: A Pyrrhic Victory". NIEHS Workshop on Children's Environmental Health Research: Past, Present and Future. January 22nd, 2007.
104. "Linking Low-level Exposures to Environmental Toxicants with ADHD". Duke Integrated Toxicology and Environmental Health Program Symposium on Developmental Neurobehavioral Disabilities and Toxic Exposures, March 23, 2007, Durham, North Carolina.
105. "Using Biomarkers to Link Environmental Influences with Disease and Disability", The Channing Laboratory, Harvard University, Boston, Massachusetts, April 4th, 2007.
106. "The Lingering Legacy of Lead Toxicity". Grand Rounds, Department of Pediatrics, St. Louis Children's Hospital, St. Louis University, St. Louis, Missouri, April 11th, 2007.
107. "Protecting Children from Environmental Toxicants", United States Council of Catholic Bishops, Washington, D.C., April 30th, 2007.
108. "Efficacy of HEPA-CPZ Air Cleaners on Unscheduled Asthma Visits and Asthma Symptoms", Pediatric Academic Societies, APA Presidential Platform Plenary Session, Toronto, Canada, May 7th, 2007.

109. "The Lingering Legacy of Lead Toxicity" Grand Rounds, Department of Pediatrics, Omaha Children's Hospital, University of Nebraska, Omaha, Nebraska, April 11th, 2007.
110. "Linking Low-level Neurotoxicant Exposures of the Developing Brain to Learning and Behavioral Problems." International Conference on Developmental Programming and Effects of Environmental Toxicants in Human Health and Disease, Faroe Islands, May 20th, 2007.
111. "Protecting Children from Environmental Toxicants: The Neglected Legacy of Rachel Carson", National Policy Consultation Series on Children's Health and Environment, Moncton, New Brunswick, Canada, May 31, 2007.
112. "Low-Level Toxicity of Environmental Toxicants: Much Ado about Nothing?" Occupational and Environmental Health Seminar Series, Health Canada, Ottawa, Canada, June 6th, 2007.
113. "Linking Low-Level Lead Exposure with Child and Adolescent Psychopathology", 13th Annual International Society for Research in Child and Adolescent Psychopathology, London, England, June 19th, 2007.
114. "The Legacy of Lead Toxicity". Pediatric Grand Rounds, New York Presbyterian Hospital-Weill Cornell Medical Center, September 18th, 2007.
115. "Protecting Children from Environmental Toxicants: The Neglected Legacy of Rachel Carson". Pediatric Grand Rounds, Children's Hospital at Dartmouth, Dartmouth Medical School, September 19th, 2007.
116. "The Legacy of Lead Toxicity: Effects of Childhood Lead Exposure in Children, Adolescents and Adults". Mid-America Conference, Philadelphia, Pennsylvania, October 4th, 2007.
117. "Low-Level Toxicity of Environmental Toxicants: Much Ado about Nothing?" International Society for Exposure Analysis (invited plenary session), Raleigh-Durham, North Carolina, October 17th, 2007.
118. The Global Elimination of Lead Toxicity: A Focus on Housing." National Institute of Public Health, Rennes, France, October 22nd, 2007.
119. Linkage of Environmental Lead Exposure with Psychopathology in Children and Adolescents" Ramazzini Collegium, Carpi, Italy, October 25th, 2007.
120. "Linking Exposures to Environmental Toxicants with Child and Adolescent Psychopathology", Symposium on Environmental Toxicity and the Brain, University of Toronto, Toronto, Canada, December 7th, 2007.
121. "Linking Exposures to Environmental Toxicants with Child and Adolescent Psychopathology." Pediatric Grand Rounds, Rochester General Hospital and Strong Memorial Hospital, Rochester, New York, April 1&2, 2008.

122. "Rochester's Role in the Ongoing Elimination of Childhood Lead Toxicity." Beaven Lecture, Rochester Academy of Medicine, Rochester, New York, April 1, 2008.
123. "The Lingering Legacy of Lead Toxicity: Lansing Legacy." Michigan's Conference for Lead Safe & Healthy Homes, East Lansing, MI, April 22, 2008.
124. First Annual Controversies in Pediatric Environmental Health, "Should the Centers for Disease Control Lower the Blood Lead Level of Concern". A debate by Bruce Lanphear and George G. Rhoads (James Sargent, Moderator). Pediatric Academic Societies Meeting, Honolulu, Hawaii, May 2nd, 2008.
125. "Linking Exposure to Environmental Toxicants with Psychopathology in Children and Youth". Visiting Professor, Alberta Child and Youth Network, Calgary Children's Hospital, Calgary, Alberta. May 13th-15th, 2008.
126. Lead Toxicity and the Teenage Brain", Youth Exploring Science Program, St. Louis Science Center, St. Louis, Missouri, June 30th, 2008.
127. "The Legacy of Childhood Lead Toxicity". Health Canada, Ottawa, Canada, October 6th, 2008.
128. "Protecting Children from Environmental Toxicants: The Neglected Legacy of Rachel Carson". The 2008 Rachel Carson Legacy Conference: Green Chemistry – Solutions for a Healthy Economy, Duquesne University, Pittsburgh, Pennsylvania, September 20th, 2008.
129. "Trials and Tribulations of Protecting Children from Environmental Hazards", Ethics in Toxicology Seminar Series, University of Champagne-Urbana, Champagne, Illinois, September 22nd, 2008.
130. "Industry's Influence on the Prevention of Childhood Lead Poisoning." In: Symposia on Insulating Environmental Health Research from Conflicting Interests. International Society for Environmental Epidemiology Annual Meeting, Pasadena, California, October 14th, 2008.
131. "The Lingering Legacy of Lead Toxicity: Implications for Research and Policy on Other Environmental Toxicants". (Keynote Presentation) BC Environmental and Occupational Health Research Network, Vancouver, BC, November 7th, 2008.
132. "Effects of Environmental Toxicants on Children's Development". DB-PREP Course, American Academy of Pediatrics, Atlanta, Georgia, December 5th, 2008.
133. "Linking Low-level Environmental Toxicants with New Morbidities of Childhood". BC Children's Grand Rounds, British Columbia, Vancouver, February 6th, 2009.
134. "Using Biomarkers to Link Exposures with Disease and Disability in Children". Workshop on Physical and Chemical Exposures in Canadian Cohort Studies, Canadian Institute of Health Research and Health Canada, February 8th-9th, 2009.

135. "How Dangerous Is Lead In Drinking Water?" An interview on "Around The Water Cooler" with Werner Troesken and Bruce Lanphear. February 18th, 2009.
136. “Linking Environmental Toxicants with ADHD in Children” (invited), Learning Disabilities Association Annual Meeting, February 25th, Salt Lake City, Utah.
137. “The Lingering Legacy of Lead Toxicity”, Norfolk Children’s Hospital, April 30th, 2009, Norfolk Virginia.
138. Second Annual Controversies in Pediatric Environmental Health Debate, “Should Pediatricians Advise Parents to Feed their Children Organic Foods?” A debate by Joel Forman and Janet Silverstein (Bruce Lanphear, Moderator and Organizer). Pediatric Academic Societies Meeting, Baltimore, MD, May 4th, 2009.
139. “A Pattern of Pathology: The Population Impact of Environmental Toxicants on Health”. Workshop on Endocrine Disruptors, Endocrine Society, Washington, DC, June 9th, 2009.
140. “The Quandary of Environmental Contaminants in Human Milk”, 25th Anniversary of US Surgeon General’s Report on Breastfeeding, Washington, DC, June 13th, 2009.
141. “Linking Exposures to Environmental Toxicants with Learning Problems and Psychopathology in Children.” Northwest Conference on Children’s Health and Environment, Tukwila, Washington, October 1st, 2009.
142. “The Second Coming of the Sanitarians”, Pediatric Grand Rounds, University of California at Davis Children’s Hospital, Sacramento, California, October 9th, 2009.
143. “The Second Coming of the Sanitarians”, National Institute of Public Health, Rennes, France, November 4th, 2009.
144. “Linking Exposure to Environmental Toxicants with ADHD in Children.” Symposium on ADHD. Riyadh, Saudi Arabia, November 7th, 2009.
145. “The Interplay of Genetic and Environmental Influences in Common Conditions of Children.” Macquarie University, Department of Geology, Sydney, Australia, November 18th, 2009.
146. “The Lingering Legacy of Lead Toxicity: A Call for the Global Elimination of Lead Exposure.” Pacific Basin Consortium Symposium on Environment and Health, Perth, Australia, November 13th, 2009.
147. “The Second Coming of the Sanitarians”, SFU President’s Lecture, Simon Fraser University, Burnaby, BC, March 4th, 2010.
148. Third Annual Controversies in Pediatric Environmental Health Debate, “Should the American Academy of Pediatrics Sponsor a Ratings Board to Provide Evidence-based Ratings for Media?” A debate by James Sargent and Donald Shifrin (Bruce Lanphear, Moderator and Organizer). Pediatric Academic Societies Meeting, Vancouver, BC, May 2nd, 2010.

149. "Efficacy of Reducing Lead Hazards in Housing on Lead-Contaminated House Dust, Blood Lead Concentration and Intellectual Abilities in Children." Pediatric Academic Societies Meeting, Vancouver, BC May 1st, 2010.
150. "Protecting Children from Environmental Toxicants: The Neglected Legacy of Rachel Carson." Pediatric Grand Rounds, Cornell Weill Medical College, New York, New York. May 25th, 2010.
151. "Excavating the Enigmas of Childhood Lead Toxicity", Guest Lecturer, "Introduction to Toxicology, Harvard School of Public Health, Boston, Massachusetts, October 27th, 2010.
152. "The Conquest of Lead Poisoning: A Pyrrhic Victory", Lead Action Collaborative, New England Carpenters Center, Boston, Massachusetts, October 28th, 2010.
153. "Protecting Children from Environmental Toxicants: The Neglected Legacy of Rachel Carson." Academy of Breastfeeding Medicine, San Francisco, California, October 29th, 2010.
154. "Bisphenol A and Behavior Problems in Children". Eastern Perinatal Conference, Kingston, Ontario, November 10th, 2010.
155. "Low-Level Toxicity of Environmental Toxicants: Much Ado about Nothing?" UBC Statistics Department Seminar, November 18th, 2010.
156. "Protecting Children from Environmental Toxicants." Children's Hospital of Quebec, University of Laval, Quebec City, Quebec, December 17th, 2010.
157. "Low-level Toxicity: Implications for Research and Policy", Joint Talks by C. Arden Pope and Bruce Lanphear, SFU, UBC and UW Annual Occupational and Environmental Health Conference, Semiahmoo, WA January 7th, 2011.
158. "Crime of the Century: Lead Toxicity in the 20th Century", Panel Presentation and Discussion, UC Davis, Sacramento, California April 7th, 2011.
159. Fourth Annual Controversies in Pediatric Environmental Health Debate, "Should Parent Slather their Children with Sunscreen?" A debate with Russell Chesney, MD and Sophie Balk, MD, (Bruce Lanphear, Moderator and Organizer). Pediatric Academic Societies Meeting, Denver, Colorado, May 1st, 2011.
160. The Conquest of Lead Toxicity: A Pyrrhic Victory", Canadian Water Network, Ecole Polytechnique de Montreal, Montreal, Canada, June 9th, 2011.
161. The Contribution of Environmental Influences on Chronic Disease, Canadian Partnership for Health and Environment, Toronto, Canada, June 16th, 2011.
162. "The Second Coming of the Sanitarians", Environmental and Occupational Health Seminar, University of Washington School of Public Health, Seattle, WA, May 12th, 2011.
163. "Crime of the Century: The Failure to Prevent the Lead Pandemic". Sterling Prize in Controversy, Wosk Centre, Simon Fraser University, Vancouver, BC, October 19th, 2011.

164. "Measuring Exposure: The Benefits and Limits of Biomarkers". Canadian Institute for Human Development, Child and Youth Research, Montreal, Canada, December 6th, 2011.
165. "Rachel Carson: Clarity of Vision". SFU, UBC and UW Annual Occupational and Environmental Health Conference, Semiahmoo, WA, January 6th, 2012.
166. "The Truth About Toxins: What Parents and Health Professionals Should Know". Environmental Influences on Neurodevelopment: Translating the Emerging Science into Public Health Policy". UCLA School of Public Health, Los Angeles, California, January 12th, 2012.
167. "Protecting Children from Environmental Toxicants: The Neglected Legacy of Rachel Carson". Mattel Children's Hospital, Los Angeles, California, January 13th, 2012.
168. "Why Should We Share Data?", Data Sharing Strategies for Environmental Health Workshop, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, February 6th and 7th, 2012.
169. "The Science and Prevention of Lead Toxicity" (Keynote Presentation), Forum on Lead Toxicity: A Little is Still Too Much", Macquarie University, Sydney, Australia, June 5th, 2012
170. "Canada Environmental Health Atlas Knowledge Translation Workshop", Canadian Public Health Association, Edmonton, Alberta, June 13th, 2012.
171. "First Annual Controversies in Pediatric Environmental Health Debate: Should organophosphate pesticides be reduced or banned?" A debate with Brenda Eskenazi and Bruce Lanphear (Rob McConnell, Moderator). International Society for Environmental Epidemiology, Columbia, SC, August 28th, 2012.
172. "Supralinear Dose-Response Relationship of Environmental Toxicants: Research and Policy Implications." Moderator and Speaker, with Arden Pope, Roel Vermeulen and Bruce Lanphear. International Society for Environmental Epidemiology, Columbia, SC, August 29th, 2012.
173. Tanya Froehlich and Bruce Lanphear, "ADHD and Environmental Toxicants: Time for Prevention?", Society for Development and Behavioral Pediatrics, Phoenix, AZ, September 9th, 2012.
174. "The Epidemic of Childhood Disabilities: A Failure to Regulate". Workshop on Children's Rights and Corporate Responsibility, Green College, University of British Columbia, Vancouver, BC, October 19th, 2012.
175. "Low-level Toxicity: Much Ado About Nothing?", Department of Preventive Medicine Seminar, University of Southern , California, Los Angeles, California, October 23rd, 2012.
176. "Reflections on Silent Spring". (Invited Keynote). International Society for Exposure Sciences, Seattle, Washington, October 28th, 2012.

177. "Randomized Controlled Trials in Children's Environmental Health: Underutilized or Unethical?" The University of Washington Northwest Pediatric Environmental Health Specialty Unit and Center for Child Environmental Health, Seattle, Washington, February 26th, 2013.
178. "Crime of the Century: Our Failure to Prevent the Lead Pandemic". Dali Lana School of Public Health and of School Environment, University of Toronto, Toronto, Ontario, March 26th, 2013.
179. "The Ongoing Search for a Threshold". International Conference of Toxicology, Seoul, Korea, July 1, 2013.
180. "Blood Lead Concentrations and Cardiovascular Mortality in the United States: The NHANES Mortality Follow-up Cohort Study". International Society for Environmental Epidemiology, Basel, Switzerland, August 2, 2013.
181. "The Conquest of Lead Poisoning: A Pyrrhic Victory". Corporations and Global Health Governance. Simon Fraser University, Burnaby, British Columbia. September 17th, 2013.
182. "Striking at the Root: Changing the Narrative on the Causes of Disease". Corporations and Global Health Governance. Simon Fraser University, Burnaby, British Columbia. September 17th, 2013.
183. "Crime of the Century: The Failure to Prevent the Lead Pandemic". Pacific Basin Consortium, East-West Center, Honolulu, Hawaii. September 26, 2013.
184. "Low-level Toxicity: Policy Implications for the 21st Century". Symposium on Policy Implications of Environmental Exposures in the 21st Century. Pacific Basin Consortium, East-West Center, Honolulu, Hawaii. September 27, 2013.
185. "Excavating the Enigmas of Childhood Lead Toxicity". Network for Soil Contamination Research (INSCR), Delhi University, New Delhi, India. October 22nd, 2013.
186. "The Lingering Legacy of Lead Toxicity: A Call for the Global Elimination of Lead Exposure", World Health Organization, New Delhi, India. October 24th, 2013. "The Environmental Health Atlas: A Portal to Discover the Promises of Environmental Health." National Institute of Environmental Health Sciences, Raleigh-Durham, NC, November 10th, 2013.
187. "Protecting Children from Environmental Toxins". Japan Dioxin and Endocrine Disruptors Preventive Action, Tokyo, Japan, November 24th, 2013.
188. "ADHD: A Preventable Epidemic?" Alberta Children's Hospital, Calgary, Alberta, December 16th, 2013.
189. "Little Things Matter: The Impact of Toxins on the Developing Brain". Early Years Conference, Vancouver, British Columbia, January 30th, 2014.
190. "Little Things Matter: The Impact of Toxins on the Developing Brain". Dalhousie University, Halifax, Nova Scotia, March 6th, 2014.

191. "Low-level Toxicity of Environmental Toxins: Much Ado About Nothing?". Dalhousie University, Halifax, Nova Scotia, March 6th, 2014.
192. "The Canadian Environmental Health Atlas: A Portal to Discover the Promises of Environmental Health." School of Occupational and Environmental Health, University of British Columbia, March 28th, 2014.
193. "Little Things Matter: The Impact of Toxins on the Developing Brain". British Columbia Healthy Child Alliance, Vancouver, British Columbia, April 2nd, 2014.
194. "Sixth Annual Controversies in Pediatric Environmental Health Debate, E-Cigarettes: A weapon in the war against tobacco or a threat to tobacco control. (Moderator). Featuring Greg Connelly and James Sargent. Pediatric Academic Societies, Vancouver, May 4th, 2014.
195. "Striking at the Root Causes of Chronic Disease in Children" (Moderator). James Sargent, Joel Bakan and David Kessler, May 5th, 2014.
196. "Little Things Matter: The Impact of Toxins on the Developing Brain" (Keynote). OHKA Healthy Homes Alliance, Omaha, Nebraska, May 15th, 2014.
197. "Excavating environmental risk factors for autism: Suspects and strategies". A workshop on examining a multi-systems approach to autism and the environment: challenges and opportunities for research". Toronto, Ontario, June 23rd-24th, 2014.
198. "Lead Poisoning: Tackling a Global Problem" (Co-Moderator and Speaker). International Society for Environmental Epidemiology, Seattle, Washington, August 25th, 2014.
199. "Interventions to Reduce Exposures to Environmental Hazards in Pregnant Women and Children", (Moderator and Speaker). International Society for Environmental Epidemiology, Seattle, Washington, August 25th, 2014.
200. 3rd Annual ISCHE-Sponsored Debate: Should there be any restrictions on universities or academicians receiving payment from industry or other sources? (Moderator). International Society for Environmental Epidemiology, Seattle, Washington, August 25th, 2014.
201. "Crime of the Century: Our Failure to Prevent the Lead Pandemic", Tulane University School of Public Health and Tropical Medicine, New Orleans, Louisiana, September 5th, 2014.
202. "Environment Matters", Children's Environmental Health Panel. Society for Environmental Journalists, New Orleans, Louisiana, September 6th, 2014.
203. "Insidious Influence of Industry on Science: How Corporations Undermine Science", 5th Annual C. Everett Koop Distinguished Lecture, "Corporate Threats to Children's Health", with Joel Bakan and James Sargent, Dartmouth University, New Hampshire, October 6th, 2014.
204. "Crime of the Century: Our Failure to Prevent the Lead Pandemic", John Rosen Memorial Lecture, Montefiore Medical Center, New York, New York, October 8th, 2014.

205. "Little Things Matter: The Impact of Toxins on the Developing Brain" (Keynote). Prenatal Environmental Health Education (PEHE) Conference, University of Ottawa. Ottawa, Ontario, November 21st, 2014.
206. "Little Things Matter: The Impact of Toxins on the Developing Brain" (Keynote). ISEE Asian Regional Meeting, Shanghai, China, November 30th, 2014.
207. "Crime of the Century: Our Failure to Prevent the Lead Pandemic", John Rosen Memorial Lecture, ISEE Asian Regional Meeting, Shanghai, China, November 31st, 2014.
208. "Data Visualization", with Joe Braun and Allan Just, Pediatric Environmental Health Scholars Retreat, Reston, VA, December 6th, 2014.
209. "Victories in Public Health: Progress or Adaptation?" SFU, UBC and UW Annual Occupational and Environmental Health Conference, Semiahmoo, WA January 8th, 2015.
210. "Food in the Industrial Era: Is Backward the Way Forward?" Children's Environmental Health Network, Austin, Texas, February 4th, 2015.
211. "Excavating the enigmas of childhood lead toxicity". Broken Hill City Council and Lead Reference Group, Broken Hill, New South Wales, Australia, March 3rd, 2015.
212. "Prevention Paradox: Why a Little Lead is Too Much". Unequal Exposure Symposium, Climate Change Research Center, University of New South Wales, March 5th, 2015, Sydney, Australia.
213. "Crime of the Century: Our Failure to Prevent the Lead Pandemic". 10th Annual Break the Cycle Conference, Emory University, Atlanta, Georgia. April 23rd, 2015.
214. "The Staggering Cost of Lead Toxicity and the Unbelievable Benefit of Preventing It". 10th Annual Break the Cycle Conference, Emory University, Atlanta, Georgia. April 24th, 2015.
215. Seventh Annual Controversies in Pediatric Environmental Health Debate, "GMOs: A Hazard or Harvest of Health?" A debate with Joel Forman, MD and Daniel Goldstein, MD, (Bruce Lanphear, Moderator and Organizer). Pediatric Academic Societies Meeting, San Diego, California, April 27th, 2015.
216. "Impact of Dwellings on Child Health", Canadian Green Building Council Conference, Vancouver Convention Center, Vancouver, BC, April 28. 2015.
217. "Impact of Tobacco on the Developing Brain", Developmental Effects of Nicotine and Implications for Emerging Tobacco Products, Rockville, Maryland, May 5th, 2015.
218. "Impact of Toxins on the Developing Brain" India Tour (Bengaluru, Trivandrum, Kolkata, and Chandigarh) Sponsored by PAN-India, September 4th-11th, 2015.
219. "Impact of Dwellings on Child Health", Green School Summit, Calgary, Alberta, September 25th. 2015.

220. "Prevention Paradox: Why a Little Lead is Too Much", A debate with George Rhoads, Montefiore Medical Center, Tarrytown, October 2nd, 2015.
221. "Crime of the Century: Our Failure to Prevent the Lead Pandemic" (Keynote Presentation), University of Cincinnati Department of Environmental Health 50th Anniversary Gala, Cincinnati, Ohio, October 9th, 2015.
222. "Impact of Toxins on the Developing Brain" (Keynote Presentation) Children's Environmental Health Centers Annual Meeting, Washington, DC, October 31, 2015.
223. "The Impact of Toxins on the Developing Brain: Our Failure to Prevent Brain-based Disorders in Children", National Core for Neuroethics, UBC November 12th, 2015.
224. "Impact of Dwellings on Child Health", Canada Green Building Council, Toronto, ON Green, December 1st, 2015.
225. "The Tortuous Road to Prevention: Are We There Yet", Air Quality and Impacts on Health: Beyond the Heart and the Lungs, The Lung Association of BC, February 28th, 2016.
226. "Lead's Long Shadow: What the Story of Flint, Michigan Means for All of Us", with Bruce Lanphear, Mona Hanna-Attisha and Marc Edwards. Collaborative on Health and the Environment Webinar, March 8th, 2016.
227. "Little Things Matter: The Impact of Toxins on the Developing Brain", Collaborative on Health and Environmental Alaska Working Group Webinar, March 9th, 2016.
228. "Victories in Public Health: Progress or Adaptation?", Symposium Against Indifference, Ashland University, Ashland, Ohio, April 5th, 2016.
229. "Little Things Matter: The Impact of Toxins on the Developing Brain" (Keynote), Children's Environmental Health: New Findings from California Research, Sacramento, California, April 7th, 2016.
230. "Crime of the Century: Our Failure to Prevent the Lead Pandemic", Distinguished Visiting Professor in Health Law, Loyola University, Chicago, Illinois April 21st, 2016.
231. "The Population Impact of Toxins on Intellectual Abilities: Implications for Policy and Prevention", in Symposia on Environmental Toxins and the Brain: Growing Evidence of Risk, Pediatric Academic Societies, Baltimore, MD, May 2nd, 2016.
232. "Data Visualization and Video Production for Public Consumption", in Symposia on Innovative Tools to Enhance Knowledge Translation of Environmental Health: Data Visualization, Videos and Message Mapping, (co-Moderated by Mark Miller and Bruce Lanphear), Pediatric Academic Societies, Baltimore, MD, April 30th, 2016.
233. "Crime of the Century: Our Failure to Prevent the Lead Epidemic", Michigan State University, Flint, MI, May 7th, 2016.

234. "Crime of the Century: Our Failure to Prevent the Lead Epidemic", Johns Hopkins University School of Public Health, Baltimore, MD, May 7th, 2016.
235. "Little Things Matter: The Impact of Toxins on the Developing Brain", Baltimore, MD, International Medical Federation Autism Research (IMFAR), May 8th, 2016.
236. "Public Health Matters: Videos on Toxic Chemicals, Air Pollutants and the Prevention Paradox", Mongolian National University of Medical Sciences, June 23, 2016.
237. "Little Things Matter: The Impact of Toxins on the Developing Brain", USC Annenberg Center for Health Journalism, July 18th, 2016.
238. "Preventing Lead Toxicity", California Environmental Protection Agency, Occupational Environmental Health Hazard Assessment, September 23rd, 2016.
239. "Unleashing the Power of Prevention: Creating Video to Re-Imagine our Approach to Disease," World Issues Forum, Fairhaven College, University of Western Washington, (with Bob Lanphear), November 2, 2016.
240. "Little Things Matter: The Impact of Toxic Chemicals on the Developing Brain", Pediatric Grand Rounds, Maimonides Hospital, November 15th, 2016.
241. "Little Things Matter: The Impact of Toxic Chemicals on the Child Health" (Keynote), Hudson Valley Perinatal Conference, November 16th, 2016.
242. "Little Things Matter: The Impact of Toxins on the Developing Brain", IPEN, San Francisco, CA, November 18th, 2016.
243. "Unleashing the Power of Prevention: Creating Video to Re-Imagine our Approach to Disease", SFU, UBC and UW Annual Occupational and Environmental Health Conference Semiahmoo, WA, January 5th, 2017.
244. "Unleashing the Power of Prevention: Creating Video to Re-Imagine our Approach to Disease", University of New Brunswick, January 25th, 2017.
245. "Little Things Matter: The Impact of Toxic Chemicals on the Developing Brain", New Brunswick Children's Environmental Health Collaborative, January 26th, 2017.
246. "Unleashing the Power of Prevention: Creating Video to Re-Imagine our Approach to Disease", Rockefeller Center, Bellagio, Italy, February 22nd, 2017.
247. "Little Things Matter: The Impact of Toxic Chemicals on the Developing Brain", The Science in Society Speaker Series, Okanagan College, Vernon, BC, April 6th, 2017.
248. "Little Things Matter: The Impact of Toxic Chemicals on the Developing Brain" (invited plenary), Vancouver, British Columbia, Canadian Pediatric Society, June 3rd, 2017.
249. "Unleashing the Power of Prevention: Creating Video to Re-Imagine our Approach to Disease", Macquarie University, Sydney, Australia, September 29th, 2017.

250. "Unleashing the Power of Prevention: Creating Video to Re-Imagine our Approach to Disease", Brown University, Providence, Rhode Island, October 13th, 2017.
251. Cause or Cure: Does the Relentless Pursuit of a Cure Endanger our Health? University of Alaska, Alaska Tribal Health Consortium, Anchorage, Alaska, November 2nd, 2017.
252. "Little Things Matter: The Impact of Toxic Chemicals on the Developing Brain" (Keynote), All Alaska Pediatric Conference, Anchorage, Alaska, November 3rd, 2017.
253. "Little Things Matter: The Impact of Toxic Chemicals on the Developing Brain", CINBIOSE 30th Anniversary, University of Quebec at Montreal, Montreal, November 9th, -10th, 2017.
254. "The Legacy of Lead Poisoning: Moving towards Prevention". East Chicago Community Meeting, Illinois, November 26th, 2017.
255. "Cause or Cure", NIEHS Environmental Health Seminar, University of Southern California, Los Angeles, California, December 1st, 2017.
256. "Little Things Matter: The Impact of Lead on Brain Development" (Keynote Presentation), Workshop on Lead-Free Schools, Pew Trust, Washington, DC, December 6th-7th, 2017.
257. "Low-level Toxicity of Chemicals: No Acceptable Threshold?" Risk Modeling, Mitigation and Modeling in Health Sciences, Centre de Recherches Mathematiques, Montreal, QC, December 11th, 2017.
258. "Little Things Matter: The Impact of Toxic Chemicals on the Developing Brain", Department of Psychology and Neuroscience, York University, Toronto, ON, December 13th, 2017.
259. "The impact of Pollutants on Human Health: No Safe Levels?", Center for Energy and Environmental Contaminants, Macquarie University, Sydney, Australia, February 13th, 2018.
260. "Cause or Cure: Does the Relentless Pursuit of a Cure Endanger our Children's Health?", Department of Pediatrics, University of Wisconsin at Madison School of Medicine, Madison, Wisconsin, March 1st, 2018.
261. "Little Things Matter: The Impact of Toxic Chemicals on the Developing Brain", Wisconsin Environmental Health Network, Madison, Wisconsin, March 2nd, 2018.
262. "Little Things Matter: The Impact of Toxic Chemicals on the Developing Brain", Biennial Atlantic Symposium on Learning Disabilities Association, Fredericton, NB.
263. "Crime of the Century: The Failure to Prevent the Lead Pandemic" (Keynote). 11th UK and Ireland Environmental and Occupational Epidemiology, John Snow Lecture Hall, London School of Hygiene and Tropical Medicine, April 27th, 2018.
264. "The Impact of Pollutants on Human Health: No Safe Levels?" From Toxicology to Planetary Health, London School of Hygiene and Tropical Medicine, April 27th, 2018.

265. Topic Symposium: “Toxic Chemicals and the Rise of Chronic Disease in Childhood: A Preventable Epidemic?” (chair and speaker), Pediatric Academic Societies, May 7th, 2018.
266. “Prevention Paradox; Why a Little Lead is Too Much”, Ontario Water Advisory, Toronto, CA, May 7th, 2018.
267. “How the Secrets of Body Care and Cleaning Products Impact your Health”, Panel with Bruce Lanphear, Muhannad Malas and Janie McConnell, Centre for Free Expression, Ryerson University, Toronto, ON, May 7th, 2018.
268. “Prevention Paradox; Why a Little Lead is Too Much” (Keynote), Pittsburgh, PA, Get the Lead Out Conference, May 9th, 2018.
269. “Low-level Lead Exposure and Mortality”, Global Health Forum, Miami, Fl, May 23rd, 2018.
270. “Unleashing the Power of Prevention: Targeting Toxic Chemicals and Pollutants”, Canadian Public Health Association, Montreal, QC, May 28th, 2018.
271. “The Impact of Pollutants on Human Health: No Safe Levels?” Chemicals Management Plan Stakeholder Advisory Council, Health Canada, May 30th, 2018.
272. “Little Things Matter: The Impact of Toxic Chemicals on the Developing Brain”, Pediatric Grand Rounds, University of California – Davis, Sacramento, CA, June 8th, 2018.
273. “Why a Little Lead is Too Much”, Health Canada, Ottawa, ON, August 29th, 2018.
274. “Unleashing the Power of Prevention: Mobilizing Science to Prevent Disease”, ISEE-ISES Workshop, Ottawa, ON, August 30th, 2018.
275. “The Lingering Legacy of Lead: Why a Little Lead is Too Much”, LA Lead Summit: A Strategy for Prevention, University of Southern California, September 14th, Los Angeles, CA.
276. “Little Things Matter: The Impact of Toxic Chemicals on the Developing Brain”, Children’s Hospital of Orange County, Orange County, CA, September 19th, 2018.
277. “The Lingering Legacy of Lead: Why a Little Lead is Too Much”, Hurley Medical Center, Flint, Michigan, October 3rd, 2018.
278. “Lead and The Mysterious Decline in Coronary Heart Disease”, National Institute of Occupational Safety and Health, Cincinnati, OH, October 11, 2018.
279. “Little Things Matter: The Impact of Toxic Chemicals on the Developing Brain”, Grand Rounds, Oregon State Health University, Portland, OR, October 23, 2018.
280. “The Impact of Pollutants on Human Health: No Safe Levels?” Oregon Environmental Council, Portland, OR, October 23, 2018.
281. “Little Things Matter: The Impact of Toxic Chemicals and Organic Food on Children’s Health”, HIPP Scientific Symposium on Organic Food, Kranzberg, Germany, October 30, 2018.

282. "The Mysterious Decline in Coronary Heart Disease", Harvard University Lead Summit, Cambridge, MA, November 15th, 2018.
283. "The Impact of Pollutants on Human Health: No Safe Levels?" Department of Epidemiology, UMass, Amherst, MA, November 16th, 2018.
284. "Little Things Matter: The Impact of Toxic Chemicals on Human Health", School of Public Health, Oregon State University, Corvallis, Oregon, April 12th, 2019.
285. Why A Little Lead is Too Much: An Intimate History", "The Impact of Pollutants on Human Health: No Safe Levels?", Graduate Course in Environmental Health, School of Public Health, University of California, Berkeley, April 17th, 2019.
286. "The Impact of Pollutants on Human Health: No Safe Levels?", Department of Environmental Health, School of Public Health, University of California, Berkeley, April 17th, 2019.

Grants

Active Grant Awards

1. Consultant (Joseph Braun, PI). Early Life Perfluoroalkyl Substance Exposure and Obesity: Mechanisms and Phenotyping. 02/01/2016-01/31/2021. National Institutes of Health, $523,725 (5% effort). The purpose of this award is to study the impact of exposure to perfluoroalkyl chemicals on the development of child obesity, adverse cardiometabolic markers and gene regulation. (2.5% effort)
2. Co-Applicant (Linda Booij, Maryse Bouchard PI). In utero exposure to Bisphenol-A and the developing brain in humans: A longitudinal study of epigenetic mechanisms. 03/01-2016 – 03/31/2019. Canadian Institutes of Health Research (CIHR), $344,025. (2.5% effort).
3. Principal Investigator (Multiple PI Award with Christine Till). "Impact of early life fluoride exposure on cognitive and behavioural outcomes in children". NIEHS, 09/30/16 – 05/01/19, $296,683 (10% effort).
4. Consultant (Aimin Chen, Principal Investigator). Developmental neurotoxicity of organophosphate and novel brominated flame retardants in children. National Institute for Environmental Health Sciences. 1RO1ES028277. 09/30/2017-06/30/22 (10% effort).
5. Mentor (Cynthia Curl, Principal Investigator). Measurement of Agricultural and Dietary Glyphosate Exposure among Pregnant Women. National Institutes of Environmental Health Sciences. 1KO1ES028745-01A1. 09/01/2018-08/31/2022 (5% effort).

Past Grant Awards

1. Principal Investigator, "Dust-Lead and Blood Lead Levels among Urban Children". The National Center for Lead-Safe Housing, $561,619, 06/15/93 to 08/31/94. Department of Housing and Urban Development Contract MDLPT0001-93. (25% effort).
2. Principal Investigator, "Determinants of Lead Exposure among Children in Monroe County, NY", NIEHS Pilot Grant, University of Rochester School of Medicine and Dentistry, Department of Environmental Medicine. $7,600, 06/15/93 to 12/31/95. (0% effort)
3. Principal Investigator, "The Effectiveness of Dust Control in Reducing Children's Blood Lead Levels" U.S. Department of Housing and Urban Development, $128,394, 04/01/94 to 05/30/95. (25% effort).
4. Principal Investigator, "Primary Prevention of Exposure to Lead". Centers for Disease Control and Prevention, $832,228, 09/30/94 to 10/01/98. (25% effort)
5. Principal Investigator, "Lead-Contaminated House Dust and Children's Blood Lead Levels". National Center for Lead-Safe Housing, $43,260, 10/01/96 to 03/30/96. (25% effort).
6. Co-investigator (Christy, PI), “Tuberculosis Screening in Children”. New York Department of Health, $15,000, 01/01/95 to 12/31/96. (0% effort)
7. Co-investigator (Weitzman, PI), “Fellowship Training in General Pediatrics” (Grant # D28PE50008). Bureau of Health Professions, HRSA, U.S. Public Health Service, $1,752,816, 06/01/96 to 05/30/97. (10% effort).
8. Principal Investigator, “Neurobehavioral Effects of Low-Level Childhood Lead Exposure”. University of Rochester School of Medicine & Dentistry, $8,560, 06/01/96 to 05/30/97. (0% effort)
9. Principal Investigator, “Neurobehavioral Effects of low-level Lead Exposure in Children”. NIEHS Pilot Grant, University of Rochester Department of Environmental Medicine, $20,035, 09/01/97 to 08/30/97. (0% effort).
10. Co-investigator (Howard, PI), “Effect on Breastfeeding of Pacifiers and Bottle Feeding”. Bureau of Maternal and Child Health, $420,333, 10/01/96 to 09/30/00. (2.5% effort)
11. Co-investigator (Canfield, PI) “Lead and Children’s Cognitive Functioning”, Research Grants Program, Cornell University. $17,000, 10/01/96 to 09/31/97 (0% effort).

12. Principal Investigator, “Neurobehavioral Effects of Low-Level Lead Exposure in Children” (RO1-ES 08338). National Institute of Environmental Health Sciences, 12/01/96 to 11/31/01, $1,946,848. (25% effort).
13. Co-investigator, (Aligne, PI). “Reduction in Passive Smoking among Children with Asthma: A Randomized Trial of HEPA Air Filtration.” 10/01/96 to 09/31/97, $6,000. KIDD Grant, Rochester General Hospital (0% effort).
14. Co-investigator, (DeWitt, PI). “Faculty Development in General Pediatrics”. Bureau of Health Professions, Health, Department of Health and Human Services 07/01/97 to 06/30/00, $338,000. (15% effort).
15. Principal Investigator, “A Side-by-Side Comparison of Allergen Sampling Methods”, U.S. Department of Housing and Urban Development, 01/02/98 to 12/31/98, $163,065. (15% effort).
16. Principal Investigator, “National Research Service Award - Fellowship Training in General Pediatrics and Adolescent Medicine” (1T32PE10027), Health Resources and Services Administration, DHHS. 07/01/98 to 06/30/03. $634,408. (0% effort).
17. Co-investigator, (Steiner, PI) “Survey of Directors and Graduates of NRSA Fellowship Training Programs”, Health Resources and Services Administration, Department of Health and Human Services. 06/01/98 to 06/30/99.
18. Principal Investigator, “Effect of Soil Remediation on Children’s Blood Lead Levels in Midvale, Utah”. U.S. Environmental Protection Agency, 08/01/98 to 07/30/99. $62,550. (15% effort).
19. Co-investigator, (Phelan, PI) Trends and Patterns in Playground Injuries among U.S. Children.” Ambulatory Pediatric Association, 05/05/99 to 05/04/00. $9,000 (0% effort).
20. Principal Investigator, “Risk Assessment for Residential Lead Hazards”. U.S. Department of Housing and Urban Development, 09/01/99 to 08/30/00. $102,435. (25% effort).
21. Principal Investigator, “Residential Exposures associated with Asthma in U.S. Children and Adolescents” U.S. Department of Housing and Urban Development, 07/16/99 to 03/15/00. $30,400. (20% effort).
22. Principal Investigator, “Effectiveness of Lead Hazard Control Interventions – A Systematic Review" National Center for Lead-Safe Housing, 10/01/99 to 06/01/00. $22,500 (10% effort).
23. Principal Investigator, “Racial Disparity in Blood Lead Levels due to Genetic Variation in Calcium Absorption”. NIEHS Pilot Grant, Center for Environmental Genetics, University of Cincinnati, 04/01/00 to 03/31/01. $28,130 (0% effort).
24. Principal Investigator, “International Pooled Analysis of Prospective, Lead-Exposed Cohorts”. National Institute of Environmental Health Sciences, National Institutes of Health, 08/15/00 to 09/14/01, $16,000. (2.5% effort).

25. Principal Investigator, “A Randomized Trial to Reduce ETS in Children with Asthma” (RO1-HL/ES65731). National Heart, Lung and Blood Institute, National Institutes of Health, 09/29/00 to 09/28/04, $1,546,848. (25% effort).
26. Co-investigator, (Geraghty, PI) “Breastfeeding Practices of Mothers of Multiples”. Ambulatory Pediatric Association, 05/01/01 to 04/30/02. $5,000 (0% effort).
27. Principal Investigator (Subcontract), “A Longitudinal Study of Lead Exposure and Dental Caries”. National Institute of Dental and Craniofacial Research, National Institutes of Health, 08/01/01 to 07/30/04. $300,000 (10% effort).
28. Co-investigator (Phelan, PI), “Fatal and Non-Fatal Residential Injuries in U.S. Children and Adolescents” U.S. Department of Housing and Urban Development, 03/01/01 to 11/31/01. $40,700. (5% effort).
29. Principal Investigator, “Prevalent Neurotoxicants in Children” (PO1-ES11261). National Institute for Environmental Health Sciences and U.S. Environmental Protection Agency, 09/01/01 to 09/31/06, $5,000,000. (30% effort).
30. Principal Investigator, “International Pooled Analysis of Lead-Exposed Cohorts”. Centers for Disease Control (RO1/CCR 521049). Centers for Disease Control, 09/15/01 to 09/14/02, $28,473. (3% effort).
31. Principal Investigator, supplement to “Prevalent Neurotoxicants in Children” (PO1-ES11261). NIEHS, 09/01/02 to 09/31/07, $1,800,000. (10% effort).
32. Co-Investigator, “ADHD Phenotype Network: Animal Model to Clinical Trial”. National Institute of Neurologic Diseases, 09/15/02 to 06/30/05 (15% effort).
33. Principal Investigator, “Linkage of ADHD and Lead Exposure”, Springfield, Ohio Department of Health, 02/01/03 to 06/01/04, $25,000. (0% effort).
34. Co-investigator (Yolton, PI) “Explorations of ETS Exposure on Child Behavior and Sleep” NIEHS, 04/01/04 to 03/30/06, $300,000. (5% effort).
35. Co-investigator (Haynes, PI) “MRI as a Biomarker of Manganese Exposure”. NIEHS, 09/01/04 to 08/30/06, $300,000. (5% effort).
36. Co-investigator (National Center for Healthy Housing, PI) “Development of a Standardized Housing Assessment for Asthma”, U.S. Department of Housing and Urban Development, 11/01/05 to10/31/07, $50,000. (5% effort).
37. Co-Investigator (Hershey, PI) “Epithelial Genes in Allergic Inflammation” National Institutes of Allergy and Infectious Diseases”, 07/01/06 to 06/30/07, $4,787.541. (3% effort).

38. Co-Investigator and Mentor (Wilson, PI), “Racial Difference in DNA Adducts in Tobacco-Exposed Children”. Dean’s Scholar Award, University of Cincinnati, 02/22/06 to 01/21/09, $150,000 (5% effort).
39. Principal Investigator, “National Research Service Award - Fellowship Training in Primary Care Research,” (1T32PE10027), Health Resources and Services Administration, DHHS. 07/01/98 to 06/30/08. $1,600,000. (0% effort).
40. Co-Investigator and Mentor (Kahn, PI). “Childhood Asthma in an Era of Genomics: Will the Generalist’s Role be Recast?“ Robert Wood Johnson Generalist Physician Faculty Scholars Program” 06/01/04 to 05/30/08, $300,000.
41. Co-Investigator and Mentor (Spanier, PI), “Exhaled Nitric Oxide to Manage Childhood Asthma”. National Heart, Lung and Blood Institute, 07/01/06 to 06/31/08, $200,000 (10% effort).
42. Co-investigator (Sub-Contract PI), BYPL Vanguard Center (Specker, Principal Investigator), “National Children’s Study”, National Institute for Child Health and Development, 11/01/05 to 10/31/10, $500,000. (20% effort). [Relinquished with relocation to SFU].
43. Associate Director and Co-Investigator, (Ho, PI). “Center for Environmental Genetics,” NIEHS, 04/01/08 to 3/31/13, $1,000,000 (10% effort). [Relinquished with relocation to SFU.]
44. Co-Investigator (Yolton, PI). “Tobacco Smoke and Early Human Behavior”. Clinical Innovator Award, Flight Attendant Medical Research Institute”, 07/01/07 to 06/30/10, $300,000. (3% effort).
45. Co-Investigator (Spanier, PI). “Low Level Prenatal Tobacco Exposure and Infant Wheeze.” Young Clinical Scientist Award, Flight Attendant Medical Research Institute, 07/01/07 to 06/30/12, $300,000. (5% effort).
46. Co-Investigator and Mentor (Spanier, PI). K23, “Prenatal Low Level Tobacco & Phthalate Exposure and Childhood Respiratory Health”. National Institute for Environmental Health Sciences, 12/1/07 to 11/30/12, $623,679 (0% funded effort).
47. Co-investigator (Yolton, PI). “Neurobehavioral effects of insecticide exposure in pregnancy and early childhood.” NIEHS, 09/01/09 to 08/31/12.
48. Principal Investigator (Bruce Lanphear, PI), “A Community-Based Trial to Prevent Lead Poisoning and Injuries,” National Institute for Environmental Health Sciences, 04/01/07 to 03/30/13, $2,000,000. (25% effort).
49. Co-Investigator (Kim N. Dietrich, PI). “Early Lead Exposure, ADHD & Persistent Criminality: Role of Genes & Environment,” National Institute for Environmental Health Sciences, 04/01/07 to 3/31/2013, $1,250,000. (2.5% funded effort).

50. Co-Investigator and Sub-Contract PI (Brenda Eskenazi, PI). This supplemental award was to conduct a pooled analysis of prenatal organophosphate pesticide exposures with birth outcomes and neurodevelopment in children using 4 US birth cohorts. NIEHS, 09/01/2009 to 08/31/2013, $96,000 (0% effort).
51. Mentor and Supervisor (Glenys Webster, PI). Michael Smith Foundation for Health Research Postdoctoral Training Award, 03/01/12 to 02/28/15, $134,500 (5% effort).
52. Co-Principal Investigator (Tye Arbuckle, PI). Maternal-Infant Research on Environmental Chemicals: Effects on Child Development (MIREC-CD). 06/26/11 to /5/25/14, Health Canada Chemical Management Program, $283,000 (10% effort).
53. Co-Investigator (Patti Dods and Amanda Wheeler, co-PIs). Phthalate Exposure and the development of asthma in the CHILD Study. 06/01/11 to 05/30/14, Health Canada Chemical Management Program, $204,000 (5% effort). Consultant (Stephanie Engel, PI). A pooled investigation of prenatal phthalate exposure and childhood obesity. 11/01/2012 – 10/31/15, NIEHS. $275,000. (5% effort).
54. Co-Investigator (Ryan Allen, PI). A randomized air filter intervention study of air pollution and fetal growth in a highly polluted community. 06/08/2012 – 05/30/15, CIHR $348,000 (10% effort).
55. Co-Investigator (William Fraser and Tye Arbuckle, co-PIs). MIREC-CD Biomonitoring Study in Vancouver. 09/01/2013 – 08/30/2014. Health Canada, $120,138 (10% effort).
56. Principal Investigator. Knowledge translation tools for capacity building for an online Canadian Environmental Health Atlas. 03/01/12 – 02/28/13, Canadian Institutes of Health Research, $98,974 (10% effort).
57. Principal Investigator (with Lawrence McCandless). Prenatal exposure to environmental contaminants and fetal growth: How to account for multiplicity when testing multiple statistical hypotheses?. 07/01/2015-06/30/2016. Canadian Institutes of Health Research (CIHR), $12,000 (5% effort).
58. Principal Investigator, Canadian Environmental Health Atlas Knowledge Translation to produce videos and interactive tools. 06/01/2015-07/30/2016. Canadian Internet Registration Authority, $50,000 (10% effort).
59. Co-Investigator (Kieran Phelan, PI). “Injury Prevention in a Home Visitation Population”. NICHD, 09/28/10 to 07/31/16, $2,000,000 (total direct costs over 5 years) (10% effort).
60. Co-applicant (Timothy F. Oberlander, PI). Developmental origins of autism: A population level linked data study of prenatal antidepressant medication exposure. 09/01/2013 – 09/31/2016, Canadian Institutes of Health Research (CIHR), $285,768.

61. Principal Investigator (Multiple PI Award with Aimin Chen and Kimberly Yolton). "Longitudinal study of exposures to PBDEs and PFCs and child behavior". NIEHS, 04/30/11 – 05/01/17, $2,150,000 (total direct costs over 5 years) (20% effort).
62. Principal Applicants (McCandless and Lanphear). Biostatistical methods for estimating the cumulative impact of environmental contaminant exposures on preterm birth. Canadian Institute for Human Development, Child and Youth Health. 12/06/16-12/05/18, $200,000 (10% effort).
63. Co-investigator (Ryan Allen, PI). Randomized Interventions to Evaluate the Effects of Air Pollution Exposure on Children's Health and Development. 03/01/2015 – 03/31/2019, Canadian Institutes of Health Research (CIHR), $720,535. (10% effort)
64. Co-investigator (Joseph Braun, PI). Endocrine Disrupting Chemicals, Thyroid Hormones and Child Neurobehavior. 06/01/2015-03/31/2019. National Institutes of Health, $471,241 (5% effort). The purpose of this study is test if and when early life exposures to phthalates, triclosan, or bisphenol A adversely impacts children's cognition and behavior.
65.

Ethics Training for Research

CITI (Collaborative Institutional Training Initiative) (Reference# 7159023). Academic and Regional Health Centers Curriculum Course, completed on December 16th, 2011.

CITI (Collaborative Institutional Training Initiative) (Reference# 7160515), Canada GCP Curriculum Course, completed on December 16th, 2011.

CITI (Collaborative Institutional Training Initiative) (Reference# 8316270), Human Subjects Core Curriculum, completed on August 17th, 2012.

CITI (Collaborative Institutional Training Initiative) (Reference# 13561457), Academic and Regional Health Centers Core Curriculum, completed on September 1st, 2014.

CITI (Collaborative Institutional Training Initiative) (Reference# 16954900), Human Subjects Research Core Curriculum, completed on October 31st, 2015.

Expert Declaration

of

Kathleen M. Thiessen, Ph.D.

May 20, 2020

Food & Water Watch et al. v. Environmental Protection Agency
No. 17-cv—02162

Oak Ridge Center for Risk Analysis, Inc.
102 Donner Drive
Oak Ridge, TN 37830

OAK RIDGE
CENTER for RISK ANALYSIS

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I, Kathleen Thiessen Ph.D., declare that:

1. I am a risk assessment scientist at Oak Ridge Center for Risk Analysis in Oak Ridge, Tennessee. For more than 30 years, I have been involved in the evaluation of exposures, doses, and risks to human health from trace levels of contaminants in the environment, including fluoride, and in the use of uncertainty analysis for environmental and health risk assessment.

2. I was asked to apply risk assessment frameworks used by the Environmental Protection Agency (EPA) to the current scientific literature on fluoride neurotoxicity to determine whether neurotoxicity is a hazard of fluoride exposure, and whether this hazard is a risk at the levels of fluoride added to drinking water for fluoridation (0.7 mg/L).

I. SUMMARY OF QUALIFICATIONS

3. A complete summary of my qualifications and publications can be found in my Curriculum Vitae, which has been marked as Plaintiffs' Exhibit 7 and attached herein.

4. In the course of my work as a risk assessment scientist, I have done work for the U.S. Environmental Protection Agency (EPA), the U.S. Department of Energy, the Centers for Disease Control and Prevention, the U.S. Nuclear Regulatory Commission, the National Cancer Institute, and the National Institute for Occupational Safety and Health, as well as a number of other government and private clients.

5. I have authored several reports for the EPA on the health effects of specific environmental contaminants, including Health Issue Assessments of fluorides (hydrogen fluoride and related compounds) and mercuric chloride.

6. More recently, I served on two subcommittees of the National Research Council, one which was asked by EPA to review the toxicologic literature on fluoride (which resulted in the 2006 publication *Fluoride in Drinking Water: A Scientific Review of EPA's Standards*), and one

dealing with guidance levels for air contaminants in submarines. For the latter review, published in 2009, the NRC asked me to write much of the chapter on hydrogen fluoride.

7. Recently, I led the Working Group on Assessment of Exposures and Countermeasures in Urban Environments for the International Atomic Energy Agency's (IAEA) program on Development, Testing and Harmonization of Models and Data for Radiological Impact Assessment. I was also involved in the preparation of an IAEA guidance document on implementation of remediation strategies following accidental releases of radioactivity.

8. Throughout my career, I have authored or contributed to a number of open literature publications in peer-reviewed journals such as *Environmental Science and Technology*, *Environmental Pollution, Atmospheric Environment, Journal of Environmental Radioactivity*, and the *International Journal of Occupational and Environmental Health*. I have also served as a peer reviewer for journals such as *American Journal of Preventive Medicine*, *Environment International*, *Environmental Pollution*, *Risk Analysis*, *Science of the Total Environment*, *Environmental Health Perspectives*, and *Journal of Environmental Radioactivity*, among others.

II. SUMMARY OF OPINIONS

9. Under EPA's *Guidelines for Neurotoxicity Risk Assessment*, there is sufficient evidence to conclude that neurotoxicity is a hazard of fluoride exposure.

10. The animal data on fluoride neurotoxicity are consistent with the epidemiological data in showing a risk of cognitive deficits at doses of fluoride ingested from fluoridated water.

11. Fluoridation chemicals present an "unreasonable risk" of neurotoxic effects, including IQ loss, if assessed under the same risk characterization and risk determination framework that EPA uses in its evaluations of other chemicals under TSCA.

III. SUMMARY OF METHODOLOGY

A. Risk Assessment

12. EPA has stated it "will follow" its *Guidelines on Neurotoxicity Risk Assessment* (hereafter, *Guidelines*) when "evaluating data on potential neurotoxicity associated with exposure to environmental toxicants."[1] I conducted a risk assessment in accordance with these *Guidelines*, including a Hazard Characterization, Quantitative Dose Response Analysis, Exposure Assessment, and Risk Characterization.

13. Hazard Characterization: Pursuant to the *Guidelines*, I conducted a Hazard Characterization, in which I considered: (1) the animal studies on neuroanatomical, neurochemical, and behavioral effects, including effects on learning and memory; (2) human case reports, including clinician observations of occupationally exposed workers; (3) human epidemiology studies of fluoride and cognitive deficits, including all prospective cohort studies; (4) the literature on fluoride's neuroendocrine effects; (5) animal and human research on possible modes of action (direct and indirect) by which fluoride affects the brain; (6) dose-response data on fluoride and neurotoxic outcomes in animal and epidemiological studies; (7) the toxicokinetics of fluoride, including data on placental transfer and uptake into the brain; and (8) *in vitro* studies investigating fluoride's effects on brain cells, including several that used low concentrations.

14. Quantitative Dose Response Analysis: Since the literature demonstrates with high confidence that neurotoxicity is a hazard of fluoride exposure, I turned to the second step of an EPA neurotoxicity risk assessment: Quantitative Dose Response. In a quantitative dose-response analysis, a "Point of Departure" (POD) is identified from the available animal and human data in order to derive a dose that will be without appreciable risk (i.e., a Reference Dose, or RfD). For

[1] EPA (1998a), p. 1.

my analysis, I focused on the animal data, as I understood that Dr. Grandjean had already calculated a POD (i.e., BMDL) from the human birth cohort data.

15. To increase confidence in the risk characterization (a later step in the analysis, discussed below), I did not identify just one POD from the animal data. Instead, I identified the full range of PODs that can be justified, including the *least protective*. After converting these PODs into Human Equivalent Doses (HED), I applied different combinations of uncertainty factors (from non-conservative to conservative) to derive the *full range of reference doses that can be justified from the animal literature.*

16. Exposure Assessment: Consistent with the *Guidelines*, I conducted an Exposure Assessment that focused solely on the condition of use at issue in this case: fluoridation of drinking water. For my initial assessment, I relied primarily, but not solely, on the National Research Council's estimates of fluoride intake from water from the 2006 report. In response to criticisms that NRC's data may no longer be representative of contemporary exposures, I considered EPA's 2019 assessment of water intake data, in which the Agency identified the most scientifically sound and up-to-date data to use for risk assessment. I compared these updated values from EPA with the values I initially used to see if they have any material effect on my risk estimates (they did not).

17. Risk Characterization: Consistent with the *Guidelines*, I integrated the information on hazards and exposures in a risk characterization by, among other things, conducting a "Margin of Exposure" analysis for each of the PODs identified through the Quantitative Dose Response analysis.

18. Risk Determination: For the risk determination, I considered the risk-related factors that EPA has identified as relevant for risk determinations under TSCA. At the time of my initial report, EPA had not yet issued any draft risk evaluations under Section 6 of TSCA, so I relied for

guidance on risk evaluations that EPA had completed under Section 5. In response to criticism on this point, I reviewed the draft risk evaluations that EPA has subsequently issued under Section 6 to assess whether the factors EPA considers under Section 6 affect my initial determination (they do not).

B. Materials Relied Upon

19. For my risk assessment, I have relied upon my background, training and expertise in risk assessment, as well as my existing familiarity with the scientific literature on fluoride, which I first developed through extensive literature reviews for both the EPA and NRC. I also considered the following materials:

20. EPA documents, including (i) the *Guidelines* and other guidance documents that EPA has issued on risk assessment; (ii) risk assessments that EPA has conducted pursuant to the *Guidelines*;[2] (iii) risk evaluations that EPA has conducted under TSCA; and (iv) EPA's water intake data.

21. The NRC's review of the toxicologic literature on fluoride (NRC 2006), which I co-authored.

22. Animal studies on fluoride neurotoxicity that have been published since the NRC's 2006 review, which I obtained through a search of the National Library of Medicine's online database PubMed, as described further below.

23. The NTP's systematic review of studies addressing fluoride's impact on learning and memory in animals (NTP 2015, NTP 2016).

24. All prospective cohort studies on fluoride and neurodevelopment in humans

[2]I obtained the complete list of risk assessments that EPA has conducted pursuant to the *Guidelines* via an interrogatory response produced by EPA, which was provided to me by counsel.

(Bashash et al. 2017; Bashash 2018; Broadbent et al. 2015; Green et al. 2019; Shannon et al. 1986; Till et al. 2020; and Valdez-Jiminez et al. 2017).

25. Meta-analyses of the cross-sectional studies on fluoride and IQ (Choi 2012, Duan 2018).

26. The deposition of Dr. Kristina Thayer, the Director of EPA's Integrated Risk Information System (IRIS) and principal author of the NTP's 2015 and 2016 systematic reviews.

27. The deposition of Casey Hannan, the Acting Director of the Oral Health Division of the Centers for Disease Control and Prevention.

28. The deposition of Dr. Tala Henry, the Deputy Director of EPA's Office of Pollution Prevention and Toxics.

29. Studies provided by counsel—much of which I was already familiar with—which I understand were also provided to EPA's experts as well, including Dr. Tsuji.

C. Literature Search for Animal Neurotoxicity Data

30. For the animal literature, I conducted a search of the National Library of Medicine's online database PubMed to identify studies published since the NRC's 2006 review. The search terms used were: "fluoride and brain," "fluoride and learning," and "fluoride and memory."

31. The titles of all studies published since 2006 were reviewed to identify potentially relevant primary studies, and, among potentially relevant studies, abstracts were reviewed to verify relevance. Reviews, studies in Chinese for which translations were not available, and *in vitro* studies were excluded. Full-text copies of all relevant studies were obtained. In total, the search identified 110 papers. Papers that appeared to be reporting effects from the same underlying rodent experiment were treated as one study, leaving 105 distinct studies.

32. The 105 studies I identified are not an exhaustive list of the studies published since

2006, as they do not include studies that were not indexed in PubMed (e.g., studies published in the journal *Fluoride* or in certain Chinese-language journals such as the *Chinese Journal of Endemiology*). In addition, the search terms probably did not identify all relevant studies available on PubMed.

Nevertheless, the studies obtained through this pre-defined search protocol should be a reasonably representative sample of the recent literature.

D. Systematic Review

33. I did not conduct a formal systematic review, but a risk assessment under the *Guidelines* has been considered the effective equivalent of a systematic review.

IV. HISTORIC CONTEXT: 1930s to 2006

34. The early epidemiological studies in the U.S. that claimed to establish the safety of waterborne fluoride (fluoride concentrations ranging from 1 to 8 mg/L in drinking water) did not address the potential for fluoride to cause neurological effects, including IQ loss.[3] The primary focus of these early studies was, instead, on skeletal health.

35. Although largely overlooked, some of the early studies of occupationally exposed workers,[4] as well as some of the early studies of fluoride-exposed animals,[5] reported central nervous system effects from fluoride exposure. In a 1953 study of monkeys, Wadhwani and Ramasway reported that monkeys with chronic fluorosis "did not conduct themselves with intelligence and agility of mind normally associated with them. There was a significant lack of co-ordination in their behaviour."[6] These early observations, some of which remained unpublished,

[3] Call et al. (1965); Leone et al. (1954; 1955a; 1955b); McCauley and McClure (1954); McClure (1944); Schlesinger et al. (1956a; 1956b); Stevenson and Watson (1957).
[4] Roholm (1937); Popov et al. (1974); Duan et al. (1995); Guo et al. (2001); Yazdi et al. (2011).
[5] Wadhwani and Ramasway (1953); Lu et al. (1961); Rice and Lu (1963); Sadilova et al. (1968).
[6] Wadhwani and Ramasway (1953).

were largely ignored at the time.

36. The first known study of fluoride and intelligence in humans was published in 1989 by Ren and colleagues in China.[7] A flurry of similar studies were published in China in the 1990s.[8] Most of these studies were published in Chinese, and they remained largely unknown outside of China until English translations started to become available after the NRC's report in 2006.

37. In 2006, the NRC concluded that "fluorides have the ability to interfere with the functions of the brain and the body by direct and indirect means."[9] The NRC reached this conclusion based on the histological, biochemical, and molecular findings from animal studies published in the 1990s and early 2000s.[10] The NRC also reviewed two studies that examined the impact of fluoride on learning and memory in animals, but the data were not yet sufficient to draw conclusions on cognitive effects.[11]

38. As part of its report, the NRC also reviewed the 4 studies on fluoride and intelligence that were then available in English.[12] Various methodological limitations were identified with these studies, but the NRC concluded that the consistency of the results (i.e., reduced intelligence among children exposed to elevated fluoride) warranted further epidemiological research into the potential of fluoride to lower IQ.

39. The NRC also reviewed the toxicologic literature on fluoride's effects on the endocrine system, including the thyroid gland. The NRC concluded that fluoride is an endocrine-disrupting chemical which can alter thyroid function at estimated average intakes as low as 0.01 to

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7 Ren et al. (1989).

8 Qin et al. (1990); Chen et al. (1991); Guo et al. (1991); Lin et al. (1991); Sun et al. (1991); An et al. (1992); Li et al. (1994); Xu et al. (1994); Yang et al. (1994); Duan et al. (1995); Li et al. (1995); Wang et al. (1996); Yao et al. (1996; 1997); Zhao et al. (1996).

9 NRC (2006), p. 222.

10 NRC (2006), pp. 221-222.

11 NRC (2006), pp. 215-216, 221.

12 Li et al. (1995); Zhao et al. (1996); Lu et al. (2000); Xiang et al. (2003a; 2003b).

0.03 mg/kg/day in individuals with iodine deficiency.[13] The NRC recognized the potential relevance of fluoride's endocrine effects to neurotoxicity, noting that depressed thyroid function during pregnancy can lower the IQ of the offspring.[14]

40. The NRC's findings on the neurotoxic potential of fluoride have been accepted as an accurate summary of the hazard by the EPA and other federal agencies, including the CDC.

41. My risk assessment builds upon NRC's hazard determinations by considering the large volume of additional research that has been published since the NRC findings were released.

V. HAZARD CHARACTERIZATION

A. The "Sufficient Evidence" Standard

42. The focus of the Hazard Characterization is whether, at some level of exposure, the chemical has a credible potential to cause neurotoxic effects (i.e., whether neurotoxicity is a *hazard* of the chemical). The question of whether this hazard is a *risk* at environmentally relevant exposures is a separate question that is addressed in the Risk Characterization phase (as discussed below).

43. Under the *Guidelines*, hazard assessment is a qualitative determination in which the risk assessor must determine whether "sufficient evidence" of a neurotoxicity hazard exists.[15] A "sufficient evidence" finding "can be based on either human or animal data."[16] EPA has a preference for using human data if suitable data exist;[17] in practice, however, animal data are almost always used.[18]

[13] NRC (2006), pp. 262-263, 266.
[14] NRC (2006), p. 263.
[15] EPA (1998a), pp. 11, 53, 55-56.
[16] EPA (1998a), p. 11.
[17] EPA (2018a), p. 2-1.
[18] EPA (1998a), p. 20.

1. Sufficient Evidence from Human Data

44. For human data, "sufficient evidence" of a neurotoxic hazard exists if epidemiologic studies show that "some neurotoxic effect is *associated* with exposure."[19] EPA contrasted this requirement of an "association" with what the Agency recognized to be the "more stringent requirement" of "causality."[20] Under the *Guidelines*, there is no requirement to prove causality; evidence of an association is enough.

45. In assessing whether epidemiological studies demonstrate an association with neurotoxicity, EPA has stated that prospective cohort studies "should weigh heavily" in the assessment.[21] The *Guidelines* recognize that prospective studies are "invaluable for determining the time course for development of dysfunction" and permit "direct estimate of risks attributed to a particular exposure."[22] The only drawback of prospective studies that the *Guidelines* identify are that they "can be very time-consuming and costly."[23]

2. Sufficient Evidence from Animal Data

46. For animal data, "sufficient evidence" of a neurotoxic hazard exists if experimental studies demonstrate a potential neurotoxic hazard in humans.[24] The "minimum evidence" necessary to demonstrate a potential hazard is "a single appropriate, well-executed study in a single experimental animal species." If no individual study is sufficient to establish a hazard, "the total

[19] EPA (1998a), p. 53.
[20] EPA (1998a), pp. 53.
[21] EPA (1998a), pp. 18.
[22] EPA (1998a), pp. 17.
[23] EPA (1998a), pp. 17.
[24] EPA (1998a), p. 53.

available data may support such a conclusion" including data on toxicokinetics[25] and mechanisms of action.[26]

47. Neurotoxic endpoints in animal studies fall into several categories, including neuroanatomical, neurochemical, and behavioral.[27]

48. Neuroanatomical endpoints include changes to the brain, including damage to brain cells, that are detectable under a microscope (i.e., "histological").[28] The *Guidelines* consider neuroanatomical changes to be "of concern," and EPA has established reference doses for chemicals based on neuroanatomical effects.

49. Neurochemical effects include biochemical changes, such as alterations in neurotransmitter function and effects on enzymes. The Guidelines state that neurochemical changes "may be regarded as

adverse because of their known or presumed relation to neurophysiological and/or neurobehavioral consequences."[29]

50. Behavioral changes include alterations to motor activity, changes in sensory abilities or motor coordination, and impairments in learning, memory, and attention.[30] EPA has repeatedly based reference doses on behavioral alterations documented in animals, including learning and memory impairments.

51. In considering the relevance of the animal data to humans, the *Guidelines* provide four default assumptions. First, EPA assumes that "an agent that produces detectable adverse

[25] The *Guidelines* use the term pharmacokinetics. Both pharmacokinetics and toxicokinetics refer to the uptake, distribution, and retention of chemicals, with the former term being more frequently used in the context of pharmaceuticals, and the latter term more frequently used in the context of toxicants.

[26] EPA (1998a), p. 56.

[27] EPA (1998a), pp. 20-21.

[28] EPA (1998a), p. 21.

[29] EPA (1998a), p. 55.

[30] EPA (1998a), p. 21.

neurotoxic effects in experimental animal studies will pose a potential hazard to humans."[31] Second, EPA assumes that neuroanatomical, neurochemical, and behavioral changes "are of concern."[32] Third, EPA assumes that "the neurotoxic effects seen in animal studies may not always be the same as those produced in humans" due to "species-specific differences in maturation of the nervous system, differences in timing of exposure, metabolism, or mechanisms of action."[33] Fourth, EPA assumes that "humans are as sensitive as the most sensitive animal species tested."[34] These four assumptions are "plausibly conservative," meaning that "they are protective of public health and are also well founded in scientific knowledge about the effects of concern."[35]

3. Data that EPA Has Found Sufficient for Hazard Determination

52. EPA has conducted 10 risk assessments pursuant to the *Guidelines*. In 9 of these risk assessments, EPA found sufficient evidence to make a hazard determination and established Reference Doses (RfDs) or Reference Concentrations (RfCs)[36] to protect against the hazard.[37] In each of these 9 assessments, EPA based its hazard determination on animal data. For 6 of these 9 assessments, the chemicals had *no* human data on neurotoxicity (Table 1). For the 3 chemicals with some human data, no prospective cohort studies were available.

53. The principal studies[38] which EPA has used to establish RfDs have not been

[31] EPA (1998a), p. 6.
[32] EPA (1998a), p. 6.
[33] EPA (1998a), p. 7.
[34] EPA (1998a), p. 7.
[35] EPA (1998a), p. 7.
[36] Reference Doses refer to oral exposures, while Reference Concentrations refer to inhalational exposure. Eight of the 9 neurotoxicity risk assessments established RfDs, while 1 set an RfC. For purposes of simplicity, I will refer to Reference Doses for the remainder of this declaration when discussing these assessments.
[37] These 9 risk assessments were performed for BDE-47 (EPA 2008a), BDE-99 (EPA 2008b), BDE-153 (EPA 2008c), BDE-209 (EPA 2008d), Chlorine Dioxide and Chlorite (EPA 2000b), 2-Hexanone (EPA 2009b), Methanol (EPA 2013a), RDX (EPA 2018a), and Trimethylbenzenes (EPA 2016).
[38] A principal study is the study that contributes most significantly to the assessment of risk and is generally the basis for the Point of Departure from which a reference value is derived.

"perfect" studies. In fact, in most of the neurotoxicity risk assessments, EPA has identified a number of methodological limitations with the studies. Some of the principal studies did not conform to EPA's testing guidelines for animal studies; some used relatively small numbers of animals (e.g., 10 per group); and the principal studies that investigated effects from prenatal exposures did not always control for "litter effects," a methodological deficiency that can skew the effect size in developmental studies. In light of these limitations, EPA had "low confidence" for the studies it relied upon for several of its risk assessments (see Table 1). This did not stop EPA from establishing RfDs for these chemicals.

54. In several of EPA's neurotoxicity risk assessments, EPA established an RfD despite a relatively small number of animal studies. In the RDX risk assessment, for example, EPA identified 16 animal studies, only two of which had been published. EPA characterized these studies as showing "consistent evidence" of neurotoxicity because 11 of the 16 studies reported neurological effects[39] and the effects were generally dose-related (although inconsistencies existed across the studies in terms of the doses that produced effects).[40] EPA has thus recognized that "consistency" of the evidence is not synonymous with unanimity.

[39] EPA (2018a), p. 1-23.
[40] EPA (2018a), pp. 1-12, 1-18.

Table 1. Chemicals with oral RfDs based on neurological endpoints, assessed according to EPA's Guidelines for Neurotoxicity Risk Assessment.[a]

Name of Chemical	Human Neurotoxicity Data?[b]	Principal Study	Confidence in Principal Study	Known Mode of Action?	Effect	Reference
BDE-47	No	Animal	Not given[c]	Inadequate data	Changes in spontaneous motor activity and habituation	EPA (2008a)
BDE-99	No	Animal	Not given[d]	Inadequate data	Neurobehavioral developmental effects; changes in motor activity	EPA (2008b)
BDE-153	No	Animal	Not given[e]	Inadequate data	Spontaneous behavior, learning and memory	EPA (2008c)
BDE-209	No	Animal	Low	Inadequate data	Changes in spontaneous behavior and habituation	EPA (2008d)
Chlorine Dioxide and Chlorite	No	Animal	Medium	No	Neurodevelopmental delay; lowered auditory startle amplitude	EPA (2000b)
2-Hexanone	No	Animal	Medium	Yes	Axonal swelling in peripheral nerves	EPA (2009b)
RDX	One cross-sectional study, 16 case reports	Animal	High	Yes	Convulsions	EPA (2018a)
Trimethylbenzenes	Occupational studies of solvent mixtures, controlled experiments with healthy adults	Animal	Low to Medium	Tentative, based on structurally similar compounds	Decreased pain sensitivity	EPA (2016)

[a] EPA (1998a); Federal Register (1998). In addition, an inhalation RfC was derived for methanol based on animal data (EPA 2013a); the confidence in the RfC was considered medium to high.

[b] Human studies of neurotoxicity endpoints.

[c] Confidence in the principal study was not stated, but the "overall confidence in the RfD assessment of BDE-47 is low" (EPA 2008a, p. 48).

[d] Confidence in the principal study was not stated, but the "overall confidence in the RfD [for BDE-99] is low" (EPA 2008b, p. 67).

[e] Confidence in the principal study was not stated, but the "overall confidence in the RfD assessment for BDE-153 is low" (EPA 2008c, p. 37).

55. EPA has taken a similar approach to animal data in some of its draft risk evaluations under Section 6 of TSCA. In its NMP risk evaluation, for example, EPA based its risk calculations for chronic exposures in humans on animal data linking NMP to reduced fertility, despite the fact that there were only six animal studies available, three of which found no effect.[41] These contradictory findings were considered a source of uncertainty, but did not stop EPA from using these animal data to assess risk in humans. In fact, EPA made findings of unreasonable risk in humans exposed to lower doses of NMP based on this small body of contradictory data.

B. Human Studies on the Neurotoxicity of Fluoride

56. As noted earlier, the *Guidelines* state that prospective cohort studies "should weigh heavily in the risk assessment process."[42] The *Guidelines* also identify other types of human studies that can inform the assessment, including case reports and cross-sectional studies.[43]

57. In contrast to 9 chemicals for which EPA has established reference doses under the *Guidelines*, there are abundant human data on fluoride neurotoxicity, including 4 high-quality prospective cohort studies with individualized measurements of exposure during the prenatal period.[44]

58. I understand that Dr. Hu and Dr. Lanphear will be addressing the ELEMENT and MIREC birth cohort studies, and I understand that Dr. Philippe Grandjean will be addressing the other epidemiological studies, so I will forego repeating the details here.

[41] EPA (2019d), pp. 173-174.
[42] EPA (1998a), p. 17.
[43] EPA (1998a), pp. 15-16.
[44] Bashash et al. (2017; 2018); Green et al. (2019); Valdez-Jiménez et al. (2017).

59. As I described in my expert report, the human data on fluoride *strongly* support a hazard determination. Most importantly, each of the 4 prospective studies with measurements of *prenatal* exposure has found large and significant adverse associations with neurodevelopment, including IQ loss and inattention. An additional prospective study has found an association between IQ deficits and fluoride exposure during *infancy*.[45] These studies—which have consistently detected a significant association between early-life fluoride exposure and cognitive deficits using the most reliable study design identified by the *Guidelines*—are by themselves enough to constitute "sufficient evidence" of a hazard.

60. The consistency of the inverse association between fluoride and IQ in cross-sectional studies also adds important weight to the hazard assessment. Although cross-sectional studies are limited in their capacity to establish causal relationships, this limitation is lessened where the study examines stable populations and stable water fluoride levels.[46] In any event, the focus of the *Guidelines* is on assessing whether there is a reliable *association* with neurotoxicity, not on definitively proving causality.[47] As several meta-analyses have demonstrated, the cross-sectional studies show large and significant inverse *associations* between fluoride and IQ, with an average loss of about 7 IQ points.[48]

61. Finally, the case reports of neurological symptoms following fluoride exposure (e.g., general malaise, fatigue, headaches, and difficulties with concentration and memory) add

[45] Till et al. (2020).

[46] Under these conditions, measurement of current water fluoride levels may be a reasonable, albeit imperfect, proxy for exposure from the prenatal period onward, and thus the temporality requirement for a causal inference is partially met. A number of the cross-sectional studies on fluoride and IQ have, in fact, expressly limited the study population to children who lived in the same area since birth, which increases the basis for inferring causation. Chen et al. (1991); Choi et al. (2015); Ding et al. (2011), Karimzade et al. (2014a; 2014b); Khan et al. (2015); Lu et al. (2000); Nagarajappa et al. (2013); Rocha Amador et al. (2007); Seraj et al. (2012); Sudhir et al. (2009); Wang et al. (2007); Yao et al. (1996; 1997); Zhang et al. (2015b).

[47] EPA (1998a), p. 53.

[48] Choi et al. 2012; Duan et al. 2018.

additional support to the hazard determination. While case reports are generally not sufficient, by themselves, to establish a hazard, the *Guidelines* consider them "useful when corroborating epidemiological data are available."[49] Further, as the NRC noted, several of the case reports on fluoride can be characterized as "experimental studies," since they involved "individuals who underwent withdrawal from their source of fluoride exposure and subsequent re-exposures under 'blind' conditions. In most cases, the symptoms disappeared with the elimination of exposure to fluoride and returned when exposure was reinstated."[50] There is credible evidence, therefore, that for some sensitive individuals, fluoride exposure may cause overt neurological symptoms, although the NRC called for more research to better understand the issue.

C. Animal Studies on Fluoride Neurotoxicity

62. The animal research on fluoride neurotoxicity was sufficient to permit the NRC to conclude, in 2006, that fluoride interferes with the functions of the brain.[51] The NRC based this finding on the neuroanatomical and neurochemical changes produced by fluoride in laboratory animals. These changes include: reduced protein and phospholipid content; inhibition of acetylcholinesterase; interference with neurotransmitters; increased production of free radicals in the brain (i.e., oxidative stress); neuronal deformations; increased uptake of aluminum; and enhancement of reactive microglia.[52]

63. Many animal studies have been published since the NRC review which add further support to the hazard determination, as I will now discuss.

1. Studies Indexed by the National Library of Medicine (PubMed)

64. In my search of PubMed, I identified 105 studies that have been published since

[49] EPA (1998a), p. 15.
[50] NRC (2006), pp. 208-209.
[51] NRC (2006), p. 222.
[52] NRC (2006), pp. 221-222.

2006. Of these studies, all but 4 reported associations between fluoride exposure and neurotoxic outcomes.[53]

65. Table A-1 in Appendix A to this declaration provides data from the 88 animal studies which investigated neuroanatomical and neurochemical endpoints (i.e., "structural" effects), while Table A-2 provides data from the 36 animal studies which investigated learning and memory endpoints (i.e., "functional" effects).[54] Twenty-nine studies investigated both types of effects and are in both lists.[55]

66. As can be seen in Table A-1, rodent studies published since the NRC review have continued to document structural (e.g., neuroanatomical and neurochemical) changes in the brains of fluoride-treated rodents. These changes include oxidative stress, neuronal degeneration, mitochondrial disturbances, reductions in nicotinic receptors, impaired synaptic plasticity, and neuroinflammation.

67. Among the studies that have investigated both structural and functional effects of fluoride, the former have sometimes (but not always) occurred at lower exposures, suggesting that fluoride can cause cellular and biochemical changes in the brain prior to the manifestation of outwardly demonstrable deficits.[56] Put another way, deficits in learning and memory likely represent a relatively advanced stage of fluoride neurotoxicity. Nevertheless, both structural and

[53] Negative results were reported by Whitford et al. (2009), Pulangan et al. (2018), McPherson et al. (2018), and Jia et al. (2019, which I discuss later.

[54] For purposes of simplicity, I have used the term "structural" to refer to both neuroanatomical and neurochemical effects. While neurochemical effects are technically "functional" in nature, I use the word "functional" to refer solely to outward manifestations of neurotoxicity (i.e., learning/memory deficits). In this declaration, therefore, "structural" changes refer to all changes observed *in the brain*, while functional effects refer to all changes in *outward behavior* (e.g., learning and memory test performance, etc).

[55] To facilitate comparisons across these studies, Tables A-1 and A-2 exclude 2 studies of non-rodents as well as four studies in which the fluoride exposure was part of a mixture involving other potentially neurotoxic chemicals, one study involving exposure by a route other than ordinary ingestion, and two behavioral studies with endpoints that did not specifically involve learning and memory.

[56] See, for example, Agustina et al. (2018); Ma et al. (2015); Niu et al. (2018a); Sun et al. (2018); Wang et al. (2018a); Zhang et al. (2019); Zhao et al. (2019).

functional harms have repeatedly been observed in rodents at water fluoride concentrations between 5 mg/L and 23 mg/L.[57] As with the RDX literature,[58] there are some inconsistencies across the studies in the reported doses that can cause certain types of harm; these differences likely result, at least in part, from differences in study design, including differences in timing of exposure, duration of exposure, and strain and sex of animal.

68. Most of the animal studies to date have used subchronic exposure scenarios, which would tend to understate the effect from lifetime exposure. EPA's testing guidelines define a chronic exposure study in rodents as one that lasts at least 12 months.[59] None of the recent learning studies has lasted 12 months, and only 1 of the recent structural studies has lasted 12 months or more.[60] Among the studies that have tested animals at multiple points in time, the effects have tended to worsen with time, with some effects not appearing at all until 3 to 6 months of chronic exposure.[61] Since most of the studies on fluoride neurotoxicity have lasted no longer than 3 months, the studies are likely not detecting the full spectrum of fluoride's effects.

69. I understand that EPA is asserting that systemic toxicity, as reflected by reduced body weight, may explain fluoride's observed effect on learning/memory in animals. The *Guidelines* provide that, "If several neurological signs are affected, but only at the high dose and in conjunction with other overt signs of toxicity, including systemic toxicity, *large decreases in body weight*, decreases in body temperature, or debilitation, there is less persuasive evidence of a direct neurotoxic effect."[62] The *Guidelines* further provide that "At doses causing moderate

[57] These concentrations of fluoride *ion* correspond to a concentration of approximately 10 to 50 mg/L of *sodium* fluoride, as there are 2.2 parts sodium for each 1 part fluoride.
[58] EPA (2018a).
[59] EPA (1998b), p. 1.
[60] Teng et al. (2018).
[61] For example, Güner et al. (2016); Liu et al. (2011); Yang et al. (2018a); Zhang et al. (2015a).
[62] EPA (1998a), p. 38.

maternal toxicity (i.e., 20% or more reduction in weight gain during gestation and lactation), interpretation of developmental effects may be confounded."[63] The fact that there is some effect on body weight, therefore, does not, by itself, negate a direct neurotoxic effect; the effect on body weight must be relatively large (i.e., >20%). While some of the animal studies on fluoride do show some body weight reductions, many do *not*—particularly at the lowest doses causing the effects. Systemic toxicity is thus an unlikely explanation of the neurotoxic effects reported.

2. NTP Systematic Review for Australian Government (2015)

70. In 2015, the National Toxicology Program (NTP) completed a systematic review of the animal literature on fluoride neurotoxicity and submitted a report to the Australian government.[64] The NTP limited its review to studies that have measured learning, memory, and other behavioral effects.[65] In total, the NTP identified 44 studies of learning and memory, 14 of which were excluded due to risk of bias from lack of randomization, lack of blinding at outcome assessment, or other design deficiencies.[66] From the remaining 30 studies, NTP concluded that there was "a moderate level-of-evidence for a pattern of findings suggestive of an effect on learning and memory in rats treated during development or adulthood."[67] Moderate level of evidence is the second highest level of evidence under NTP's 5-grade classification criteria.[68]

[63] EPA (1998a), p. 46.
[64] NTP (2015a).
[65] NTP (2015a), pp. 1, 28.
[66] In addition to PubMed, NTP searched several additional databases. NTP (2015a), p. 1.
[67] NTP (2015a), p. 1.
[68] NTP (2015a), p. 11. Under NTP's Hazard Identification Scheme, a chemical that has a moderate level of evidence of neurotoxicity in animals and a moderate level of evidence of neurotoxicity in humans is a "presumed" neurotoxicant (NTP 2015b, p. 67, Figure 8).

3. NTP Systematic Review (2016)

71. In 2016, the NTP published an updated version of its systematic review.[69] In the updated review, NTP identified an additional four studies on learning and memory, two of which were excluded for bias, resulting in a total of 32 studies for its analysis.[70] NTP maintained its conclusion that the animal evidence is "suggestive" that fluoride impairs learning and memory, but downgraded its confidence in the developmental studies to "low."[71] NTP had less confidence in the developmental studies due to their general failure to control for litter effects, as well as the relatively few developmental studies that used fluoride concentrations lower than 25 mg/L in drinking water.[72]

72. The NTP identified several common methodological limitations with the learning and memory studies, including failure to rule out fluoride-induced motor effects as the cause of the apparent cognitive deficits; failure to control for "litter effects" in the developmental studies; lack of blinding; and lack of reported information on the study conditions, including the purity of the fluoride added to the water and the concentrations of fluoride in the rodent chow.

73. In contrast to NTP's 2015 report, the 2016 report considered the absence of animal studies using 0.7 mg/L (the current recommended fluoride concentration for human drinking water[73]) to be an important limitation in the research in terms of its relevance to human exposure levels.[74]

69 NTP (2016).
70 NTP (2016), p. vi.
71 NTP (2016), p. vii.
72 NTP (2016), p. 57.
73 USDHHS (2015).
74 NTP (2016), pp. 55, 58.

4. Assessment of NTP's Review

74. The suggestion by NTP that rodent studies should use fluoride concentrations of 0.7 mg/L in order to be relevant to human exposures is at odds with EPA's approach to risk assessment.[75] As I discuss later, humans are considered much more sensitive to toxicants than are rats and mice, and the EPA has developed procedures to account for this increased sensitivity. The net effect of EPA's procedures is that what might initially seem to be a "high" dose in animal studies may be very relevant to assessing risk in humans at lower doses.

75. By limiting its review to studies investigating learning and memory, the NTP did not consider the much larger number of studies that have investigated neuroanatomical and neurochemical effects, endpoints that are more sensitive and also potentially less susceptible to bias associated with outcome assessment.

76. The NTP correctly identified a number of methodological limitations in the learning/memory studies. The lack of blinding in some studies, for example, does create some uncertainty because lack of blinding can bias results in the direction of the anticipated effect.[76] Some of the limitations, however, would not be expected to skew the results in a consistent direction across laboratories (e.g., lack of information on the purity of the fluoride compounds). Similarly, litter effects can produce false negatives as well as false positives, and can both inflate and deflate the true effect size.[77] The impact of these limitations on the reported results is thus unclear, particularly when considering that the studies also have limitations that will make it harder

[75] The principal author of the NTP study, Kristina Thayer, testified at her deposition that she is no longer comfortable with the assumption of a 1-to-1 equivalence between fluoride exposures in animals and humans; Thayer testified that she would approach the issue differently today, with greater attention to interspecies differences in toxicokinetics and toxicodynamics. (Thayer Deposition at 151:9-152:3, 302:21-303:23). These issues are discussed further below.

[76] Holman et al. (2015).

[77] Zorrilla (1997), p. 144; Lazic and Essioux (2013), p. 3.

to detect effects, including the absence of chronic studies and the absence of studies investigating neonatal exposures that are comparable to formula-feeding exposures in human infants, as discussed further below.

77. Although the NTP expressed concern about the difficulty of distinguishing fluoride's effects on learning/memory from its effects on the motor/sensory system, each of these effects is neurotoxic and a matter of concern.

5. Developmental Studies Published Since the NTP Review

78. Subsequent to the NTP's review, 11 additional developmental studies have reported learning and memory outcomes.[78] Ten of these studies found deficits in the fluoride-treated groups. Notably, the Bartos et al. studies, which controlled for litter effects, found impairments in learning and memory at a fluoride concentration of just 5 mg/L. I will discuss these studies further in the Quantitative Dose Response section below.

6. McPherson (2018) and Other "No Effect" Studies

79. McPherson et al. (2018) is the one developmental study published since the NTP review that did not find clear adverse effects on learning and memory, although it did find a significant increase in pain sensitivity (a neurotoxic effect).

80. There are several features of the McPherson study that may help to explain the absence of a clear effect on learning and memory. First, unlike the overwhelming majority of previous studies on fluoride neurotoxicity, the McPherson study used Long Evans Hooded rats, which some have suggested may have lower sensitivity to fluoride than other strains.[79] To date,

[78] Bartos et al. (2018; 2019); Chen et al. (2018a); Cui et al. (2017); Ge et al. (2018); McPherson et al. (2018); Sun et al. (2018); Wang et al. (2018a); Zhao et al. (2019); Zhu et al. (2017); Zhou et al. (2019).

[79] Elliott (1967).

three studies[80] have examined the effect of fluoride on learning in Long Evans rats, and all three have failed to find an effect.[81]

81. Second, in contrast to most of the other developmental studies, McPherson et al. did not start the exposure until the 6th day of gestation.[82] As pregnancy in rats lasts approximately 21 days, any effects due to exposures early in, or preceding, the pregnancy may not have been detected by McPherson's study design.

82. Third, the offspring in the McPherson study had virtually no fluoride exposure during the neonatal period because the rat pups were breastfed during the pre-weaning period. This is important because the fluoride content of breast milk in rats (as with other mammals, including humans) is negligible, even when the mother is consuming large quantities of fluoride.[83] The rats in the McPherson study thus missed a potentially key period of vulnerability (early infancy)—an important limitation given the widespread use of infant formula among human neonates.[84]

83. In addition to the McPherson study, three other studies (with weaker study designs) reported no neurotoxic effects from fluoride exposure.[85] These three studies include Whitford et al. and Pulungan et al. which started with adult animals, and an unusual study by Jia et al. which started at gestational day 9. All or part of the gestational period was thus missed in each of these studies.

[80] Elliott (1967); Varner et al. (1994); McPherson et al. (2018).

[81] The plausibility of strain-specific differences between Long Evans and other rats is supported by other research which has found that Long Evans Hooded rats have different sensitivities to teratogenic substances in utero than Sprague-Dawley rats (Kang et al. 1986).

[82] McPherson et al. (2018).

[83] Fluoride concentrations in mammalian milk are very low in comparison to the mother's fluoride intake, even when the mother's fluoride intake is quite high (NRC 2006, pp. 33, 36; Drinkard et al. 1985).

[84] This limitation is not unique to the McPherson study, as all other developmental studies on fluoride have failed to supplement the pup's exposure during the breastfeeding stage.

[85] Whitford et al. (2009); Pulungan et al. (2018); Jia et al. (2019).

84. According to the *Guidelines*, "To judge that an agent is unlikely to pose a hazard for neurotoxicity, the minimum evidence would include data from a host of endpoints that revealed no neurotoxic effects."[86] This evidence does not exist for fluoride. To the contrary, almost all studies, including McPherson et al. (2018), have reported adverse effects on at least one of the endpoints measured.

D. Other Considerations

1. Dose Response

85. The *Guidelines* recognize that "determining a hazard often depends on whether a dose-response relationship is present,"[87] and thus "dose-response evaluation is a critical part of the qualitative characterization of a chemical's potential to produce neurotoxicity."[88] Because "human studies covering a range of exposures are rarely available," the *Guidelines* state that the dose-response evaluation will typically be limited to animal data.[89]

86. In contrast to the chemicals that EPA has evaluated under the *Guidelines*, there is abundant dose-response data for fluoride from *human* studies. Most importantly, the ELEMENT and MIREC birth cohort studies have found linear dose-response relationships between maternal urinary fluoride and IQ in the offspring.[90] The linearity of the dose-response relationships in these studies was not simply assumed—it was scrutinized through several methods, which I understand Drs. Hu and Lanphear will be explaining as part of their testimony.

87. Dose-response trends have also been observed in cross-sectional studies as a function of childhood urine and serum fluoride levels, although these are inherently less certain.[91]

[86] EPA (1998a), pp. 55-56.
[87] EPA (1998a), p. 2.
[88] EPA (1998a), p. 50.
[89] EPA (1998a), p. 50.
[90] Bashash et al. (2017; 2018); Green et al. (2019).
[91] Cui et al. (2018); Ding et al. (2011); Xiang et al. (2011); Zhang et al. (2015b).

An important limitation with dose-response data from cross-sectional studies is that the exposures are tested after the effect (reduction in IQ) has occurred. The data, however, are not without value, as current exposures can be reflective of developmental exposures in areas with stable populations and stable water fluoride concentrations. In the Zhang study, for example, most of the children had been living in the same household and drinking from the same wells since birth.[92]

88. In addition to dose-response data from human studies, there is also considerable dose-response data from animal studies. A prerequisite for dose-response analysis in animal studies is that there be multiple treatment groups with different exposures to the test substance. Many of the animal studies on fluoride have used multiple treatment doses, and thereby permit evaluation of dose response. Of the studies published since the NRC review (summarized in Table A-1), 1 used four treatment doses, 17 used three treatment doses, and 16 used two treatment doses (in addition to the control groups). Of these 34 studies, 30 show visually apparent dose-response trends for at least one of the effects being investigated.

2. Neuroendocrine Effects

89. EPA's *Guidelines* recognize the relevance of a chemical's ability to alter the function of the thyroid gland.[93] According to the *Guidelines*, "the development of the nervous system is intimately associated with the presence of circulating hormones such as thyroid hormone."[94] A thyroid disturbance during a specific developmental period may cause a "nervous system deficit, which could include cognitive dysfunction, altered neurological development, or visual deficits, [depending] on the severity of the thyroid disturbance and the specific developmental period when exposure to the chemical occurred."[95] Elsewhere, EPA has recognized

92 Zhang et al. (2015b), p. 4.
93 EPA (1998a), p. 50.
94 EPA (1998a), p. 50.
95 EPA (1998a), p. 50.

that "thyroid hormones are essential for normal brain development in humans and that hypothyroidism during fetal and early neonatal life may have profound adverse effects on the developing brain."[96]

90. Thyroid toxicity may be a significant mechanism by which fluoride affects neurodevelopment. In 2006, the NRC had enough information to conclude that fluoride is an "endocrine disrupter" which may lower thyroid function.[97] Sodium fluoride was once prescribed as a therapeutic agent for *lowering* thyroid activity in cases of *hyper*thyroidism.[98] The NRC reported that fluoride can lower thyroid function at estimated average intakes of 0.05-0.13 mg/kg/day in humans with adequate iodine intake, and at estimated average intakes as low as 0.01 to 0.03 mg/kg/day in individuals with iodine deficiency.[99] Put differently, fluoride affects thyroid function at lower doses in people with iodine deficiency than in those with optimal intake of iodine.

91. Epidemiological research published subsequent to the NRC's report is consistent with and further supports NRC's findings. In 2018, Malin et al. reported a relationship between urinary fluoride and elevated TSH (thyroid stimulating hormone) among iodine-deficient adults in Canada, but not in the general population as a whole (excluding those with known thyroid disease and excluding pregnant individuals).[100] Elevated TSH is indicative of a decrease in thyroid function. Ten percent of women of child-bearing age in the US are iodine deficient.[101]

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[96] EPA (2008a), p. 40, citing Morreale de Escobar et al. (2000) and Haddow et al (1999). See also EPA (2008b), p. 54, citing Morreale de Escobar et al. (2000). EPA's Science Advisory Board in 2013 found that "the most sensitive life stages are the fetus, neonates and infants because these are the stages when thyroid-dependent brain development occurs" (EPA 2013b, cover letter, p. 2).

[97] NRC (2006), pp. 262-263.

[98] Galletti and Joyet (1958).Consistent with this thyroid use (i.e., lowering thyroid function), fluoride exposure has been associated with hypothyroidism in animal and human studies (Hillman et al. 1979; Peckham et al. 2015; Yang et al. 2019).

[99] NRC (2006), pp. 262-263.

[100] Malin et al. (2018). Barberio et al. (2017) found no association between fluoride exposure and thyroid status, but the iodine-deficient part of the population was not specifically addressed.

[101] CDC (2008), Chapter 4a, pp. 91-100; see also Pearce (2015); Caldwell et al. (2011).

92. In 2015, a nationwide study from England reported a significant association between water fluoridation and increased prevalence of hypothyroidism.[102]

3. Toxicokinetics

93. Under the *Guidelines*, consideration should be given to the toxicokinetics of the chemical with "particular importance" given to the chemical's capacity to get through the blood-brain barrier.[103] The permeability of the blood brain barrier is particularly important when a chemical, such as fluoride, is able to make it through the placenta. Studies in humans have repeatedly demonstrated that fluoride crosses the placenta and reaches the fetus,[104] and thus it is generally accepted that "fluoride readily crosses the placenta."[105] In general, measured concentrations of fluoride in umbilical cord blood and in blood of neonates are similar to concentrations in maternal blood.[106] In short, the fluoride that a mother ingests will cause exposure to the fetus.

94. Fluoride is also known to cross the blood-brain barrier,[107] and passage of fluoride into the brain can be expected to be higher during the fetal and neonatal life stages when the blood brain barrier is not yet fully developed.[108] As the EPA has recognized, "Because the blood-brain barrier limits the passage of substances from blood to brain, in its absence, toxic agents can freely enter the developing brain."[109] Consistent with EPA's observation, the recent rat study by

[102] Peckham et al. (2015).
[103] EPA (1998a), p. 47.
[104] See for example, Feltman and Kosel (1961); Gedalia et al. (1964); Blayney and Hill (1964); Armstrong et al. (1970); Hanhijärvi et al. (1974); Forsman (1974); Shen and Taves (1974); Ron et al. (1986); Malhotra et al. (1993); Gupta et al. (1993); Brambilla et al. (1994); Shimonovitz et al. (1995).
[105] NRC (2006), p. 193.
[106] Feltman and Kosel (1961); Gedalia et al. (1964); Hudson et al. (1967); Armstrong et al. (1970); Hanhijärvi et al. (1974); Ron et al. (1986); Malhotra et al. (1993); Gupta et al. (1993); Shimonovitz et al. (1995).
[107] Geeraerts et al. (1986); Mullenix et al. (1995); Zhang et al. (2013c); Niu et al. (2015b).
[108] EPA (2009b), p. 58.
[109] EPA (2009b), p. 58.

McPherson et al. found sharply elevated concentrations of fluoride in the brain following prenatal exposure.[110]

4. Mode of Action

95. EPA's *Guidelines* recognize that hazard identification is strengthened by, but not dependent upon, an identifiable mechanism by which the chemical can exert neurotoxic effects.[111] For most of the chemicals for which EPA has established RfDs pursuant to the *Guidelines*, the mode of action has not been known (see Table 1). As noted recently by the NAS, "solid conclusions about causality can be drawn without mechanistic information, for example, when there is strong and consistent evidence from animal or epidemiology studies."[112] The NAS added that "mechanistic frameworks today could probably be completed for only a few chemicals."[113]

96. Several plausible mechanisms—both indirect and direct—have been identified that could help explain the neurotoxicity of fluoride.

97. *Indirect Mechanisms*: Depression of thyroid function is likely a principal indirect mechanism and could account for some of the neurotoxic effects reported in the literature. A thyroid mechanism is particularly plausible as a cause of IQ loss among offspring born to women with suboptimal iodine intakes.

98. *Direct Mechanisms* A recent study by Zhao et al. provides *in vitro*, *in vivo*, and epidemiological data that, together, suggest that disturbances in hippocampal mitochondrial dynamics (marked by fission inhibition and fusion promotion) play an important role in fluoride-induced cognitive loss.[114] The hippocampus is an important region in the brain for learning and

[110] McPherson et al. (2018).
[111] EPA (1998a), pp. 10, 53.
[112] NAS (2018), p. 9.
[113] NAS (2018), p. 9.
[114] Zhao et al. 2019.

memory, and many of the studies investigating the neuroanatomical and neurochemical effects of fluoride exposure have identified adverse effects in this region (see Table A-1). Other potential modes of action have also been identified, including signaling disruption, oxidative stress, and selective reductions in nicotinic receptors.[115]

5. *In Vitro* Studies

99. EPA's *Guidelines* also call for consideration of *in vitro* data. While positive *in vitro* data are not sufficient, by themselves, to demonstrate a neurotoxic hazard in humans, the existence of such data helps enhance the reliability of *in vivo* data.[116]

100. Fluoride's ability to damage brain cells has been documented in *in vitro* experiments. While most of the *in vitro* studies have used high concentrations that are unlikely to be present in the human brain, several studies have examined environmentally realistic fluoride concentrations. Gao et al. found increased lipid peroxidation and reduced α7 nicotinic acetylcholine receptors in brain cells at fluoride concentrations (i.e., 9.5 parts per billion) that are commonly found in the blood of people living in fluoridated areas.[117] Increases in markers of neuroinflammation have also been found at low concentrations.[118] Under the *Guidelines*, these data do not demonstrate a hazard in humans, but they do enhance the reliability of the animal studies, as similar effects have been reported in fluoride-treated rodents.[119]

6. Validity of the Database

101. Under the *Guidelines*, the validity of the database should be evaluated by assessing

[115] Bartos et al. (2018); Chen et al. (2003; 2018a); Gao et al. (2008); Liu et al. (2010); Long et al. (2002); Shan et al. (2004); Zhang (2017b); Zhu et al. (2017).
[116] EPA (1998a), p. 49.
[117] Gao et al. (2008), Figures 1A, 3A.
[118] Goschorska et al. (2018).
[119] Bartos et al. (2018); Dong et al. (2015); Yang et al. (2018a); Yan et al. (2016); Zhao et al. (2019).

the content validity, construct validity, concurrent validity, and predictive validity of the data.[120]

102. *Content validity* addresses "whether the effects result from exposure."[121] This factor weighs decisively in favor of a neurotoxicity hazard determination for fluoride. The NRC concluded that fluoride interferes with the brain,[122] and the evidence has gotten stronger since. Kristina Thayer, the Director of EPA's IRIS Division, has explained that "experimental animal studies are designed to let you draw causal inferences," and that the animal studies show that fluoride damages the brain at some level of exposure.[123] Further, while the human cross-sectional studies are limited in their ability to produce causal inferences, the *Guidelines* provide that prospective cohort studies permit "direct estimates of risk attributable to a particular exposure."[124]

103. *Construct validity* addresses whether the neurologic effects that have been observed "are adverse or toxicologically significant."[125] This factor is satisfied in the fluoride database. Animal studies have linked fluoride to learning and memory deficits, which are an adverse effect upon which EPA has established reference doses for other neurotoxicants (e.g., BDE-153).[126] Further, the human epidemiological data have linked fluoride with IQ detriments, including an approximate 5 to 6 point drop in IQ as maternal urinary fluoride increased from 0 to 1 mg/L.[127] EPA has recognized that a loss of a single IQ point is associated with a loss in lifetime earnings,[128] and EPA's Clean Air Science Advisory Council has stated that "a population loss of 1-2 IQ points

[120] EPA (1998a), pp. 10-11.
[121] EPA (1998a), pp. 10-11.
[122] NRC (2006), p. 222.
[123] Thayer Deposition at 225:8-15, 226:13-16, 270:23-25.
[124] EPA (1998a), p. 17.
[125] EPA (1998a), pp. 10-11.
[126] EPA (2008c), p. 36. Effects on memory were also noted in the RfD determination for BDE-99 (EPA 2008b, p. 27).
[127] Bashash et al. (2017); Green et al. (2019).
[128] EPA (2008e), p. 5-28.

is highly significant from a public health perspective" and should be prevented in 99.5% of the population.[129]

104. *Concurrent Validity* addresses "whether there are correlative measures among behavioral, physiological, neurochemical, and morphological endpoints.[130] Studies have correlated fluoride's cognitive effects in animals with various neurochemical and neuroanatomical changes,[131] and a few studies have correlated fluoride-associated cognitive loss in humans with increased TSH and alterations in mitochondrial dynamics.[132] For example, Zhao et al.[133] reported lower circulating levels of a mitochondrial protein (fission-related protein-1, Fis1) in children from high fluoride areas (compared with children in low fluoride areas), and higher circulating levels of a second mitochondrial protein (mitofusin-2, Mfn2) in the same children. The levels of circulating Fis1 were positively associated with children's IQ scores, while the levels of circulating Mfn2 were negatively associated with the IQ scores. In addition, several plausible mechanisms of fluoride neurotoxicity have been described (discussed above).

105. *Predictive validity* addresses "whether the effects are predictive of what will happen under various conditions."[134] The condition of perhaps greatest interest with respect to prediction of fluoride neurotoxicity is exposure during the prenatal period. Studies in both animals and humans have, with one exception,[135] reported neurologic effects following prenatal exposure. The database, therefore, does have some degree of predictive validity, although further research remains necessary to determine to what extent other conditions (e.g., nutrition, genetics, neonatal

[129] Federal Register (2008), p. 67000.
[130] EPA (1998a), pp. 10-11.
[131] For example, see Bartos et al. (2018); Zhao et al. (2019); Zhou et al. (2019).
[132] For example, Zhang et al. (2015b); Zhao et al. (2019).
[133] Zhao et al. (2019).
[134] EPA (1998a), pp. 10-11.
[135] McPherson et al. (2018).

exposure, and kidney function) may modify or predict outcomes. Exposure during the early postnatal period also requires further research.

7. Data Gaps

106. EPA's *Guidelines* point to the need to address "significant data gaps."[136] One of the major data gaps for fluoride is the lack of research on the impact of fluoride during the neonatal and early infancy period. EPA has recognized that the neonatal period represents a critical window of vulnerability to neurotoxicants,[137] yet most developmental rodent studies do not address neonatal exposures to fluoride (due to exclusive breastfeeding of the rat or mouse pups and absence of gavage exposures). Other data gaps include the absence of long-term animal studies, and the scarcity of epidemiological research into fluoride's neurologic effects in the elderly. Data gaps also remain with respect to how the dose which causes neurologic effects varies across susceptible subsets of the population, including those with nutrient deficiencies, genetic polymorphisms, kidney disease, and the elderly.

E. Conclusion: There Is Sufficient Evidence that Neurotoxicity Is a Hazard of Fluoride

107. The large and substantial body of evidence that now exists for fluoride, from both animal and human studies, satisfies EPA's "sufficient evidence" standard for hazard determination.

108. The *Guidelines* provide that "the minimum evidence sufficient would be data on a single adverse endpoint from a well-conducted study."[138] The *Guidelines* also recognize that prospective cohort studies are the optimal type of epidemiological study that permit direct

[136] EPA (1998a), p. 12.
[137] See for example, EPA (2008a), p. 42.
[138] EPA (1998a), p. 55.

estimates of risk. The minimum evidence threshold is thus met for fluoride because there is not just one, but *four* high-quality prospective cohort studies that support the endpoint of IQ loss, and another high-quality prospective cohort study that supports the endpoint of inattention.[139]

109. EPA's *Guidelines* also permit consideration of the collective evidence when no study, by itself, is sufficient to permit a hazard determination. This, again, supports a hazard determination for fluoride because the prospective studies are most compelling when viewed in the context of (i) the toxicokinetic data showing that fluoride crosses the placenta and enters the fetal brain; (ii) animal data showing neurochemical and neuroanatomical damage following fluoride exposure; (iii) animal data finding impairments in learning and memory following prenatal exposure to fluoride; (iv) cross-sectional studies consistently finding reductions in IQ in communities with elevated fluoride exposure; (v) *in vitro* studies reporting effects on brain cells at concentrations of fluoride found in the blood of individuals living in fluoridated communities; and (vi) animal and human studies finding that fluoride can depress thyroid function, a known risk factor for neurodevelopmental harm.

110. Based on the collective data—which are far more robust than the data EPA has relied upon for prior hazard determinations—I conclude with a reasonably high degree of confidence that neurotoxicity is a hazard of fluoride exposure.

VI. QUANTITATIVE DOSE RESPONSE

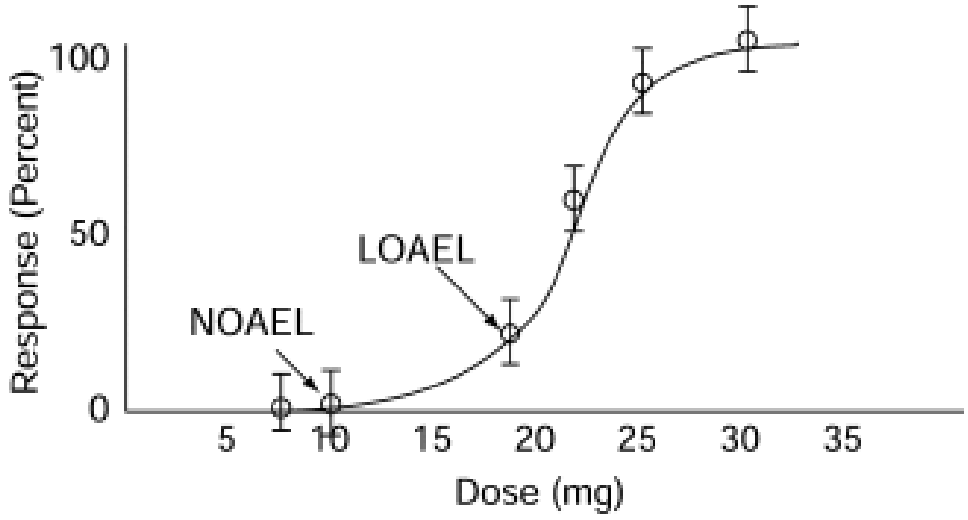
111. If a chemical is identified as posing a neurotoxic hazard, EPA's *Guidelines* call for a quantitative dose-response analysis to determine the reference dose (RfD). The RfD is "an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the

[139] Bashash et al. (2017; 2018); Green et al. (2019); Till et al. (2020); Valdez-Jiménez et al. (2017).

human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime."[140]

112. In the Quantitative Dose Response analysis, human or animal data are assessed to determine an appropriate "Point of Departure" (POD). As the name implies, the Point of Departure (POD) is the datapoint from which the RfD is ultimately derived. The POD can be one of three types of values: the No Observed Adverse Effect Level (NOAEL), the Lowest Observed Adverse Effect Level (LOAEL) or the Benchmark Dose Level (BMDL). While EPA now has a preference for using BMD, it still uses both the NOAEL and LOAEL approaches in its assessments.

113. The following figure provides a visual illustration of the difference between a NOAEL and LOAEL on a dose-response curve.



A. Basis for Using Animal Data

114. When human data are available, EPA's preference is to use human data for the Point of Departure.[141] In the case of fluoride, the recent prospective cohort studies[142] with individual-level biomonitoring data provide suitable data for this purpose. If one had to choose,

[140] EPA (1998a), p. 57. See also EPA (2009a).
[141] EPA (2018a), p. 2-1.
[142] Bashash et al. (2017; 2018); Valdez-Jiménez et al. (2017); Green et al. (2019).

therefore, between deriving the POD for fluoride from the human or animal data, *the choice would clearly be to use the human data*. But this does not mean that the animal data are without value. In EPA's assessment of methylmercury, for example, the EPA derived its RfD from human prospective cohort data, but it also considered what the RfD would be if it were derived from the animal literature.[143] As the EPA noted, "[i]t is informative to compare RfDs derived from animal studies with those derived from the epidemiological literature."[144] In the case of methylmercury, the animal-based RfD supported the human-based RfD, and EPA cited this as a factor that increased its "confidence" in the assessment.[145]

115. In this case, Dr. Philippe Grandjean conducted a dose-response analysis of the prospective cohort data where he derived a BMDL. To avoid duplication of Dr. Grandjean's effort, and to determine whether Dr. Grandjean's BMDL is consistent with potential RfDs derived from the animal data, I focused my assessment on the animal literature.

116. In this assessment, I did not seek to select a single value for the RfD. Instead, I sought to identify the full range of RfDs that can be derived, including the *least* protective. If human exposures exceed RfDs that use non-protective assumptions, there would be greater confidence that a human risk does, in fact, exist.

117. There are several considerations that support the use of animal data to establish an RfD for fluoride. First, EPA has used animal studies as the principal studies for each of the neurotoxicity risk assessments it has thus far conducted under the *Guidelines*. Second, EPA has used impairment in learning and memory in rodents as the adverse effect upon which to base the RfD for other chemicals,[146] thus this is an accepted endpoint to use in deriving an RfD. Third, a

[143] EPA (2001), pp. 17-18.
[144] EPA (2001), pp. 17.
[145] EPA (2001), pp. 18-19.
[146] For example, BDE-153 (EPA 2008c, p. 36).

substantial number of animal studies of fluoride neurotoxicity have used 2 or 3 treatment groups (in addition to control groups), and EPA has found this to be sufficient for identifying Points of Departure,[147] including in animal studies with as few as 10 rats per group (2-Hexanone).[148]

B. Selecting Points of Departure

118. In the literature review discussed earlier, 37 rodent studies were identified that have investigated fluoride's impact on learning and memory since the NRC report (Table A-2). All but 3 of these studies found adverse effects in the fluoride-treated rodents, including 16 of the 17 studies that investigated prenatal fluoride exposures. Since the prenatal period represents a point of heightened vulnerability to neurotoxicants, the prenatal studies are a logical candidate for the point of departure.

119. To avoid studies at high risk of bias, the three studies that did not specifically mention using a randomization procedure were excluded from further consideration.[149] Further, in order to focus the analysis on those studies best suited for identifying a Point of Departure (POD), four studies that only used one treatment dose were excluded.[150]

120. Table 2 and the figures below summarize the 10 prenatal studies that remained for POD consideration. Most of the studies used a similar dosing regimen with 2 or 3 treatment groups and at least 10 rodents per group, which is consistent with several of the principal studies that EPA has used to establish an RfD. The figures show the lowest-observed and no-observed effect levels in each study and help to visually compare the data across studies.

121. Nine of the 10 studies found dose response trends for one or more effects, which

147 EPA (2000b; 2008a; 2008c; 2008d; 2009b).
148 EPA (2009b).
149 Bera et al. (2007); Basha et al. (2011b); Ge et al. (2018).
150 Niu et al. (2014); Banala and Karnati (2015); Dong et al. (2015); Zhu et al. (2017).

adds confidence to a causative role of the fluoride treatment.[151] Six of these studies also provide data on the body weights of the pups, and no bodyweight changes were seen in any of the studies at the lowest concentrations producing the effects.[152] Only one of the six studies found any bodyweight changes among pups in the higher-dose groups.[153] Of the two studies that reported maternal weight, neither found any changes.[154]

122. One limitation with these studies is that only three of them specifically mention controlling for litter effects,[155] which introduces some uncertainty since the failure to control for litter effects can result in false positives, as well as false negatives.[156] While a source of uncertainty, the failure to control for litter effects does not preclude use for risk assessment purposes. As noted earlier, EPA has used studies that do not control for litter effects as the principal studies upon which it has based RfDs for developmental neurotoxicity.[157]

[151] See for example, Jiang et al. (2014b), Table 3; Cui et al. (2017), Table 3; Chen et al. (2018a), Figure 1d,e; Sun et al. (2018), Tables 2 and 3; Wang et al. (2018a), Figure 4b,c; Zhao et al. (2019), Figure 5e.

[152] Bartos (2018; 2019); Cui et al. (2017); Jiang et al. (2014b); Wang et al. (2018a). The study by McPherson (2018) also showed no changes in bodyweight, although it did not find effects on learning/memory.

[153] Jiang (2014b) found reduced body weight gain among the pups in the 23 mg/L and 45 mg/L groups.

[154] Bartos (2018; 2019).

[155] Bartos et al. (2018; 2019); McPherson et al. (2018).

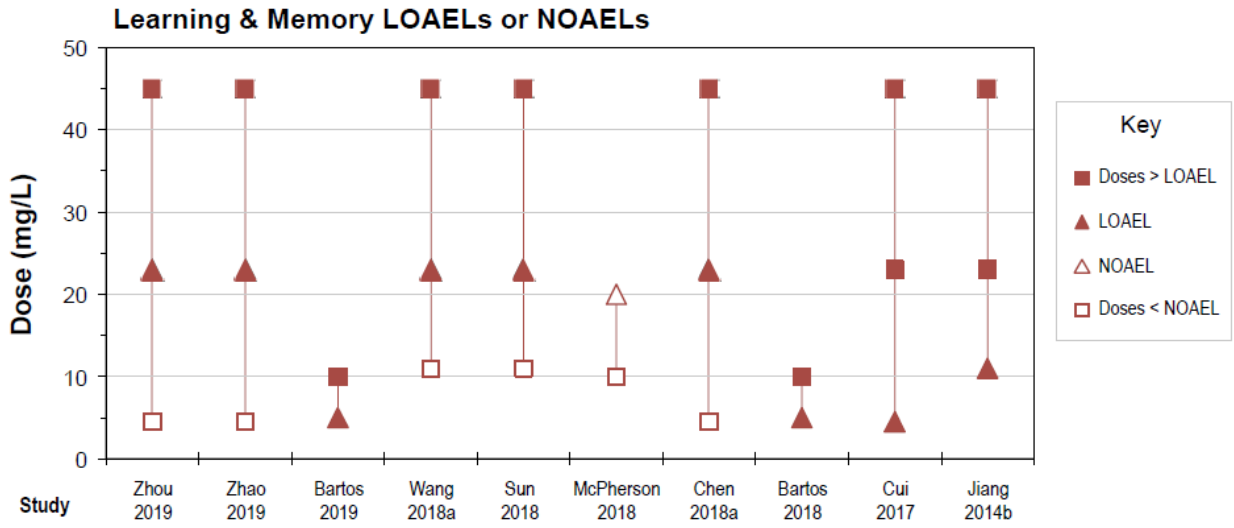
[156] Zorrilla (1997), p. 144; Lazic and Essioux (2013), p. 3.

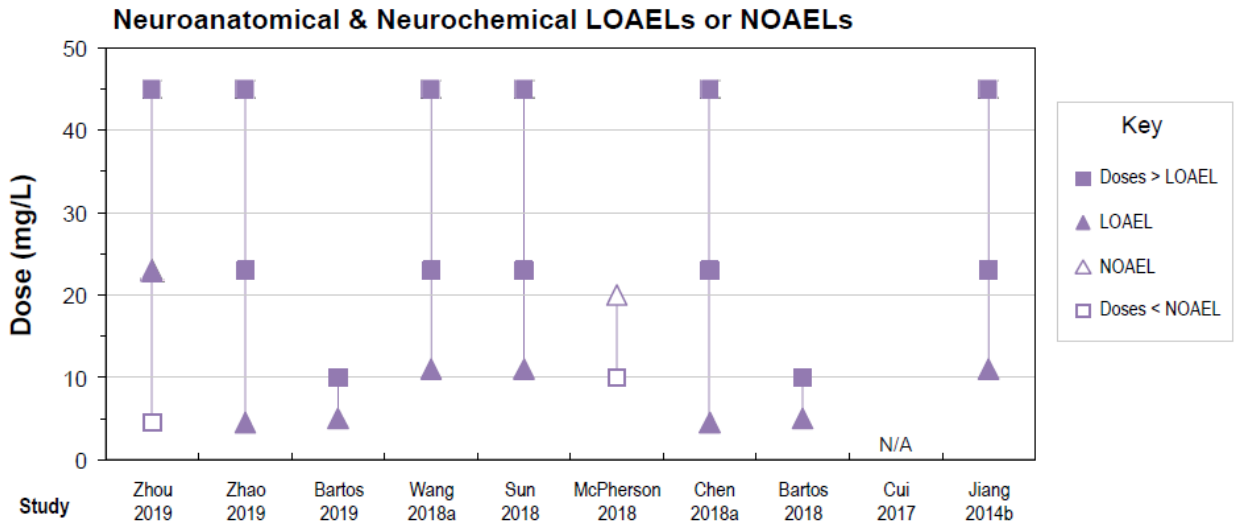
[157] See for example EPA (2008a), pp. 44, A-4; EPA (2008b), pp. 59, A-3; EPA (2008c), pp. 32, A-3.

Table 2. Examples of rodent studies of prenatal exposure to fluoride that could provide LOAELs or NOAELs for neurotoxicity.

Study	Animal	Exposure period	[F^-] in drinking water[a] (mg/L)	Number of animals per group (n)	Learning and memory		Neuroanatomical or neurochemical effects	
					LOAEL (mg/L)	NOAEL (mg/L)	LOAEL (mg/L)	NOAEL (mg/L)
Zhou et al. (2019)	Rats, Sprague-Dawley	Prenatal[b] + 6 months	4.5, 23, 45	6	23	4.5	23	4.5
Zhao et al. (2019)	Rats, Sprague-Dawley	Prenatal[b] + 60 days	4.5, 23, 45	5	23	4.5	4.5	None
Bartos et al. (2019)	Rats, Wistar (female)	Prenatal + 21 days	5, 10	9-10	5	None	5	None
Wang et al. (2018a)	Mice, ICR (female)	Prenatal (from day 7) + 21 days	11, 23, 45	15	23	11	11	None
Sun et al. (2018)	Mice, Kunming	Prenatal + 21 days	11, 23, 45	6	23	11	11	None
McPherson et al. (2018)	Rats, Long Evans Hooded (male)	Prenatal (from day 6) + 90 days	10, 20[c]	11-23	None	20	None	20
Chen et al. (2018a)	Rats, Sprague-Dawley	Prenatal[b] + 6 months	4.5, 23, 45	6	23	4.5	4.5	None
Bartos et al. (2018)	Rats, Wistar (female)	Prenatal + 21 days	5, 10	9-10	5	None	5	None
Cui et al. (2017)	Rats, Sprague-Dawley	Prenatal[b] + 60 days	4.5, 23, 45	12	4.5	None	N/A	N/A
Jiang et al. (2014b)	Rats, Sprague-Dawley	Prenatal[b] + 2 months	11, 23, 45	12	11	None	11	None

[a] Treatment groups in addition to the control group.
[b] Exposure of the mother began before pregnancy.
[c] Animals were given 0, 10, or 20 mg/L fluoride in drinking water, plus 3.24 ppm fluoride in feed. An additional control group had 0 mg/L fluoride in drinking water plus 20.5 ppm fluoride in feed (McPherson et al. 2018).





123. Based on the dose-response data from these studies, the following values could be used as the Point of Departure.

124. **LOAEL of 5 mg/L**: The lowest observed adverse effect levels in the studies were fluoride concentrations of 4.5 and 5 mg/L. Of the six studies that used this concentration, three

found adverse effects on learning,[158] and two of the other three studies, which did not find effects on learning, *did find alterations in the brain.*[159] Two of the three studies reporting effects on learning at 5 mg/L controlled for litter effects, which suggests that the failure to control for litter effects is unlikely to explain the reported effects at this concentration.[160] A 5 mg/L LOAEL was selected, therefore, as one of the Points of Departure (PODs) for learning impairment from prenatal fluoride exposure.

125. **LOAEL of 23 mg/L**: Seven of the 10 studies used 23 mg/L as one of the treatment doses, and all 7 of these studies found impaired performance on the cognitive tests, with 6 of the 7 studies finding changes in the brain as well. 23 mg/L appears, therefore, to be a reliable "Observed Adverse Effect Level," particularly in light of the six studies (discussed above) which found adverse effects at < 5 mg/L. Although not the *lowest* observed effect level, it is assumed to be one for purposes of this Point of Departure.

126. **LOAEL of 45 mg/L**: As can be seen in the above figures, 45 mg/L is clearly an "observed adverse effect level," just as it has been in many other animal studies on fluoride neurotoxicity. It would be difficult to justify selecting 45 mg/L as the LOAEL because it is the *highest* observed adverse effect level in this group of studies, not the *lowest*. Nevertheless, for purposes of capturing the broadest possible range of RfDs that can be derived from the animal literature, a 45 mg/L LOAEL was selected as one of the Points of Departure.

[158] Cui et al. (2017); Bartos et al. (2018; 2019). In the Chen study (which had only six rats per group), there is some indication of an effect on learning in the 4.5 mg/L group, albeit not statistically significant (Chen et al. 2018a, Figure 1).

[159] Chen et al. (2018a); Zhao et al. (2019). Other studies have also found alterations in the brain at ≤ 5 mg/L, including Liu et al. (2010; 2011); Zhang et al. (2015a); Niu et al. (2018a); Varner et al. (1998); and Yu et al. (2019).

[160] Bartos et al. (2018; 2019).

127. **NOAEL of 11 mg/L**: Four of the prenatal studies used 10 or 11 mg/L for the low-dose group.[161] The two studies of mice failed to find a significant effect on learning at this level,[162] and, as such, 11 mg/L could be selected as a NOAEL. The fact that the two studies that did not find effects at 11 mg/L found them at higher concentrations (23 and 45 mg/L) would be a factor weighing in favor of this choice, as the animal models were sensitive enough to find an effect. It bears considering, however, that the two studies finding no effects on learning at 11 mg/L did find alterations in the brain at this level,[163] which is consistent with 11 mg/L being a LOAEL, rather than a NOAEL. However, for purposes of reflecting the spectrum of RfDs that can be derived from the animal literature, 11 mg/L was treated as a NOAEL for one of the PODs.

128. **NOAEL of 20 mg/L**: The highest possible NOAEL that can be selected from these prenatal studies is the 20 mg/L no-effect finding from McPherson et al.[164] As discussed earlier, there are limitations with the McPherson study that may have made it less sensitive to detecting an effect, including strain of rat used and lack of first trimester exposure. Further, the study did find an adverse neurotoxic effect in the 20 mg/L group (i.e., increased pain sensitivity), and, as such, 20 mg/L is not a true NOAEL in the study. Nevertheless, for the purpose of illustrating the upper-bound range of RfDs that can be derived from the animal literature, a 20 mg/L NOAEL will be treated as a POD for the analysis.

C. Conversion of POD Concentrations (mg/L) to Doses (mg/kg/day)

129. Reference Doses (RfDs) are expressed in terms of dose (i.e., milligrams per kilogram of bodyweight, or mg/kg/day), not in terms of water concentration. To calculate RfDs from the Points of Departure, therefore, the unit of measurement (i.e., water fluoride concentration)

[161] Wang et al. (2018a); Sun et al. (2018); McPherson et al. (2018); Jiang et al. (2014b).
[162] Sun et al. (2018); Wang et al. (2018a).
[163] Sun et al. (2018); Wang et al. (2018a).
[164] McPherson et al. (2018).

needs to be converted into a dosage metric.

130. The NTP's 2016 review provides data that facilitate this analysis.[165] In its review, the NTP estimated the doses for dozens of rodent studies by using EPA's default water consumption rates and body weight data for the species, strain, and sex of the animals studied.[166] A review of NTP's data shows that the average ratio of fluoride concentration (mg/L) to intake rate or dose (mg/kg/day) is 6.8, and that this ratio is generally higher for rats (typically 6 to 10) than for mice (typically 3.8 to 5). For purposes of this analysis, the low end of this range was chosen for each species (6 for rats, 3.8 for mice). The practical effect of selecting the low-end of this range, is that the estimated doses will likely *overestimate* the actual dose, and thereby *inflate* the RfDs derived from these Points of Departure.[167] The net result of this non-conservative approach will be RfDs that are *less* protective of human health.

D. Selecting the Uncertainty Factors

131. Consistent with EPA's standard risk assessment procedures,[168] the *Guidelines* provide that "uncertainty factors" (UFs) should be applied to the point of departure (POD) to ensure that the resulting RfD is protective of health.[169]

132. Uncertainty factors are applied to account for expected variations in susceptibility among humans (*intra*species variability, or UF_H), expected differences in susceptibility between animals and humans (*inter*species variability, or UF_A), and, where applicable, differences in the

[165] NTP (2016), Appendix 19.
[166] NTP (2016), p. 118.
[167] For example, using this method gives an intake rate of 0.83 mg/kg/day for rats for the 5 mg/L fluoride concentration (Table 5). However, Bartos et al. (2018; 2019) give an estimate of 0.6 mg/kg/day for their rats at this fluoride concentration. Using the same approach described below with Table 5 for a LOAEL of 5 mg/L, equivalent to an intake rate of 0.6 mg/kg/day, gives an RfD of 0.0005, compared with 0.0007 in Table 5.
[168] EPA (2018a), pp. xvii-xxiv.
[169] EPA (1998a), pp. 58-59.

length of exposure between the study and human conditions (subchronic to chronic, or UF_S), research gaps in the overall database (database deficiency, UF_D), and converting from a LOAEL to a NOAEL.[170] These uncertainty factors are "typically multiples of 10," although they can be reduced to factors of 3 or 1 if warranted by available information.[171,172]

1. *Intra*species Variability (UF_H)

133. EPA recognizes that susceptibility to toxic substances is not uniform across the human population, and that due to differences in *toxicokinetics* and/or *toxicodynamics* some subsets of the population will be more vulnerable to harm than others.[173]

134. *Toxicokinetics* refers to the "processes which determine the extent and duration of exposure of the target organ or site of toxicity to the active chemical species," while *toxicodynamics* refers to the "processes involved in the translation of such exposure of the target organ or site of action into the generation of a toxic effect."[174] Put more simply, toxicokinetics governs how much of the chemical gets to the target site (i.e., access), while toxicodynamics governs how much of the chemical is necessary at the target site to cause the adverse effect (i.e., sensitivity).

135. If there are no chemical-specific data on toxicokinetics and toxicodynamics, EPA uses a default UF_H of 10.[175] This default factor of 10 is "considered to be appropriate in the absence of convincing data to the contrary."[176] Consistent with this, EPA has used a UF_H of 10 in each of

[170] EPA (1998a), p. 59; EPA (2018a), p. xxii; EPA (2016), pp. xix-xx.
[171] EPA (1998a), p. 59; EPA (2018a), p. xxii; EPA (2016), p. xix.
[172] As discussed by Martin et al. (2013), default uncertainty factors, while sometimes viewed as overly protective, do not represent worst-case situations and cannot be safely assumed to be adequately protective of the most exposed individuals or the most susceptible individuals, nor can they be safely assumed to be protective for effects of mixtures of chemicals.
[173] EPA (2011b), p. 14; EPA (2016), p. 2-15; EPA (2018a), p. 2-12.
[174] Renwick (1993), p. 276.
[175] EPA (2018a), pp. 2-12, 2-13.
[176] EPA (2013a), p. 5-17.

the nine risk assessments where it has established an RfD or RfC pursuant to the *Guidelines* (Table 3).

136. In the case of fluoride, there is evidence that affirmatively demonstrates substantial variability in how humans respond to fluoride, including differences in retention (toxicokinetics) and differences in response (toxicodynamics). These data are discussed below in the Risk Characterization. While the magnitude of this variability is difficult to quantify, the data *support* the need for an uncertainty factor as opposed to providing "convincing data" *against* one. Accordingly, pursuant to standard EPA procedure, a value of 10 for UF_H was assigned.

Table 3. Summary of RfDs or RfCs developed in compliance with EPA's Guidelines for Neurotoxicity Risk Assessment.

			Uncertainty Factors						
Chemical	LOAEL	NOAEL	UF_H	UF_A	UF_S	UF_D	Composite	RfD or RfC[a]	Reference
BDE-47	10.5 mg/kg	0.7 mg/kg	10	10	3	10	3000	0.1 µg/kg/day	EPA (2008a)
BDE-99	0.8 mg/kg	0.4 mg/kg	10	10	3	10	3000	0.1 µg/kg/day	EPA (2008b)
BDE-153	0.9 mg/kg	0.45 mg/kg	10	10	3	10	3000	0.2 µg/kg/day	EPA (2008c)
BDE-209	20.1 mg/kg	2.22 mg/kg	10	10	3	1	300	7 µg/kg/day	EPA (2008d)
Chlorine Dioxide and Chlorite	6 mg/kg/day	3 mg/kg/day	10	10	1	1	100	0.03 mg/kg/day	EPA (2000b)
2-Hexanone	143 mg/kg/day	Not observed	10	10	1	10	1000	0.005 mg/kg/day	EPA (2009b)
Methanol	1000 ppm (1310 mg/m^3)	500 ppm (655 mg/m^3)	10	3	1	3	100	20 mg/m^3	EPA (2013a)
RDX	8 mg/kg/day	4 mg/kg/day	10	3	1	10	300	0.004 mg/kg/day	EPA (2018a; 2018h)
Trimethylbenzenes	492 mg/m^3	123 mg/m^3	10	3	3	3	300	0.01 mg/kg/day	EPA (2016)

[a] Where EPA established both an RfD (mg/kg/day) and an RfC (mg/m^3) for a chemical, the RfD is presented.

Table 4. Comparison of $BW^{1/1}$ and $BW^{3/4}$ in estimating oral exposure in humans from a 10 mg/kg exposure to rats, mice, and a dog.[a]

			Scaling = $BW^{1/1}$		Scaling = $BW^{3/4}$	
Absolute animal intake or administered dose	Species	BW(h)/BW(a)	BW scaling factor	BW scaled human intake or oral dose (mg/kg)	BW scaling factor	BW scaled human intake or oral dose (mg/kg)
0.25 mg / 0.025 kg	Mouse	70 / 0.025 = 2800	$2800^{1/1} = 2800$	(2800 × 0.25 mg = 700 mg) 700 mg / 70 kg = 10 mg/kg	$2800^{3/4} = 385$	(385 × 0.25 mg = 96 mg) 96 mg / 70 kg = 1.4 mg/kg
2.5 mg / 0.25 kg	Rat	70 / 0.25 = 280	$280^{1/1} = 280$	(280 × 2.5 mg = 700 mg) 700 mg / 70 kg = 10 mg/kg	$280^{3/4} = 68$	(68 × 2.5 mg = 170 mg) 170 mg / 70 kg = 2.4 mg/kg
120 mg / 12 kg	Dog	70 / 12 = 5.8	$5.8^{1/1} = 5.8$	(5.8 × 120 mg = 700 mg) 700 mg / 70 kg = 10 mg/kg	$5.8^{3/4} = 3.7$	(3.7 × 120 mg = 444 mg) 444 mg / 70 kg = 6.4 mg/kg

[a] Taken from Table A-1 in EPA (2011b), p. 29.

2. *Inter*species Variability (UF_A)

137. EPA recognizes that susceptibility to toxic substances can differ across species. As with human-to-human variability, animal-to-human variability is also rooted in principles of toxicokinetics and toxicodynamics.

138. To adjust for differences in toxicokinetics between animals and humans, EPA has developed a hierarchical framework of approaches for ascertaining the "human equivalent dose" (HED) of doses given to animals.[177] EPA's "optimal" approach for determining the HED is to use a physiologically based toxicokinetic model (PBTK).[178] Where a PBTK model is not available, the "intermediate" approach is to use chemical-specific information that, while falling short of a full PBTK model, provides some reliable guidance.[179] Where there is no reliable chemical-specific information on kinetics, EPA uses a default allometric scaling method.[180]

139. Allometric scaling is "scaling of physiological rates or quantities to relative growth and size (mass or volume) of one animal species relative to another species."[181] Under EPA's recommended method for allometric scaling ($BW^{¾}$ Method), the HED equates to 24% of the dose given to rats, and 14% of the dose given to mice (see Table 4 above).[182]

140. The $BW^{¾}$ Method "predominantly addresses factors involved in estimating toxicokinetics, as well as some toxicodynamic factors."[183] EPA thus maintains a residual default UF of 3 to allow for residual uncertainty from toxicodynamics, unless there is chemical-specific information available.[184]

[177] EPA (2011b), pp. 18-21; EPA (2018a), p. 2-10.
[178] EPA (2011b), p. 19.
[179] EPA (2011b), p. 19.
[180] EPA (2011b), p. 19.
[181] EPA (2011b), p. 1.
[182] EPA (2011b), p. 29, Table A-1; EPA (2018a), p. 2-12.
[183] EPA (2011b), p. 17.
[184] EPA (2011b), p. 21; EPA (2016), p. 2-15; EPA (2018a), pp. 2-12, 2-13.

141. The following factors were considered to account for interspecies differences in both the toxicokinetics and toxicodynamics of fluoride.

142. *Toxicokinetic Considerations:* A full PBTK model has not yet been developed for fluoride that would allow for the calculation of HEDs from doses given to animals. As such, EPA's preferred approach for controlling for interspecies toxicokinetics is not available. By contrast, there is chemical-specific information for fluoride that could support application of EPA's intermediate approach. As discussed by the NRC, rats require higher levels of fluoride in their water to achieve the same level of fluoride in their blood.[185] Dunipace estimated that rats require about 5 times more fluoride in water than humans to reach the same plasma concentration of fluoride,[186] while Den Besten's team has reported a larger margin for mice, with a difference of about a factor of 10.[187] The data from Dunipace and Den Besten support a toxicokinetics adjustment of 5 for rats and 10 for mice, which are slightly *higher* than, but roughly consistent with, the adjustments under the default BW ¾ Method (4 for rats, 7 for mice). The chemical-specific information for fluoride thus supports the general validity of the BW¾ Method, but would be more protective. The BW¾ Method, which is roughly consistent with the chemical-specific information, but slightly *less* protective, was selected as the method for the toxicokinetics adjustment.

[185] NRC (2006), pp. 98-99; pp. 442-446, Appendix D; NRC (2009), pp. 88-89.
[186] NRC (2006), pp. 98, 442.
[187] Zhang et al. (2014).

143. *Toxicodynamic Considerations:* It has long been recognized that rodents are less susceptible (i.e., more resistant) to certain toxic effects from fluoride ingestion than are humans.[188] Rats, for example, have been reported to require 10 to 25 times more fluoride than humans to develop dental fluorosis.[189] Differences in toxicokinetics contribute to rodents being less sensitive to fluorosis, but the differences appear larger than would be expected if they were due solely to kinetics. The fluorosis data support the existence of differential toxicodynamics between rodents and humans, but it is unclear if this difference would also apply to neurotoxicity, as this has not yet been the subject of study. Conversely, there are no data to suggest that humans are *more resistant* to fluoride neurotoxicity than animals. In the absence of data, EPA's default uncertainty factor of 3 was selected to account for interspecies differences in toxicodynamic differences.

3. LOAEL to NOAEL

144. When EPA uses a LOAEL from animal data as the Point of Departure, it applies an additional uncertainty factor of 10 to convert the LOAEL into an estimated NOAEL.[190] Consistent with EPA practice, the three LOAEL-based PODs were adjusted by a factor of 10.

4. Composite Uncertainty Factor

145. The "composite" uncertainty factor is the product of all uncertainty factors used in an analysis. The composite uncertainty factor applied here to the NOAEL-based PODs is **30**, which is the same value that EPA has been using in its draft risk evaluations under TSCA.[191] The

[188] Roholm (1937), pp. 265, 318; Lehman and Fitzhugh (1954), p. 33; Angmar-Mansson and Whitford (1982), p. 339.

[189] Roholm (1937), pp. 265, 318; Angmar-Mansson and Whitford (1982), p. 339.

[190] EPA (1998a), p. 59.

[191] In my expert report, I also calculated alternate RfDs where I applied additional uncertainty factors that EPA uses to account for subchronic animal exposures and deficiencies in the fluoride database (e.g. no data on formula-feeding during the neonatal period). For purposes of simplicity, I have not included those calculations in this declaration.

composite uncertainty factor applied here to the LOAEL-based PODs is **300**, which is on the low-end of the range of the composite uncertainty factors that EPA has used in its neurotoxicity risk assessments (see Table 3 above).

E. RfD Calculations from Animal Data

146. Table 5 summarizes the RfD calculations for each of the five Points of Departure (POD) listed above. The RfDs range from 0.0007 to 0.006 mg/kg/day for the LOAEL-based PODs, and 0.01 to 0.03 mg/kg/day for the NOAEL-based PODs. The least protective RfD that can be derived from the literature in a manner consistent with EPA practice is thus **0.03 mg/kg/day**.

Table 5. Calculation of the RfD from the selected Points of Departure (POD), based on the studies summarized in Table 2.

A Observation	B Intake rate	C POD_{HED}	D NOAEL	E $UF_H = 10$	F $UF_A = 3$	G RfD
LOAEL or NOAEL from Table 6	Column A / 6 (rats) or 3.8 (mice)	Column B × 0.24 (rats) or 0.14 (mice)	Column C / 10 (LOAEL) or 1 (NOAEL)	Column D / 10	Column E / 3	Column F
mg/L	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day
5 mg/L, LOAEL (rats)	0.83	0.20	0.020	0.0020	0.00067	0.0007
23 mg/L, LOAEL (rats)	3.8	0.91	0.091	0.0091	0.0030	0.003
45 mg/L, LOAEL (rats)	7.5	1.8	0.18	0.018	0.0060	0.006
11 mg/L, NOAEL (mice)	2.9	0.41	0.41	0.041	0.014	0.01
20 mg/L, NOAEL (rats)	3.3	0.79	0.79	0.079	0.026	0.03

Column A: The observed LOAEL or NOAEL from Table 2.

Column B: The observed LOAEL or NOAEL converted from mg/L to an intake rate (dose) in mg/kg/day. For rats, the LOAEL or NOAEL is divided by 6; for mice, the NOAEL is divided by 3.8 (see explanation in text).

Column C: The intake rate for rats or mice converted to a human equivalent dose (HED) using the $BW^{3/4}$ method (see explanation in text). The HED = 24% of the intake rate for rats or 14% of the intake rate for mice.

Column D: NOAEL as already obtained (NOAEL / 1) or as estimated from a LOAEL (LOAEL / 10).

Column E: The estimated NOAEL after application of an intraspecies uncertainty factor (UF_H), where $UF_H = 10$. The NOAEL from Column D is divided by UF_H (i.e., NOAEL / 10).

Column F: The estimated NOAEL after application of an additional uncertainty factor for interspecies variability (UF_A), where $UF_A = 10$. The adjusted NOAEL from Column E is divided by UF_A (i.e., NOAEL / 3).

Column G: The value of the Reference Dose (RfD) obtained with only UF_H and UF_A. RfD = the NOAEL value in Column F, rounded to 1 significant digit.

VII. EXPOSURE ASSESSMENT

147. The only condition of use at issue in this case, as I understand it, is the addition of fluoridation chemicals to drinking water. Because of this, I limited the scope of my exposure assessment to exposures directly attributable to fluoridated water (0.7 mg/L). The purpose of my assessment was to enable a comparison of the doses people ingest from fluoridated water with the toxicity values (LOAELS and NOAELs) derived from the animal studies. I did not consider fluoride intake from dental products, pesticides, industrial pollution, occupational exposures, black tea, or other sources.

148. In my assessment, I considered fluoride exposures among both the general public as well as subsets of the population known to consume elevated amounts of water. For the source data, I relied primarily on the NRC's 2006 report which presented estimates of fluoride intake from water containing 0.7 mg/L fluoride. The NRC's estimates were based on an EPA analysis of community water intake data that were collected in a national survey by the US Department of Agriculture (USDA) in the 1990s.[192] The USDA survey was "designed to obtain a statistically representative sample of the United States population," and EPA stated that data from this survey "may be used in risk assessment analyses where exposures that occur through ingestion of water are of concern."[193]

149. Based on NRC's data, human exposure to fluoride from fluoridated water is estimated to range from an average of 0.011 mg/kg/day for adults to a "high" of 0.14 mg/kg/day for 95th percentile-exposed infants.

150. Following my initial report, a criticism was raised that I should have conducted a

[192] The USDA survey is called the "Continuing Survey of Food Intakes by Individuals," or CSFII for short.

[193] EPA (2000a), p. 5-5.

systematic review of all water intake data published subsequent to the NRC's report. In response to this criticism, I reviewed an updated and comprehensive review of water intake data that EPA published in 2019. The review was published as an update to EPA's *Exposure Factors Handbook* ("*Handbook*"), which is a document "intended for use by exposure and risk assessors both within and outside the U.S. EPA as a reference tool and primary source of exposure factor information."[194]

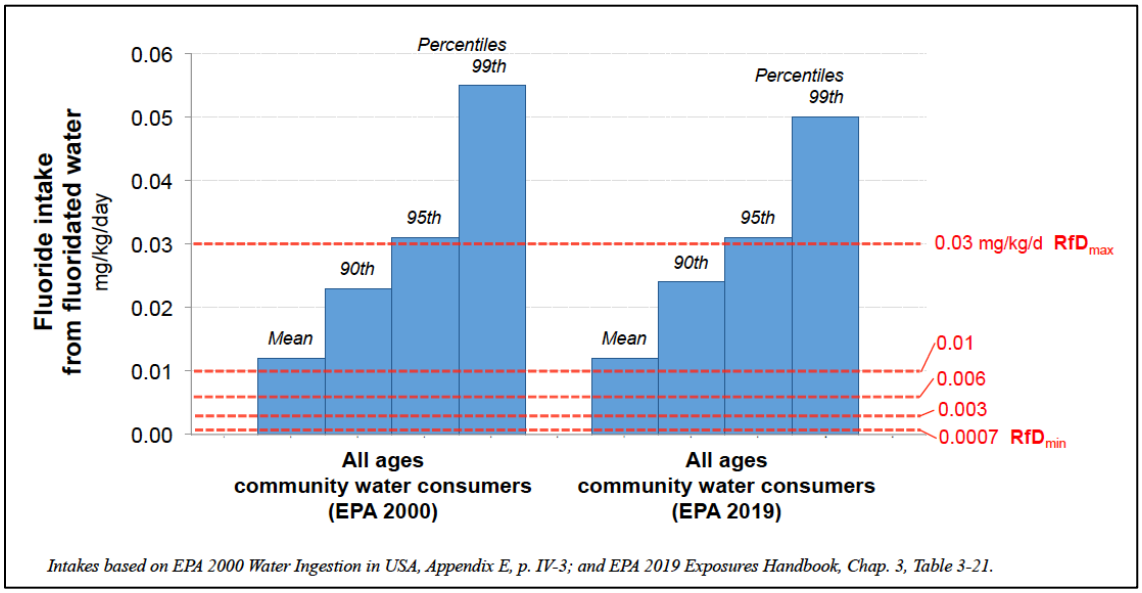
151. In its 2019 report, EPA presented the results of its "comprehensive review of the scientific literature [on water intake] through 2017" and provided EPA's determination as to "the most up-to-date and scientifically sound" data[195] to use for tap water consumption in the US.[196] The report thus provides the community water intake values[197] that EPA now recommends using for risk assessment for each age group in the population.[198]

152. The water intake data that EPA identifies in its 2019 report are consistent with EPA's older water intake data that I relied upon in my initial assessment. For example, whereas I selected 0.011 mg/kg/day as an average adult exposure, the EPA's updated data produce mean intakes by adults of 0.011-0.013 mg/kg/day (i.e., the same as or slightly higher than my estimate).[199] Further, whereas I selected 0.14 mg/kg/day as the 95th percentile exposure among

[194] EPA (2011a), p. 1-3.
[195] EPA (2019b), p. 1-5.
[196] EPA selected its own analysis of water intake data from NHANES's 2005-2010 surveys as the "key study" to use for all age groups in the general population and for pregnant and lactating women. For formula-fed babies, EPA selected an analysis by Kahn of the USDA's CSFII survey, which is the same survey that the NRC relied upon for its estimates in 2006.
[197] EPA's report presents water intake in terms of milliliters of water consumed per kilogram of bodyweight per day (mL/kg/day). This permits a direct estimation of fluoride exposure from fluoridated water because the concentration of fluoride is known (0.7 micrograms per milliliter). By way of example, if a person drinks 100 milliliters of fluoridated water per kilogram of bodyweight, they will receive a dose of 70 *micro*grams of fluoride per kilogram, which is more commonly expressed as 0.07 *milli*grams per kilogram (i.e., 0.07 mg/kg/day).
[198] EPA (2019b), pp. 3-1, 3-4, 3-7, & 3-9.
[199] EPA (2019b), pp. 3-4.

bottle-fed infants, EPA's updated data produce 95th percentile values ranging from 0.l3 mg/kg/day to 0.2 mg/kg/day (i.e., higher than my estimate).[200]

153. The similarity between the two EPA datasets can be seen in the following figure. The figure shows the fluoride exposure from water for *all* community water consumers for *all* age groups combined. The left side of the figure shows EPA's 2000 data (that NRC and I relied upon), while the right side of the figure shows EPA's 2019 data. To help put these exposures in context, the figure also shows the five reference doses from the animal neurotoxicity data (Table 5).



154. As can be seen in the figure, the two datasets show that a *substantial* percentage of the population that consume fluoridated tap water exceed each of the 5 RfDs for neurotoxicity, including the least protective RfD.

155. One limitation with EPA's water intake data (from both 2000 and 2019) is that they do not include consumption of community water that is added to commercial beverages, such as soda and juice.[201] This underestimates actual exposure to fluoridated water, since commercial

[200] EPA (2019b), pp. 3-9.
[201] EPA (2000a), p. viii.

beverages have become a significant source of exposure to fluoridated water for many people.[202]

156. Another limitation with EPA's water intake data is that they are based on short-term surveys (i.e., surveys taken on two non-consecutive days), which creates a source of uncertainty when extrapolating to long-term exposures. This uncertainty is minimized, however, by the large numbers of people surveyed in the studies, and the use of non-consecutive days for the survey. While not perfect, EPA has recognized these data as the most scientifically sound data to use for risk assessment.

VIII. RISK CHARACTERIZATION

157. The risk characterization step of a risk assessment integrates the evidence of hazard, exposure, and dose-response in a clear and transparent manner, and provides a description of the risk. The *Guidelines* recognize multiple ways of describing risk, including (i) characterization of highly-exposed and/or susceptible individuals; (ii) estimation of the number of individuals exposed; (iii) comparing human exposures against the RfD; and (iv) "Margin of Exposure" analysis.[203]

A. Characterization of Highly Exposed and/or Highly Susceptible Populations

158. Susceptibility to a chemical may be "intrinsic" (biological, e.g., life stage) or "extrinsic" (acquired, e.g., lifestyle),[204] although many individuals may have *both* intrinsic *and* extrinsic susceptibility.

159. EPA has recognized that life stage is an important source of intrinsic susceptibility to neurotoxicants, and has identified the prenatal, infant, and elderly stages of life as "critical periods for exposure."[205] According to the EPA, "It is a well-established principle that there are

[202] E.g., Heilman et al. (1999); Kiritsy et al. (1996); Turner et al. (1998).
[203] EPA (1998a), pp. 63-66.
[204] EPA (2017).
[205] EPA (1998a), p. 65.

critical developmental periods for the disruption of functional competence, which include both the prenatal and postnatal periods to the time of sexual maturation, and the effect of a toxicant is likely to vary depending on the time and degree of exposure."[206] In light of this, a "population subgroup is susceptible if exposure occurs during a period of sensitivity."[207]

160. As described below, there are large, identifiable subsets of the population that are likely more susceptible to the neurotoxic effects of fluoride than the general population, including pregnant women and their fetuses, bottle-fed infants, the elderly, and individuals with renal impairment.

1. Pregnant Women and Their Fetuses

161. Multiple converging lines of evidence support the fetal period as a critical period of susceptibility to fluoride's neurotoxic effects. First, it is well established that fluoride crosses the placenta and reaches the fetus.[208] Second, due to the absence of an effective blood brain barrier,[209] the fluoride that reaches the fetus also reaches the brain—a fact that has been confirmed by both animal and human studies.[210] Third, fluoride has the capacity to lower thyroid function, particularly among individuals with low iodine intakes, and EPA has recognized that alterations to thyroid function (e.g., reductions in thyroid hormone concentrations) during pregnancy can cause cognitive disorders and other neurological harm to the child.[211] Fourth, most studies of prenatal fluoride exposures in animals have documented neuroanatomical, neurochemical, and/or cognitive problems. Fifth, all prospective cohort studies that included individual measurements of

[206] EPA (1998a), p. 46.
[207] EPA (2008a), p. 42.
[208] NRC (2006), p. 193.
[209] EPA (2009b), p. 58.
[210] E.g., McPherson et al. (2018); Mullenix et al. (1995); Du et al. (1992).
[211] EPA (1998a), p. 50; EPA (2008a), p. 40; EPA (2008b), p. 54; EPA (2013b), cover letter, p. 2. See also Rodier (1995); Zoeller and Rovet (2004); Patel et al. (2011); Suárez-Rodríguez et al. (2012); Modesto et al. (2015); Bellinger (2018).

prenatal fluoride exposure have found significant adverse associations with neurocognitive harm, including IQ loss and inattention.[212]

162. The number of pregnant women exposed to fluoridated water each year is large. The CDC estimates that there are approximately 4 million children born in the U.S. each year, and therefore about 4 million pregnancies.[213] With approximately two-thirds of the U.S. population living in communities where fluoridation chemicals are added to water, about 2.5 million pregnancies can be expected to occur each year in fluoridated areas.

163. Of paramount concern are pregnant women who have an iodine deficiency. The CDC considers the average iodine status (median urinary iodine concentration) of women of childbearing age (12-19 years and 20-39 years) in the U.S. to be in the "adequate intake" range, but the 10th percentiles by ethnicity and for the total population are in the "insufficient intake" range, indicating that more than 10% of women of childbearing age in the U.S. are deficient in iodine.[214] Caldwell et al. report that 35% of pregnant women and 38% of nonpregnant women in the U.S. have urinary iodine concentrations below the level considered adequate.[215] In addition, the CDC notes that even higher intakes of iodine are required for pregnant and lactating women; thus an even greater percentage of American women are likely to be deficient in iodine with respect to the demands of pregnancy and lactation.[216] Pearce suggests that iodine deficiency in the U.S. may be becoming more prevalent, especially among pregnant women.[217]

164. While the effects of fluoride exposure among pregnant women with iodine

[212] Bashash et al. (2017; 2018); Green et al. (2019); Valdez-Jiménez et al. (2017).
[213] Centers for Disease Control. Births and Natality. Available at: http://www.cdc.gov/nchs/fastats/births.htm
[214] CDC (2008), Chapter 4a, pp. 90-100.
[215] Caldwell et al. (2011).
[216] CDC (2008), Chapter 4a, pp. 90-100.
[217] Pearce (2015).

deficiency have not yet been specifically studied, there is a clear basis for concern. The NRC reported that high fluoride intake appears to exacerbate the effects of low iodine intake on thyroid function in both animals and humans.[218] Consistent with this, Malin et al. found that an increase in urinary fluoride was associated with an increase in thyroid stimulating hormone (TSH)—an indicator of decreased thyroid function—among iodine-deficient adults in Canada.[219] A decrease in thyroid function during pregnancy, even in the absence of clinical symptoms in the mother, is associated with reduced IQ and other neurological effects in the offspring.[220]

2. Bottle-Fed Infants

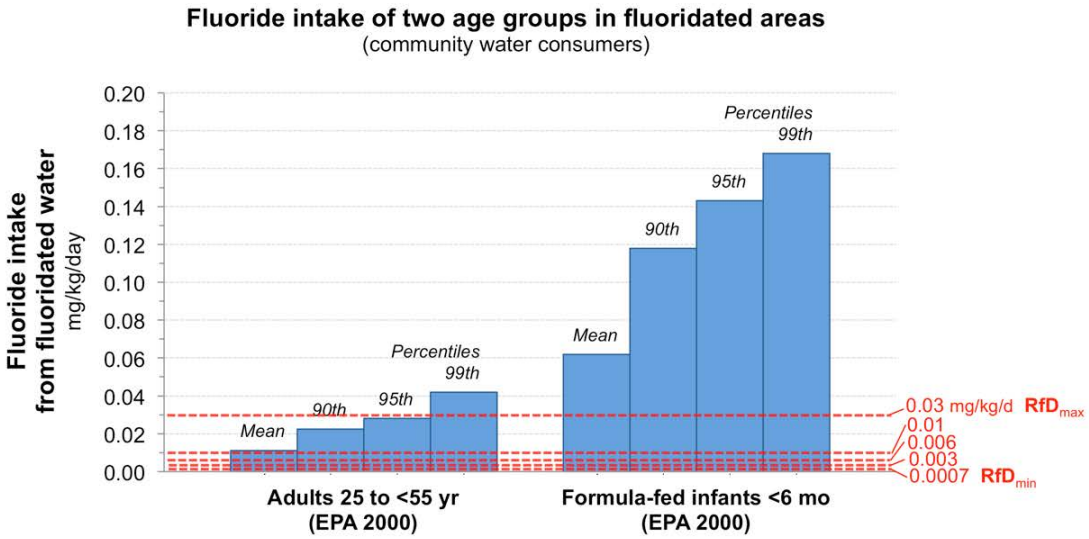
165. A bottle-fed infant has a combination of *both* intrinsic *and* extrinsic susceptibility to fluoridated water.

166. *Intrinsic Susceptibility*: The blood brain barrier does not finish developing until 6 months of age,[221] and, as such, the fluoride ingested during early infancy will likely reach the brain more readily than during the later childhood and adult years. The brain is also undergoing "rapid development" during infancy, with the growth rate of the brain peaking at 4 months of age.[222] The EPA has thus described the neonatal stage of life as "a critical window of development."[223]

167. *Extrinsic Susceptibility*: Infants have the highest intake of fluid per unit body weight of any age group among humans, given their mostly liquid diet at that age. This can be seen in the following figure, which uses EPA's 2000 water intake data to compare the community water

[218] NRC (2006), pp. 227, 234, 262.
[219] Malin et al. (2018).
[220] For example, see Haddow et al. (1999); Pop et al. (1999; 2003); Morreale de Escobar et al. (2000; 2004); Klein et al. (2001); Vermiglio et al. (2004); LaFranci et al. (2005); Kooistra et al. (2006); Roman (2007); Zoeller and Rovet (2004); Patel et al. (2011); Suárez-Rodríguez et al. (2012); Modesto et al. (2015); Moleti et al. (2016).
[221] EPA (2009b), p. 58.
[222] EPA (2013a), p. 5-4; EPA (2008a), p. 42.
[223] EPA (2008a), p. 42.

intake of adults (on the left) with the community water intake of bottle-fed infants (on the right).



Intakes based on EPA 2000 Water Intake Estimates in US, p. IV-3.

168. According to the CDC, 75% of infants born in 2015 were formula-fed at least partially during their first six months, including 17% of infants who were *exclusively* formula-fed.[224] Data vary by ethnicity, with Hispanics, whites and Asians having breastfeeding rates similar to or greater than the national averages and African Americans having substantially lower rates. Breastfeeding rates tend to be highest for higher family income and maternal education levels.

169. Breastfeeding rates in the U.S. have increased substantially in recent years from a low point in the early 1970s.[225] While increased breastfeeding rates are to be encouraged for a number of reasons, it is important to remember that for many infants in the U.S., breastfeeding is not an option; these include cases of infant adoption or fostering, as well as cases of death or illness of the mother.

[224] CDC (2018; n.d.).
[225] DHEW (1979), pp. 2-6, especially Tables A and B.

170. Most commercial infant formula, historically and currently, has been in powder form, for which the cost is approximately half that of ready-to-feed formula, per unit volume of formula as fed.[226] Based on national data collected during 2005-2007, the CDC reported that approximately 83-93% of babies are fed formula prepared from powder from cans.[227] For approximately 70-78% of infants in the same national survey, formula is reconstituted with tap water at least some of the time.[228]

171. Based on the available information, it can reasonably be assumed that the majority of formula-fed infants in the U.S. are fed powdered formula reconstituted with water, often or usually tap water. Especially for low-income homes (where breastfeeding is less likely), it is reasonable to assume that many or most infants are fed formula prepared from powder using tap water, which in much of the country is fluoridated. In addition, for approximately 20% of infants, tap water is boiled before it is used to prepare formula;[229] if this tap water is fluoridated, the resulting fluoride concentration in the formula will be higher than if the water had not been boiled.[230]

172. Fomon et al. estimated that infants consuming powdered formula prepared with fluoridated water (1 mg/L) will ingest between 0.116 and 0.164 mg/kg/day.[231] If Fomon's estimate is adjusted to account for the lower concentration of fluoride now added to water (0.7 mg/L), the result is a daily intake of 0.08 to 0.115 mg/kg/day, which is 80 to 115 times higher than the amount that Fomon et al. estimated for breast-fed infants (0.001 mg/kg/day).[232] By Fomon's estimates,

[226] O'Connor (2009).
[227] CDC (2017), Table 3.16.
[228] CDC (2017), Table 3.97.
[229] CDC (2017), Table 3.98.
[230] For example, see Juárez-López et al. (2011).
[231] Fomon et al. (2000), Table 2.
[232] Fomon et al. (2000), Table 2.

essentially all formula-fed infants will exceed the RfDs for neurotoxicity if their formula is prepared with fluoridated tap water.

173. Fomon's estimates agree well with recent data from Harriehausen et al., who surveyed 114 parents in Houston to determine brand and type of formula, total volume of formula consumed over 24 hours, and infant weight.[233] Most of the parents in the study (corresponding to 92.1% of the infants) reported using powdered formula, which is consistent with the literature described above.[234] Harriehausen et al. estimated that over 50% of infants fed formula made with fluoridated water will exceed 0.1 mg/kg/day during the first 4 months of life (Table 6).

Table 6. Estimated fluoride ingestion from infant formula, assuming fluoridated water at 0.7 mg/L.[a]

	Age				
Category	2 months	4 months	6 months	9 months	12 months
Number of infants	32	23	27	21	11
Predicted fluoride intake					
Mean (mg/kg/day)	0.110	0.112	0.090	0.066	0.053
Variance	0.0033	0.0016	0.0018	0.0012	0.0009
Standard deviation[b]	0.057	0.040	0.042	0.035	0.03
Distribution of fluoride intake					
> 0.1 mg/kg/day (%)	59.4	56.5	33.3	14.3	9.1
< 0.1 mg/kg/day (%)	40.6	43.5	66.7	85.7	90.9

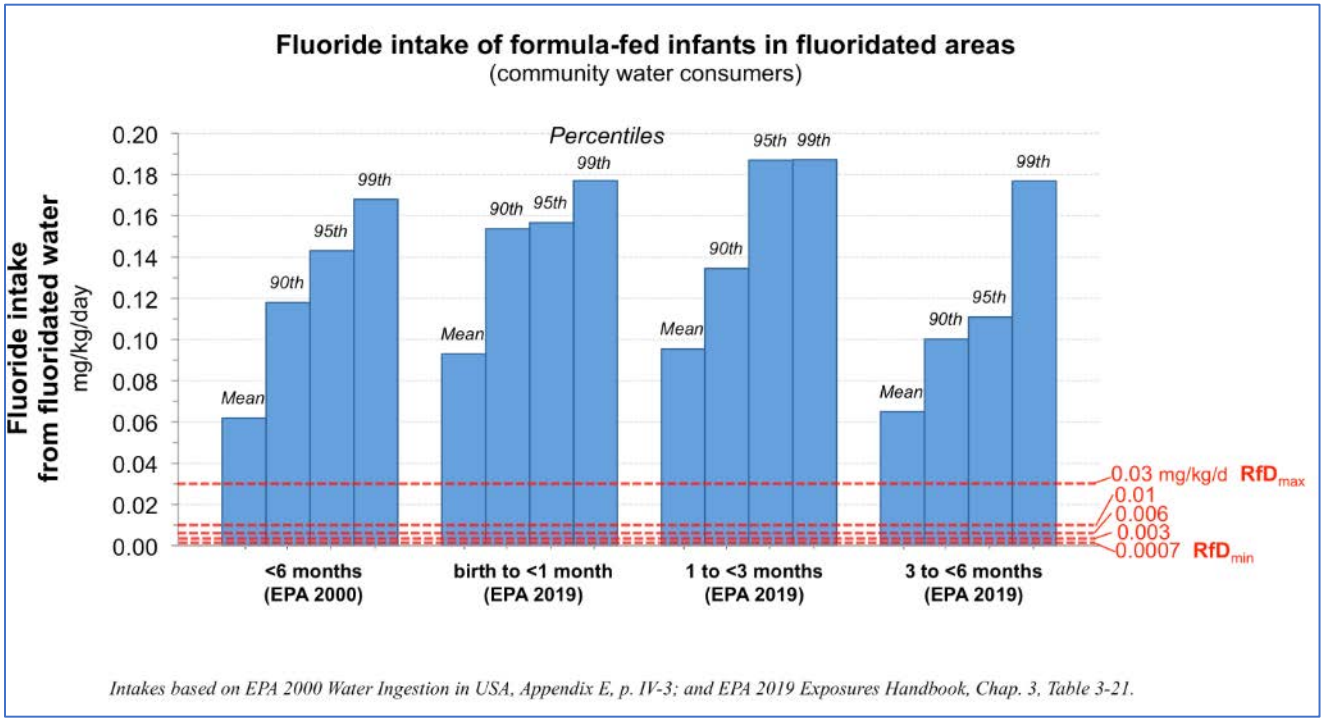
[a] Data from Harriehausen et al. (2019), Table 3.

[b] Calculated from the variance reported by Harriehausen et al. (2019), Table 3.

[233] Harriehausen et al. (2019).

[234] Harriehausen et al. (2019), Table 2.

174. The estimates from both Harriehausen and Fomon are consistent with EPA's most up-to-date and scientifically sound estimates for formula-fed infants.[235] According to EPA's updated estimates, mean fluoride exposures during the first 6 months of life for infants receiving formula reconstituted with fluoridated water are **0.07 to 0.10 mg/kg/day** (age-dependent), with 95th percentile exposures of **0.13 to 0.2 mg/kg/day** for the first 3 months and **0.13 mg/kg/day** for the next three months.[236] These intakes are very high, and far exceed even the least protective RfD, as shown in the following figure.



Intakes based on EPA 2000 Water Ingestion in USA, Appendix E, p. IV-3; and EPA 2019 Exposures Handbook, Chap. 3, Table 3-21.

175. In its *Guidelines*, EPA considers the potential for postnatal toxicant exposures to interact with breastmilk composition.[237] EPA was referring to animal studies, but the principle would apply to humans as well: Replacement of the mother's milk with a substitute that contains a toxic agent would be an extremely important source of postnatal exposure for infants and children

[235] EPA (2019b), p. 3-9.
[236] EPA (2019b), p. 3-9.
[237] EPA (1998a), p. 46.

to that toxic agent. Few, if any, animal studies reproduce the effect of formula-feeding of human infants, in terms of a water-based formula containing fluoride being substituted for the mother's milk; thus this very important developmental period is routinely missed in most developmental studies on fluoride.

176. Consistent with the high fluoride intakes produced by formula feeding, studies have found that bottle-fed babies have higher rates of dental fluorosis (a disorder of enamel caused by excess fluoride intake) in their permanent teeth.[238] Studies have also documented an increased prevalence and severity of dental fluorosis in the African American community, which is consistent with the high rate of formula feeding in this population.[239]

177. While fluoride exposure during infancy is known to produce abnormal physiological changes in the body (e.g., dental fluorosis), there has been a paucity of research on the neurodevelopmental effects of this exposure. In the developmental studies on fluoride neurotoxicity to date, the pups have been *breastfed*. Consequently, the existing animal data do not reflect the neurotoxic effects that may occur during the neonatal period.

178. Studies in humans have found lower IQ scores among formula-fed babies versus breastfed babies,[240] but up until this year,[241] no study had investigated the role that fluoridated water may have in this association. Specific differences in brain activation and regional volumes of gray matter have been reported among formula-fed children, indicating developmental changes in children in comparison with breastfed children.[242] Such effects (and other adverse effects of

[238] Hong et al. (2006a; 2006b); Forsman (1977); Walton and Messer (1981); Fomon and Ekstrand (1999); Fomon et al. (2000).

[239] EPA (2010), pp. 33-34; Exhibit 34 to Casey Hannan Deposition; CDC (2005), Table 23.

[240] For example, see Fomon (2001); Wolf 2003; Belfort et al. (2013); Horta et al. (2015; 2018); Victora et al. (2015; 2016); Kanazawa (2015); Boutwell et al. (2018). Many studies have controlled for possible confounders such as maternal IQ, maternal education, and family income.

[241] Till et al. (2020).

[242] Ou et al. (2016).

formula-feeding compared with breastfeeding, especially compared with exclusive breastfeeding for at least the first several months) could, in principle, be due to loss of the enhanced mother-child bonding associated with breast-feeding,[243] to deficiency of an essential nutrient (e.g., long-chain saturated fatty acids) in the formula,[244] to the presence of a toxic contaminant in the water used to prepare the infant formula,[245] or to some combination of these factors.

179. Given the *a priori* basis for concern that fluoridated water may adversely affect the neurological system of bottle-fed infants, the recent findings from Till et al. must be taken very seriously.[246] Using a prospective cohort study design, Till et al. found that fluoridated water consumption during infancy is associated with a large and significant reduction in non-verbal IQ at age 4 (i.e., a loss of 9.3 non-verbal IQ points for each 0.5 mg/L increase in exposure). Although the study did not find a statistically significant association with Full-Scale IQ after excluding several outliers, this could be a result of imprecision in the exposure estimates, or might reflect differential impacts of pre- and post-natal exposure.

180. As noted earlier, CDC data indicate that 17% of babies are *exclusively* fed formula for their first six months of life (i.e., never breast-fed).[247] Assuming 2.5 million live births per year in fluoridated areas, approximately 1.9 million infants living in fluoridated areas will be formula-fed for at least part of the time during their first six months, including 425,000 infants who are *exclusively* formula-fed.[248] Approximately 70-78% of these infants will have their formula made

[243] Horta et al. (2018).
[244] Horta et al. (2018).
[245] Goyer (1995).
[246] Till et al. (2020).
[247] CDC (2018; n.d.).
[248] CDC (2018; n.d.).

with fluoridated tap water (some of which will be boiled and have higher concentrations), at least part of the time.[249]

3. Elderly

181. The elderly have also been identified by the EPA as an at-risk group for neurotoxicity.[250] According to the EPA, the elderly are "at particular risk because of the limited ability of the nervous system to regenerate or compensate to neurotoxic insult."[251]

182. The NRC has described the possible relationship of fluoride exposure, especially exposure to aluminum fluoride complexes, to the development of Alzheimer's disease.[252] The NRC based its concern, in part, on studies reporting pathological lesions in the brain of fluoride-treated rodents that parallel the changes in humans with dementia.[253] A recent study by Cao et al. found that exposure to fluoride for 3 months among mice genetically prone to degenerative brain changes, produced more severe, and earlier development of, neuropathological lesions than in controls, including lesions associated with Alzheimer's.[254] Goschorska et al. have recently postulated that fluoride plays a likely role in the initiation and progression of Alzheimer's disease, based largely on the neuroanatomical and neurochemical changes seen in the brains of fluoride-treated animals.[255]

183. While epidemiological data on fluoride and cognition in the elderly remain relatively sparse, Li et al. reported a very high rate of cognitive impairment (81.1%) in an endemic fluorosis area.[256] Li did not find a linear relationship between urinary fluoride and the severity of

[249] CDC (2017), Table 3.97; Juárez-López et al. (2011).
[250] EPA (1998a), p. 65; see also NRC (2006), p. 351.
[251] EPA (1998a), p. 65.
[252] NRC (2006), pp. 210-212.
[253] NRC (2006), pp. 222.
[254] Cao et al. (2019).
[255] Goschorska et al. (2018).
[256] Li et al. (2016), p. 59.

cognitive impairment within the endemic fluorosis area; however urinary fluoride levels among those with any form of cognitive impairment were significantly higher than those with normal cognition.[257] Russ et al. described a longitudinal study involving nearly all people born in Scotland in 1921, who were passively followed for diagnoses of dementia after 2004.[258] Residential locations after age 60 (or at death or at time of diagnosis of dementia) were used to estimate exposure to aluminum and fluoride (separately) in drinking water. The authors found that even relatively low levels of aluminum and fluoride were associated with an increased prevalence of dementia and suggested further research.[259]

184. While more research is needed to clarify fluoride's effects in the elderly population, there are a multitude of factors which support an increased vulnerability to fluoride's neurological effects among the elderly. Studies have found that water fluoridation significantly increases the level of fluoride in bone, and these levels increase with age.[260] In the post-menopausal and elderly years, the fluoride that is taken into bone can be released back into the blood stream as bones begin to break down, leading to increased levels of fluoride in the blood.[261] Compounding this, renal function declines with age, and because of this the elderly kidney can be expected to be less efficient in clearing fluoride from the bloodstream. The net result is that more fluoride will be circulating in the bloodstream, and due to age-related increases in the permeability of the blood-brain barrier, will reach the brain more readily.[262]

185. Although the impact of fluoride on the elderly brain has not received as much

[257] Li et al. (2016), Figure 2, Table 3.
[258] Russ et al. (2019).
[259] Russ et al. (2019).
[260] Alhava et al. (1980); Arnala et al. (1985); Eble et al. (1992); Chachra et al. (2010).
[261] Itai et al. (2010).
[262] Increased permeability of the blood-brain barrier is associated with ordinary aging, as well as with diseases such as Alzheimer's and Parkinson's, both of which are common among elderly people. For example, see Mooradian (1994); Zeevi et al. (2010); Rosenberg (2014); and Pan and Nicolazzo (2018).

scholarly attention as the impact on the developing brain, this population is likely at higher risk of toxicity than healthy adults, particularly among those with elevated accumulation of fluoride in the bone following long-term residence in a fluoridated area.

Renal Impairment

186. It is well recognized that people with renal impairment (kidney disease) are less able to excrete fluoride, resulting in higher concentrations of fluoride in the body and greater susceptibility to adverse health effects from fluoride exposure.[263] The World Health Organization states that it "is known that persons suffering from certain forms of renal impairment have a lower margin of safety for the effects of fluoride than the average person."[264] In addition, a number of papers report an association between renal impairment and reduced IQ or other cognitive impairment,[265] which is consistent with higher fluoride retention (and often higher water intake and consequent higher fluoride intake). The role of fluoride in these IQ deficits has not yet been the subject of epidemiological study.

4. Other Predisposing Factors

187. There are a number of other factors that are known, or reasonably anticipated, to increase susceptibility to the chronic toxic effects of fluoride exposure, including neurotoxicity. These factors include:

188. *Diseases that Increase Water Intake*: The NRC identified population subgroups whose water intake "is likely to be substantially above the national average for the corresponding sex and age group" as susceptible subpopulations with respect to fluoride exposure.[266] Health

[263] For example, see Marumo and Iwanami (2001); NRC (2006), pp. 30, 292, 351; Ibarra-Santana (2007); Schiffl (2008).
[264] WHO (2004), p. 6.
[265] For example, see Madero et al. (2008); Mendley et al. (2015); Chen et al. (2018b).
[266] NRC (2006), p. 30.

conditions that affect water intake include "diabetes mellitus, especially if untreated or poorly controlled; disorders of water and sodium metabolism, such as diabetes insipidus; [and] renal problems resulting in reduced clearance of fluoride."[267] According to the NRC, adults with diabetes mellitus can ingest 0.05 mg/kg/day from fluoridated water alone, while children with diabetes mellitus can have fluoride intakes as high as 0.07 mg/kg/day.[268] For children and adults with nephrogenic diabetes insipidus, NRC estimated waterborne fluoride intakes of 0.11 mg/kg/day.[269,270] Each of these intakes exceeds the least protective RfD.

189. *Nutrient Deficiencies*: Nutritional deficiencies can contribute to increased susceptibility to fluoride toxicity.[271] Calcium deficiency and iodine deficiency are expected to be particularly important in terms of vulnerability to neurotoxic effects of fluoride, but deficiencies of magnesium, vitamin C, protein, and other nutrients have also been associated with increased susceptibility to the effects of fluoride exposure.

190. *Genetic Susceptibilities*: A number of studies have shown associations between specific genetic arrangements and a greater susceptibility to the chronic effects of fluoride exposure,[272] including dental fluorosis and alterations to reproductive hormones.[273] While a complete picture of the relationship between genes, gene regulation, and adverse effects of fluoride exposure remains to be developed, it is already quite clear that some people or groups of people

[267] NRC (2006), p. 30.
[268] NRC (2006), p. 35, Table 2-4.
[269] NRC (2006), p. 35, Table 2-4.
[270] Consistent with this, case reports have documented moderate to severe dental fluorosis among children with diabetes insipidus who drank water with 0.5 to 1 mg/L NRC (2006), p. 33.
[271] See for example, NRC (2006). p. 265; Pandit et al. (1940); Marier (1977).
[272] Reviewed by Pramanik and Saha (2017). See also Lavryashina et al. (2003); Tu et al. (2011); Liu et al. (2006); Huang et al. (2008); Ba et al. (2011); Zhao et al. (2015); Zhou et al. (2016); Zhang et al. (2013b); Pei et al. (2017); Jiang et al. (2015); Zhang et al. (2015b); Cui et al. (2018); Küchler et al. (2018); Bhagavatula Naga (2009).
[273] Zhao et al. (2015); Zhou et al. (2016); Ma et al. (2017); An et al. (2019).

are inherently more vulnerable than others to adverse effects of fluoride exposure and require a greater level of protection from fluoride exposures.[274] The implications to neurotoxicity have not yet been extensively studied, but two recent studies from China, including one with extensive control for covariates, suggest that certain genotypes may significantly magnify fluoride's impact on IQ in some individuals.[275] A third, smaller study reported a contrary result.[276] More research is needed to clarify this issue, but in light of the broader literature on genetic susceptibility to chronic fluoride toxicity, it is reasonable to suspect that genetics plays a role in rendering some individuals more vulnerable to fluoride's neurological effects.

B. Margin of Exposure (MOE)

1. Introduction to the MOE Approach and Its Similarity to the RfD Approach

191. Under the *Guidelines*, neurotoxic risk can be described either through a comparison of the human exposures to the RfD, or by calculating the "Margin of Exposure" (MOE).[277] Although the two approaches use slightly different frameworks, they produce the same results. If comparison of human exposure with the RfD shows a risk, a risk will be shown by MOE as well, and vice versa.

192. RfD and MOE analyses produce the same results because they use the same Point of Departure (i.e., NOAEL, LOAEL, or BMDL) for the toxicity value, the same data for human exposure, and the same composite uncertainty factor to assess whether human exposure poses a risk. Where the two methods differ is in how they put these three pieces together and the terminology they use, as will now be discussed.

193. In an RfD analysis, human exposure is compared against the Reference Dose. As

[274] Wu et al. (2015); Yang et al. (2016); Pei et al. (2017); Li et al. (2017); Yang et al. (2018b).
[275] Cui et al. (2018); Zhang et al. (2015b).
[276] Pang et al. (2018).
[277] EPA (1998a), pp. 65-66; Federal Register (1998), pp. 26949-26950.

discussed earlier, the Reference Dose is the Point of Departure (i.e., NOAEL, LOAEL, or BMDL) divided by the composite uncertainty factor. In an MOE analysis, by contrast, human exposure is *compared directly against the Point of Departure.* If the ratio (i.e., Actual MOE) between the Point of Departure and human exposure is less than the composite uncertainty factor (i.e., Acceptable MOE), an unacceptable risk is presumed to exist.[278,279] In short, the composite uncertainty factor is the standard for judging whether human exposure is unacceptably close to the toxicity value under both frameworks.

2. MOE Analysis

194. As part of the risk assessment, I conducted an MOE analysis to characterize risk because this is EPA's preferred method to characterize non-cancer risk under TSCA, as evident by its risk evaluations under both Section 5 (new chemicals)[280] and Section 6 (existing chemicals).[281]

195. *Points of Departure*: The same five Points of Departure (converted into Human Equivalent Doses) that were used for the derivation of the Reference Doses, as discussed above (see Table 5), were used for the MOE analysis.

196. *Acceptable MOEs (Benchmark MOEs)*: The same composite uncertainty factors that were used for the RfD derivation were selected as the Acceptable MOEs: 30 for the NOAEL-based PODs, and 300 for the LOAEL-based PODs. In EPA's draft risk evaluations under Section 6 of TSCA, EPA has used composite uncertainty factors of 30 for NOAEL-based PODs, and has

[278] EPA (2016), p. 61; EPA (2012), p. 13-8.
[279] EPA sometimes refers to the risk as a "risk of concern." EPA (2007), p. 13; EPA (2000c), p. C-12.
[280] See for example EPA (2018b; 2018c; 2018d; 2018e; 2018f; 2018g; 2019a).
[281] In its draft risk evaluations under Section 6 thus far, EPA has used MOE to characterize non-cancer risk. (EPA 2019c; 2019d; 2020). In its Final Rule for Risk Evaluation under Section 6, however, EPA described the MOE method as "just one of several approaches to risk characterization" that may be used under TSCA (Federal Register 2017, p. 33735).

characterized this as a relatively small uncertainty factor that "indicates greater certainty in the data (because fewer of the default UFs relevant to a given POD . . . were applied)."[282] EPA has contrasted this with a composite uncertainty factor of 1,000, which "would indicate more uncertainty in risk estimation and extrapolation."[283]

197. *Human Exposure*: At the time I conducted this analysis, EPA had not yet released any of its Section 6 draft risk evaluations. I relied, therefore, on EPA's risk evaluations under Section 5 for guidance on the human exposure assessment. In the Section 5 risk evaluations, EPA considers the highest-exposed group in the population. When dealing with chemicals that may be present in drinking water, therefore, EPA's MOE analyses separately consider the exposures of *infants*.[284]

198. Based on the guidance from the Section 5 risk evaluations, I relied on the NRC's 2006 data to calculate a range of exposures representing the general adult population along with highly exposed population subgroups, including bottle-fed infants and individuals with high water intakes (for example, due to medical conditions or to physical exertion).[285]

199. In EPA's draft risk evaluations under Section 6, EPA has used the 95th percentile exposure to represent highly exposed individuals.[286] This is the same percentile exposure I used

[282] EPA (2019d), p. 301.
[283] EPA (2019d), p. 301.
[284] See for example EPA (2018b; 2018c; 2018d; 2018e; 2018f; 2018g; 2019a).
[285] For the general adult population, I combined NRC's estimates for adult consumers of municipal water, ages 20-24 and 25-54 years (0.011 mg/kg/day). As an example of elderly adults (ages 65+), I included the 90th percentile of adult consumers of municipal water (0.022 mg/kg/day). To account for individuals with high water intakes, I used the NRC's waterborne fluoride intake estimates (at 0.7 mg/L) for adult athletes and physical laborers (0.05 mg/kg/day), children with diabetes mellitus (0.07 mg/kg/day), and individuals with nephrogenic diabetes insipidus (0.1 mg/kg/day). For bottle-fed infants**,** I estimated a typical (0.1 mg/kg/day) and high (0.14 mg/kg/day) exposure based on the data from Fomon et al. (2000), Harriehausen et al. (2019), and NRC (2006). None of these exposure estimates, even those labeled "high," is an upper bound or maximum exposure.
[286] E.g., EPA (2019d), pp. 266, 300; EPA (2020), p. 108.

for high exposures among bottle-fed infants, and a higher percentile exposure than I used for the elderly (90th percentile).

200. Table 7 and the two figures below show the results of the MOE analyses. The first figure shows the results using the three LOAEL-Based PODs, while the second figure shows the results using the NOAEL-based PODs. As can be seen, the Actual MOEs are below the Acceptable MOEs for each group using every POD (including the least protective), with the exception of *average* adults and 90th percentile elderly when using the NOAEL-based PODs. If EPA's recommended 95th percentile exposure data (0.031 mg/kg/day) is used as the exposure for adults, risks are present even when using the least protective PODs.

201. The margins between the neurotoxicity levels in animals and the exposure levels in humans are far smaller than what EPA considers "acceptable." In fact, the Actual MOEs are so small that unacceptable risks would still be indicated for infants for each POD if the doses from animal studies had no adjustment to convert to the Human Equivalent Doses (HEDs) (i.e., no allometric scaling). Under EPA's framework for characterizing risk, therefore, it is apparent that fluoridation chemicals in drinking water present an unacceptable risk of neurotoxicity.[287]

[287] EPA (2016), p. 61.

Table 7. Calculated Margins of Exposure (MOEs)[a] for selected subgroups of the human population for the NOAELs and LOAELs for fluoride in Table 5.

Observation[b]	Intake rate[c]	Human Equivalent Dose (HED)[d]	Estimated human exposures[e]					
LOAEL or NOAEL	LOAEL or NOAEL	LOAEL or NOAEL	Adults (average)	Elderly adults (90th percentile)	Athletes and laborers (high)	DM patients (high)	Bottle-fed infants (typical) NDI patients (high)	Bottle-fed infants (high)
mg/L	mg/kg/day	mg/kg/day	0.011 mg/kg/day	0.022 mg/kg/day	0.05 mg/kg/day	0.07 mg/kg/day	0.1 mg/kg/day	0.14 mg/kg/day
5 mg/L, LOAEL (rats)	0.83	0.20	18	9.1	4.0	2.9	2.0	1.4
23 mg/L, LOAEL (rats)	3.8	0.91	83	41	18	13	9.1	6.5
45 mg/L, LOAEL (rats)	7.5	1.8	163	82	36	26	18	13
11 mg/L, NOAEL (mice)	2.9	0.41	37	19	8.2	5.9	4.1	2.9
20 mg/L, NOAEL (rats)	3.3	0.79	72	36	16	11	7.9	5.6

[a] A Margin of Exposure (MOE) is equal to the LOAEL or NOAEL (mg/kg/day) divided by an estimated human exposure (mg/kg/day). Usually, the benchmark MOE = 1000 for assessments based on a LOAEL and 100 for assessments based on an NOAEL. Since allometric scaling between animals and humans has been used to obtain the Human Equivalent Dose, the benchmark MOE is 300 for LOAELs and 30 for NOAELs. An MOE less than the benchmark MOE indicates an "unacceptable risk."

[b] These LOAEL and NOAEL values (mg/L) for fluoride are summarized in Table 2.

[c] The intake rates (mg/kg/day) in this column correspond to the LOAELs and NOAELs in the first column (mg/L), converted to intake rates (mg/kg/day) as summarized in Table 5. For rats, the intake rate equals the LOAEL or NOAEL divided by 6. For mice, the intake rate equals the NOAEL divided by 3.8.

[d] The Human Equivalent Dose (HED) is calculated from the intake rate for rats or mice as summarized in Table 5. The HED = the intake rate for rats × 0.24 or the intake rate for mice × 0.14.

[e] The estimated human exposures are for fluoride exposures from drinking water alone, assuming a fluoride concentration of 0.7 mg/L in the drinking water. Sources are as follows:
Adults (average), NRC (2006), p. 430, Table B-11, average consumers ages 20-54;
Elderly adults (90th percentile), NRC (2006), p. 431, Table B-12, 90th percentile consumers ages 65+;
Athletes and laborers (high), NRC (2006), p. 35, Table 2-4, high consumers (but not upper bound);
DM patients (high), NRC (2006), p. 35, Table 2-4, patients with diabetes mellitus, high consumers (but not upper bound);
Bottle-fed infants (typical), based on Fomon et al. (2000) and Harriehausen et al. (2019);
NDI patients (high), NRC (2006), p. 35, Table 2-4, patients with nephrogenic diabetes insipidus, high consumers (but not upper bound); and
Bottle-fed infants (high), NRC (2006), p. 432, Table B-13, infants < 0.5 years old, 95th percentile consumers (but not upper bound).

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Table 8. Calculated Margins of Exposure (MOEs)[a] for selected human population subgroups for the NOAELs and LOAELs for fluoride in Section 4.

Observation[b]	Intake rate[c]	Human Equivalent Dose (HED)[d]	Actual MOEs — Estimated human exposures[e]					
LOAELs from animal studies			Adults (average)	Elderly adults (90th percentile)	Athletes and laborers (high)	DM patients (high)	Bottle-fed infants (typical) NDI patients (high)	Bottle-fed infants (high)
LOAEL or NOAEL	LOAEL or NOAEL	LOAEL or NOAEL	0.011 mg/kg/day	0.022 mg/kg/day	0.05 mg/kg/day	0.07 mg/kg/day	0.1 mg/kg/day	0.14 mg/kg/day
mg/L	mg/kg/day	mg/kg/day						
5 mg/L, LOAEL (rats) ◇	0.83	0.20	18	9.1	4.0	2.9	2.0	1.4
23 mg/L, LOAEL (rats) □	3.8	0.91	83	41	18	13	9.1	6.5
45 mg/L, LOAEL (rats) △	7.5	1.8	163	82	36	26	18	13
11 mg/L, NOAEL (mice)	2.9	0.41	37	19	8.2	5.9	4.1	2.9
20 mg/L, NOAEL (rats)	3.3	0.79	72	36	16	11	7.9	5.6

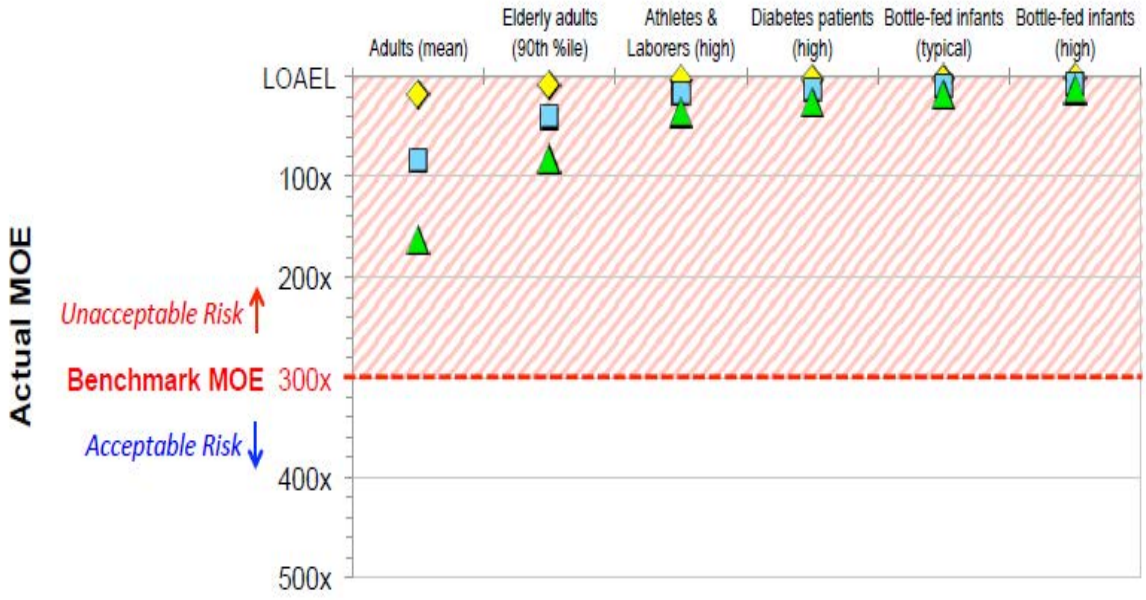

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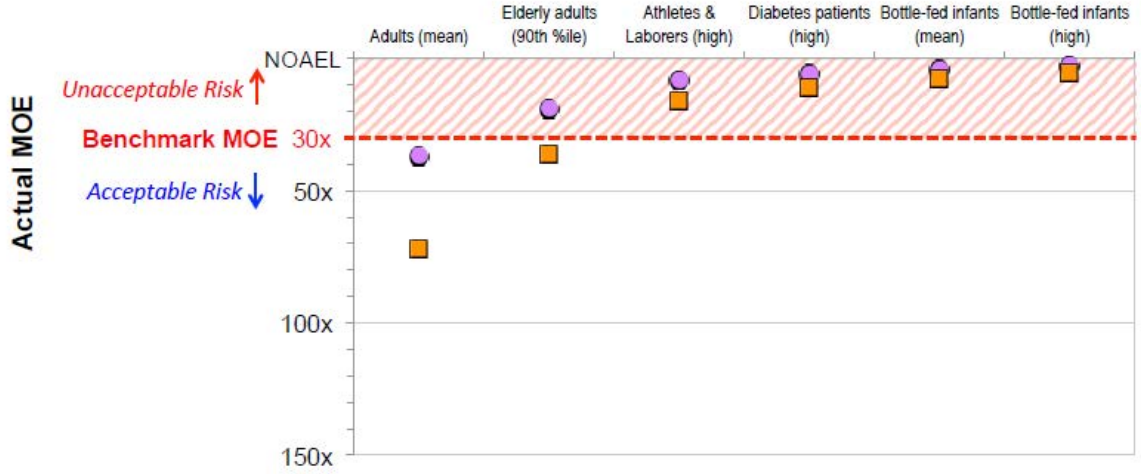
Table 8. Calculated Margins of Exposure (MOEs)[a] for selected human population subgroups for the NOAELs and LOAELs for fluoride in Section 4.

Observation[b]	Intake rate[c]	Human Equivalent Dose (HED)[d]	Actual MOEs Estimated human exposures[e]					
NOAELs from animal studies			Adults (average)	Elderly adults (90th percentile)	Athletes and laborers (high)	DM patients (high)	Bottle-fed infants (typical) NDI patients (high)	Bottle-fed infants (high)
LOAEL or NOAEL	LOAEL or NOAEL	LOAEL or NOAEL	0.011 mg/kg/day	0.022 mg/kg/day	0.05 mg/kg/day	0.07 mg/kg/day	0.1 mg/kg/day	0.14 mg/kg/day
mg/L	mg/kg/day	mg/kg/day						
5 mg/L, LOAEL (rats)	0.83	0.20	18	9.1	4.0	2.9	2.0	1.4
23 mg/L, LOAEL (rats)	3.8	0.91	83	41	18	13	9.1	6.5
45 mg/L, LOAEL (rats)	7.5	1.8	163	82	36	26	18	13
11 mg/L, NOAEL (mice)	2.9	0.41	37	19	8.2	5.9	4.1	2.9
20 mg/L, NOAEL (rats)	3.3	0.79	72	36	16	11	7.9	5.6



C. Assumptions and Key Sources of Uncertainty

202. Uncertainties are inherent to the field of risk assessment; they are to be expected. As discussed throughout my expert report, there are uncertainties involved in a risk assessment of fluoride neurotoxicity,[288] including:

203. *Uncertainties in the Animal Data*: The Points of Departure for both the RfDs and MOEs are derived from developmental animal studies that, while published in the peer-reviewed biomedical literature, have methodological limitations, including lack of control for litter effects, lack of blinding, lack of exposure during the full window of vulnerability (in utero *and* infancy), lack of long-term chronic exposures, and failure to rule out a contributing role of motor and sensory effects in the observed learning/memory deficits. As discussed earlier, the net effect of these limitations is uncertain. On one hand, lack of blinding can inflate the effect size, while on the other hand, lack of exposure during the full window of vulnerability and lack of chronic exposures can deflate it. Similarly, while lack of control for litter effects can create false positives, it can also create false negatives as well.[289] Further, to the extent that fluoride is causing the learning/memory deficits indirectly through a motor/sensory mechanism,[290] this would still be a neurotoxic effect and is thus not a basis to forego risk assessment, particularly since body weight changes do not appear to be a mediating mechanism in the studies from which the Points of Departure have been derived.

[288] For purposes of brevity, my initial expert report did not reiterate each of these uncertainties in the risk characterization section, although I considered them as part of my assessment.

[289] Zorrilla (1997), p. 144; Lazic and Essioux (2013), p. 3.

[290] NTP (2016), p. vii.

204. While there are some uncertainties in the animal data (which is not unusual[291]), there is reasonable confidence that the observed effects are both real and relevant. First, the animal studies have been overwhelmingly consistent—across numerous laboratories and study designs—in finding adverse effects on the brain, both structural and functional, which supports the conclusion that the effects are not an artifact of a methodological limitation. Second, the effect of fluoride on cognition has been detected in studies that have specifically controlled for litter effects and body weight changes, thus suggesting that fluoride's effect on the brain is independent of these concerns.[292] Third, there are extensive human epidemiological data reporting associations between fluoride and reduced IQ, and the existence of these data adds plausibility to the animal data, and vice versa. Fourth, the finding of unacceptable risk through an MOE analysis of the animal toxicity values is consistent with Dr. Grandjean's BMD analysis of the human data, which shows that the level of exposure associated with reduced IQ in humans is well below the levels of exposure produced by fluoridation. The confluence of the animal and human data thus adds strong overall confidence to the assessment.

205. *Uncertainties in the Extrapolation to Humans*: As discussed above, the extrapolation of animal data to humans involves some inherent uncertainty. There does not yet exist a physiologically based toxicokinetic model (PBTK) for fluoride, which would be the optimal method for adjusting for toxicokinetics.[293] This uncertainty has been accounted for by EPA's use of allometric scaling method which accounts for the expected difference in

[291] As discussed earlier, the principal animal studies that EPA has relied upon for its neurotoxicity risk assessments have also had methodological limitations, including failure to control for litter effects. There was also significant uncertainty in the animal data that EPA used for its unreasonable risk determinations for its draft NMP evaluation (e.g., there were only 6 studies available for the endpoint of concern, and three found no effect).

[292] Bartos (2018; 2019).

[293] EPA (2011b), p. 19.

toxicokinetics), and use of an uncertainty factor of 3 (to address the expected difference in toxicodynamics). The use of default allometric scaling for fluoride is consistent with chemical-specific research on fluoride showing that rats and mice require approximately 5 to 10 times more fluoride, respectively, to obtain the same concentration of fluoride in the blood.[294] The allometric scaling thus has a chemical-specific justification for fluoride, which provides confidence to the assessment. But, importantly, even if *no* allometric scaling is done to assess the risk of infant exposures, the MOEs still indicate unacceptable risks for *all* PODs.

206. The use of non-protective (i.e., non-conservative) assumptions provides additional confidence to the assessment. These non-protective assumptions include: (1) the use of 45 mg/L as a LOAEL, despite the fact that studies have found adverse effects well below this concentration; (2) the use of 20 mg/L as a NOAEL in McPherson (2018), despite the fact that the study found a neurotoxic effect at this concentration (i.e., increased pain sensitivity); and (3) conversion of water fluoride concentrations (mg/L) into doses (mg/kg/day) using the lowest end of the reported ratio, which results in Points of Departure that are likely higher than the actual dosages the animals received.

207. *Uncertainties in the Exposure Assessment*: As discussed above, I obtained most of my initial exposure estimates from the NRC's 2006 report, which in turn were based on EPA's own water intake data from 2000,[295] and have also reviewed EPA's 2019 report in which the Agency identified the "most up-to-date and scientifically sound" water intake data to use for risk assessment. Both of EPA's water intake reports (from 2000 and 2019) are based on short-term (2-day) surveys, which introduces some uncertainty when extrapolating to long-term exposures.

[294] NRC (2006), pp. 98, 442; Zhang et al. (2014).
[295] NRC (2006), Appendix B; EPA (2000a).

Long-term surveys, however, do not exist, and the uncertainty of using 2-day surveys is minimized by the large, nationally-representative scale of the survey data. EPA has stated that it has medium-to-high confidence in the reliability of these data, and that the data are well suited for risk assessment of water-based exposures.[296]

208. *Uncertainties in the Human Data*: One of the major strengths of the database on fluoride neurotoxicity is that there is a large body of human data, including five prospective cohort studies that have individual measurements of exposure during the fetal and neonatal period. The large extent of human data for fluoride far surpasses what EPA has used for its draft risk assessments of other chemicals under Section 6,[297] where the Agency has often had to rely *solely* on animal data.

209. The emergence of prospective cohort data on early life exposures to "optimal" levels of fluoride (from salt and water fluoridation programs)[298] addresses the two primary criticisms that have been made with respect to the cross-sectional studies of populations with elevated levels of fluoride in water: i.e., (1) that cross-sectional studies are limited in establishing causation because the exposures are measured after the effect (i.e., IQ loss) has occurred; and (2) the cross-sectional studies involve exposures that are generally higher than what people receive through artificially fluoridated water. The fact that the prospective cohort studies have found cognitive deficits at "optimal" levels of exposure that are consistent with the effects observed in the cross-sectional studies adds *substantial* confidence to the risk characterization.

210. While the human data are very robust, data gaps do remain, particularly with

[296] EPA (2000a), p. 5-5; EPA (2019b), pp. 3-6 & 3-10.

[297] As discussed earlier, the data available for fluoride are also substantially more robust than the data EPA has considered in making hazard determinations for other neurotoxicants.

[298] I understand that Dr. Hu and Dr. Lanphear will be addressing the criticisms with respect to imprecise exposure estimates, and thus I do not address that issue here.

respect to how the causative doses may vary across the population based on life-stage (e.g., the elderly), and other intrinsic sources of susceptibility, such as renal impairment, nutritional deficiencies, and genetic predisposition. These data gaps make it difficult to quantify the extent to which susceptibility varies across the population; the available data on chronic fluoride toxicity, however, provide a high level of confidence that human susceptibility to fluoride varies by a considerable margin, particularly in a population as large and diverse as the United States. Of particular concern are individuals with co-existing susceptibilities, such as pregnant women with iodine deficiencies, neonates that are bottle-fed with fluoridated water, and elderly individuals with diabetes.

211. To account for the *known* (but not yet quantified) variability in human susceptibility, I utilized EPA's default uncertainty factor of 10. This is consistent with EPA's standard practice, including EPA's Section 6 risk evaluations under TSCA. While I derived the Points of Departure from studies on susceptible (i.e., prenatally exposed) animals, the studies did not account for the full range of expected susceptibility in the human population. The studies did not, for example, attempt to replicate the formula-feeding practices of human infants, as all rodents were breast-fed during the critical neonatal period. Nor did the studies attempt to examine the effect of a co-existing iodine deficiency in the mother, or any other factor (e.g., renal impairment, calcium deficiency, etc) that would be expected to exacerbate the effects of prenatal fluoride exposure. Since hundreds of millions of Americans are now exposed to fluoridation chemicals on a regular basis, the spectrum of susceptibility will likely exceed the susceptibility examined in the available animal studies. An uncertainty factor of 10 is thus appropriate and necessary.

IX. RISK DETERMINATION

212. Under TSCA, a risk evaluation has a fifth and final step that is not included within the *Guidelines*: the Risk Determination. In the Risk Determination, EPA assesses whether the risks identified by the Margin of Exposure (MOE) analysis are "unreasonable." In making this determination, EPA considers "relevant risk-related factors," including (i) the effects of the chemical substance under the conditions of use; (ii) number of people exposed; (iii) whether susceptible subpopulations are exposed; (iv) the severity of the hazard; and (v) uncertainties in the data.

213. In practice, EPA's Risk Determination analyses do not address each of the "relevant risk factors" identified above. Severity of the hazard, for example, is rarely discussed. Assessments of uncertainties in EPA's Risk Determinations has also been rather cursory. In the NMP risk evaluation, for instance, the discussion of uncertainties in the analysis was largely limited to the assumptions involved in estimating worker exposure to chemicals in the absence of actual monitoring data.[299] Although EPA's risk estimates were based on an endpoint for which there were only 6 animal studies (with only 3 showing an effect), EPA did not re-address the underlying uncertainties in these data. The Risk Determination should thus not be mistaken as an exhaustive re-examination of all issues previously addressed; instead they tend to be brief and written in summary form.

214. At the time I conducted my initial assessment in this case, EPA had not yet released any risk evaluations under Section 6. For guidance, therefore, I relied on the risk characterization

[299] EPA (2019d), pp. 301-335.

considerations identified in the *Guidelines*,[300] as well as risk evaluations that EPA had recently completed on "new chemicals" under Section 5.

215. The factors that EPA considers under Section 5 substantially overlap with the factors that EPA considers under Section 6. Specifically, EPA considers the following three factors: (i) the hazardous nature of the chemical (as determined by toxicity values in animal studies);[301] (ii) the extent of human exposure to the chemical, and (iii) the Margin of Exposure (MOE). As I described in my report, fluoride meets each of these three criteria for unreasonable risk.

216. Importantly, whether one considers the factors under Section 5 or Section 6, the risk of neurotoxicity posed by fluoridation chemicals constitutes a clear and unreasonable risk, as will now be discussed.

A. Effects of Fluoridation Chemicals Under the Condition of Use

217. In most of the risk evaluations that EPA has conducted thus far under Section 6, the Agency did not have actual human data on health effects associated with the condition of use. EPA had to rely, therefore, on animal data alone. This is not the case with fluoridation. Critically, there are four prospective cohort studies that have examined the impact of optimal fluoride exposures, including two that examined the specific condition of use (water fluoridation) at issue.[302] Under the *Guidelines*, prospective cohort data permit "direct estimates of risks attributed to a particular

[300] EPA (1998a), pp. 63-66.

[301] Under Section 5, a chemical is "considered to have high human health hazard if there is evidence of adverse effects in humans or conclusive evidence of severe effects in animal studies with a **N**OAEL of less than or equal to 10 mg/kg/day." EPA (2018b; 2018c; 2018d; 2018e; 2018f; 2018g; 2019a). This criterion is readily satisfied with fluoride, as the **L**OAELs for cognitive deficits and brain abnormalities are below 10 mg/kg/day. Fluoride is thus a "high human health hazard" under Section 5.

[302] Bashash et al (2017, 2018); Green et al. (2019); Till et al. (2020).

exposure."[303] The effects of fluoridation chemicals under the condition of use are thus well characterized, particularly in comparison to chemicals (e.g., NMP, 1-BP) for which EPA has made unreasonable risk findings under TSCA.

B. Number of Peopled Exposed to Fluoridation Chemicals

218. EPA has recognized that "the significance of the risk is dependent upon both the hazard (or toxicity) of the chemical substance and *the extent of exposure* to the substance."[304] Although EPA made this statement in the context of Section 5, EPA considers the extent of exposure to be a relevant factor under Section 6 as well. In the Section 6 risk determinations, the number of people (usually workers) who are exposed to the chemical are identified under each condition of use.[305]

219. This factor weighs in favor of an unreasonable risk finding for fluoridation chemicals. The extent of human exposure to fluoridation chemicals is nothing short of massive, much like lead exposure was during the era of leaded gasoline. Today, approximately 200 million Americans, or nearly 2/3 of the population, have municipal water to which fluoridation chemicals are added. Moreover, most of the remaining population living in "non-fluoridated" areas will routinely consume fluoridation chemicals in processed beverages and foods, as many beverages and foods are produced in fluoridated areas.[306] To put these numbers in perspective, EPA has found unreasonable risks for conditions of use involving as few as 1,046[307] and 1,900 occupationally-

[303] EPA (1998a), p. 17.
[304] EPA (2018b; 2018c; 2018d; 2018e; 2018f; 2018g; 2019a).
[305] EPA (2019d), pp. 299, 303-335; EPA (2019c), pp. 255-289.
[306] See, for example, Kiritsy et al. (1996); Turner et al. (1998); Heilman et al. (1999).
[307] EPA (2019c), p. 264.

exposed workers.[308] With such widespread exposure to fluoridation chemicals among the general population, even small risks can amount to widespread harm.

C. Exposure of Susceptible Subpopulations to Fluoridation Chemicals

220. One of the consequences from widely dispersing a toxicant through the environment (versus the use of industrial chemicals *within* manufacturing facilities) is that susceptible members of the general public may be exposed. This is the case with fluoridation chemicals. Each year, there are approximately **2.5 million pregnancies** in fluoridated areas; *in utero* exposures are thus widespread. Many of those exposed *in utero* will also be exposed during the sensitive neonatal period, with upwards of **1.9 million infants** living in fluoridated areas being fed formula at least part of the time, including **400,000 infants** who are *exclusively* formula-fed for their first six months. While these numbers do not account for those who use bottled water, the numbers will be substantial regardless.

D. The Severity of the Hazard (Cognitive Deficits/IQ Loss)

221. The principal hazard at issue from exposure to fluoridation chemicals is IQ loss. The prospective studies have found an approximate 5 to 6 point drop in IQ as maternal urinary fluoride levels increase from 0 to 1 mg/L.[309] To put this in perspective, EPA has recognized that a loss of a single IQ point is associated with a loss in lifetime earnings,[310] and EPA's Clean Air Science Advisory Council has stated that "a population loss of 1-2 IQ points is highly significant from a public health perspective" and should be prevented in 99.5% of the population.[311]

[308] EPA (2019d), pp. 307, 311.
[309] Bashash et al. (2017); Green et al. (2019).
[310] EPA (2008e), p. 5-28.
[311] Federal Register (2008), p. 67000.

Consistent with this, EPA has established reference doses for chemicals based on observed cognitive deficits in animal studies (see Table 1 above). Cognitive deficits, including in the range observed in fluoridated areas, are a sufficiently severe effect on human health to warrant prevention, as EPA has recognized in other contexts.

E. Uncertainties

222. Uncertainties are a pervasive aspect of risk assessment; their existence does not negate a finding of risk. As would be expected, there are uncertainties in the fluoride dataset, arising in part from methodological limitations in the available animal studies (e.g., lack of control for litter effects, lack of blinding, lack of studies on neonatal exposures, lack of chronic experiments, etc.). The impact of these limitations on the observed learning and memory deficits is not yet defined. The clear suggestion from the observed findings, however, is that fluoride causes alterations to the brain and behavior. Further, the uncertainties that remain in the animal data are largely offset by the existence of high-quality prospective studies that have *consistently* detected significant associations between "optimal" fluoride exposures and cognitive deficits. While I understand that EPA's experts in this case question whether the "causal" relationship between fluoridation and IQ loss has been proven, the *Guidelines* do not require proof of causation; they require sufficient evidence of association.[312]

223. Another factor weighing in favor of an unreasonable risk finding is that the exposure estimates are more straightforward—and permit greater confidence—than the exposure estimates that EPA has had to extrapolate for other chemicals under TSCA. In its NMP risk evaluation, for example, EPA had to make "assumptions about glove use, glove effectiveness,

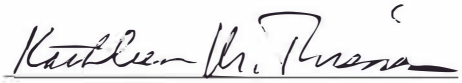
[312] EPA (1998a), p. 53.

duration of contact with NMP, concentration of NMP, and amount of skin surface contact with NMP" in order to come up with estimates of human exposure under the conditions of use.[315] Estimating exposure to fluoridation chemicals involves much less uncertainty, as the concentration of fluoride in the water is defined (0.7 mg/L), and the EPA has extensive empirical data on water consumption in the U.S. that the Agency has described as "scientifically sound."

224. Based on the available scientific evidence that now exists on the hazards, exposures, and risks of fluoride ingestion, the widespread addition of fluoridation chemicals to drinking water and processed foods in the United States presents an unreasonable risk to human health.

I declare under penalty of perjury, under the laws of the United States, that the foregoing is true and correct to the best of my knowledge and belief.

Executed on May 20, 2020, in Oak Ridge, Tennessee.



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[315] EPA (2019d), Table 5-1.

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Appendix A

Recent Animal Studies of Fluoride Neurotoxicity (Tables A-1 and A-2)

Table A-1. Summary of animal studies that have investigated neuroanatomical and neurochemical endpoints of fluoride toxicity.

Paper	Animal	Sex	Maturity at Start of Exposure	Length of Exposure	Animals per group
Adebayo et al. 2013	Albino Rats	Male	Post-Weaning[f]	1 week	6
Adedara et al. 2017a & b	Wistar Rats	Male	8 weeks old	45 days	12
Agustina et al. 2018	Wistar Rats	Male	Adults	30 days	8
Akinrinade et al. 2015a & b	Wistar Rats	Male	Adults	30 days	5
Ameeramja et al. 2018	Wistar Albino Rats	Female	2 to 3 months old	30 days	6
Atmaca et al. 2014	Wistar Rats	Male	Post-Weaning[f]	21 days	7
Balaji et al. 2015	Swiss Albino Mice	Female	Adults	30 days	6 (of 7)
Banala and Karnati 2015	Wistar Rats	Both	Prenatal	Prenatal + 14, 21 & 30 days	5
Banji et al. 2013	Wistar Rats	Both	Gestational day 6	Prenatal + 15 days	6
Bartos et al. 2018	Wistar Rats	Female	Prenatal	Prenatal + 21 days	5
Bartos et al 2019	Wistar Rats	Both	Pre-Pregnancy	Prenatal + 21 days	5
Basha and Madhusudhan 2010	Wistar Albino Rats	Both	Pre-Pregnancy	Prenatal + 21 days	6
Basha et al. 2011a & b	Wistar Albino Rats	Both	Multigenerational	Prenatal + 12 weeks (3rd generation)	6
Basha and Sujitha 2012a & b	Wistar Rats	Male	3 months old	1 month	6
Basha and Saumya 2013	Albino Mice	Both	Adults	45 days	6
Bharti and Srivastava 2009	Wistar Rats	Female	Adults	28 days	6
Bharti et al. 2012	Wistar Rats	Female	Adults	7 days	6
Chauhan et al. 2013	Sprague-Dawley Rats	Female	6 months old	3 to 6 weeks	4 (of 8)
Chen et al. 2018a	Sprague-Dawley Rats	Female	Pre-Pregnancy	Prenatal + 6 months	6
Chouhan and Flora 2008	Albino Rats	Male	Adults	10 weeks	6
Chouhan et al. 2010	Wistar Albino Rats	Male	Adults	12 weeks	5-6 (of 6)
Dec et al. 2019	Wistar Rats	Males	Pre-Pregnancy	Prenatal + 90 days	6 (of 12)
Dong et al. 2015	Sprague-Dawley Rats	Both	1 month old	>10 months	30
Dong et al. 2015	Sprague-Dawley Rats	Both	10 months pre-birth	Prenatal + 1, 7, 14, 21, & 28 days	10
Flora et al. 2009	Swiss Mice	Male	Adults	10 weeks	5
Flora et al. 2012	Swiss Mice	Male	Adults	28 weeks	5 (of 12)
Ge et al. 2011	Wistar Albino Rats	Both	Pre-Pregnancy	Prenatal + 20 days	8
Ge et al. 2018	ICR Mice	Both	Pre-Pregnancy	Prenatal + 90 days	6
Güner et al. 2016	Wistar Albino Rats	Both	Adult	Prenatal + 1, 3, & 5 months	5

Table continued next page

Table A-1. Summary of animal studies that have investigated neuroanatomical and neurochemical endpoints of fluoride toxicity - *Continued*

Paper	Treatment groups	LOAEL[b]	Specific Effect	Hippocampus?
Adebayo et al. 2013	100 mg/L	100 mg/L	Oxidative stress, reduced brain weight	No
Adedara et al. 2017a & b	6.8 mg/L	6.8 mg/L	Oxidative stress, reduced AChE activity, inflammation, Caspase-3 activity	No
Agustina et al. 2018	2.3, 4.5 & 9 mg/kg/day	4.5 mg/kg/day	Reduced number of Purkinje cells	No
Akinrinade et al. 2015a & b	1 & 5 mg/L	1 mg/L	Oxidative stress, inflammation, neuronal damage	No
Ameeramja et al. 2018	136 mg/L	136 mg/L	Oxidative stress	No
Atmaca et al. 2014	100 mg/L	100 mg/L	Oxidative stress & neuronal degeneration	Yes
Balaji et al. 2015	45 & 90 mg/L	45 mg/L	Inhibition of cholinesterase & increased oxidative stress	No
Banala and Karnati 2015	9 mg/L	9 mg/L	Oxidative stress	No
Banji et al. 2013	9 mg/kg/day	9 mg/kg/day	Oxidative stress	No
Bartos et al. 2018	5 & 10 mg/L (=0.6 & 1.2 mg/kg/d)	5 mg/L	Decreased nicotinic receptors & oxidative stress	Yes
Bartos et al. 2019	5 & 10 mg/L (=0.6 & 1.2 mg/kg/d)	5 mg/L	Increased oxidative stress as reflected by decreased CAT, GPT, and GOT	Yes
Basha and Madhusudhan 2010	50 & 150 mg/L	50 mg/L	Oxidative stress & reduced brain protein content	No
Basha et al. 2011a & b	100 & 200 mg/L	100 mg/L	Oxidative stress, reduced brain weight, and histological changes	Yes
Basha and Sujitha 2012a & b	270 mg/L	270 mg/L	Oxidative stress & decreased acetylcholinesterase activity	No
Basha and Saumya 2013	270 mg/L	270 mg/L	Mitochondrial disturbances & Oxidative stress	No
Bharti and Srivastava 2009	150 mg/L	150 mg/L	Oxidative stress	No
Bharti et al. 2012	150 mg/L	150 mg/L	Decreased acetylcholinesterase activity	No
Chauhan et al. 2013	11.3 mg/kg/day	11.3 mg/kg/day	Oxidative stress	No
Chen et al. 2018a	4.5, 23, 45 mg/L	4.5 mg/L	Impaired synaptogenesis	Yes
Chouhan and Flora 2008	10, 50, & 100 mg/L	100 mg/L[c]	Oxidative stress	No
Chouhan et al. 2010	1, 10, 50 & 100 mg/L	1 mg/L	Oxidative stress, alterations in neurotransmitters, neuronal lesions, & increased AChE activity	No
Dec et al. 2019	23 mg/L	23 mg/L	Evidence of inflammatory processes (reduced activity of cyclooxygenases (COX1 & COX2) and increase in prostaglandins)	Yes
Dong et al. 2015	50 mg/L (adults)	50 mg/L	Decrease in muscarinic nicotinic receptors	No
Dong et al. 2015	50 mg/L (offspring)	50 mg/L	Decrease in muscarinic nicotinic receptors	No
Flora et al. 2009	50 mg/L	50 mg/L	Oxidative stress, alteration in neurotransmitters, DNA damage, increased AChE activity	No
Flora et al. 2012	50 mg/L	50 mg/L	Oxidative stress, neuronal degeneration, DNA damage, Protein interaction	Yes
Ge et al. 2011	100 mg/L (+25 mg/kg in food)	100 mg/L	Alteration in protein expression	No
Ge et al. 2018	50 & 100 mg/L	50 mg/L	Alterations of synapse-related proteins	No
Güner et al. 2016	13.6 & 45 mg/L	13.6 mg/L	Neurodegenerative changes & catalase immunoreactivity	Yes

Table continued next page

Table A-1. Summary of animal studies that have investigated neuroanatomical and neurochemical endpoints of fluoride toxicity - *Continued*

Paper	Animal	Sex	Maturity at Start of Exposure	Length of Exposure	Animals per group
Hamza et al. 2015	Wistar Albino Rats	Male	Adults	30 days	10
Han et al. 2014	Kumming Mice	Male	Sexually matured mice	180 days	4 (of 15)
Hassan and Abdel-Aziz 2010	Wistar Albino Rats	Male	Adults	5 weeks	6
Inkielwicz-Stepniak and Czarnowski 2010	Wistar Han Rats	Male	6 weeks old	4 weeks	6
Jia et al. 2019	CD1 Mice	Both	Prenatal	Prenatal (day 9) + 19 days	5 (of 20)
Jiang et al. 2014a	Sprague-Dawley Rats	Male	Weaned	3 months	8
Jiang et al. 2014b	Sprague-Dawley Rats	Both	Pre-pregnancy	Prenatal + 2 months	3-12 (of 12)
Jiang et al. 2019	Sprague-Dawley Rats	Male	Post-weaning[f]	10 weeks	7
Kaur et al. 2009	Sprague-Dawley Rats	Female	Adults	8 weeks	6-7 (of 8)
Khan et al. 2018	Wistar Rats	Both	Post-weaning[f]	28 days	6
Kinawy 2019	Rats	Male	Prenatal (6th day)	Prenatal + Weaning or 70 days	8
Li et al. 2019	Kumming Mice	Both	Adults	90, 120 & 150 days	8 (of 30)
Liu et al. 2010	Sprague-Dawley Rats	Both	Post-weaning[f]	6 months	10 (of 24)
Liu et al. 2011	Sprague-Dawley Rats	Both	Post-weaning[f]	3 & 6 months	12 (of 24)
Lou et al. 2013	Sprague-Dawley Rats	Both	Post-weaning[f]	6 months	20
Ma et al. 2015	C57/BL Mice	Male	4 weeks old	4 weeks	8
Mansour and Tawfik 2012	Albino Rats	Male	Adults	5 weeks	6
McPherson et al. 2018	Long Evans Hooded Rats	Male	Prenatal	Prenatal (day 6) + 90 days	6 (of ~23)
Nabavi et al. 2012a	Wistar Rats	Male	8 to 12 weeks old	1 week	10
Nabavi et al. 2012b	Wistar Rats	Male	Post-weaning[f]	1 week	10
Nabavi et al. 2013	Wistar Rats	Male	7 days old	7 days	10
Niu et al. 2009	Wistar Albino Rats	Both	Day of birth	6, 8, 10, & 12 weeks	8
Niu et al. 2014	Kumming Mice	Male	Prenatal	Prenatal + 56 days	15
Niu et al. 2015a	Kumming Mice	?	Adults	60 days	5 (of 15)
Niu et al. 2015b	Kumming Mice	Both	Prenatal	Prenatal + 56 days	6
Niu et al. 2018a	Sprague-Dawley Rats	Female	Post-weaning[f]	60 days	3 (of 10)
Niu et al. 2018b	Kumming Mice	Both	Adults	60 days	5 (of 12)

Table continued next page

Table A-1. Summary of animal studies that have investigated neuroanatomical and neurochemical endpoints of fluoride toxicity – *Continued*

Paper	Treatment groups	LOAEL	Specific Effect	Hippocampus?
Hamza et al. 2015	4.7 mg/kg/day	4.7 mg/kg/day	Increased oxidative stress	No
Han et al. 2014	11, 23, and 45	23 mg/L[c]	Altered mRNA expression	Yes
Hassan and Abdel-Aziz 2010	4.7 mg/kg/day	4.7 mg/kg/day	Oxidative stress	No
Inkielwicz-Stepniak and Czarnowski 2010	25 mg/L	25 mg/L	Oxidative stress	No
Jia et al. 2019	6 & 113 mg/L	None	No reduction in neuronal density	No
Jiang et al. 2014a	54 mg/L	54 mg/L	Decreased glutamate levels	Yes
Jiang et al. 2014b	11, 23, and 45 mg/L	11 mg/L	Neuronal degeneration, decreased glucose utilization	Yes
Jiang et al. 2019	23 & 45 mg/L	23 mg/L	Impaired neurogenesis & synaptic plasticity	Yes
Kaur et al. 2009	125 mg/L	125 mg/L	Oxidative stress, alteration in neurotransmitters, & neuronal degeneration	No
Khan et al. 2018	20 mg/L	20 mg/L	Inhibition of AChE and increase in oxidative stress	No
Kinawy 2019	678 mg/L	678 mg/L	Oxidative stress	Yes
Li et al. 2019	68 mg/L	68 mg/L	Altered mRNA expression of anxiety & depression-related genes	Yes
Liu et al. 2010	5 & 50 mg/L	5 mg/L	Reductions in nicotinic receptors & activation of photoho-ERK1/2	No
Liu et al. 2011	5 & 50 mg/L	5 mg/L	Increased apoptosis & phosphorylation	No
Lou et al. 2013	10 & 50 mg/L	10 mg/L	Mitochondrial disturbances in neurons, altered protein expression	No
Ma et al. 2015	23 & 45.6 mg/L	23 mg/L	Increased BDNF expression	Yes
Mansour and Tawfik 2012	4.7 mg/kg/day	4.7 mg/kg/day	Oxidative stress	No
McPherson et al. 2018	10 & 20 mg/L (+ food exposure group)	None	No neuronal damage or glia reactivity	Yes
Nabavi et al. 2012a	270 mg/L	270 mg/L	Oxidative stress	No
Nabavi et al. 2012b	270 mg/L	270 mg/L	Oxidative stress	No
Nabavi et al. 2013	270 mg/L	270 mg/L	Oxidative stress	No
Niu et al. 2009	68 mg/L	68 mg/L	Decreased glutamate levels & altered enzyme activity	Yes
Niu et al. 2014	68 mg/L	68 mg/L	Altered protein expression	Yes
Niu et al. 2015a	11, 23, and 45 mg/L	23 mg/L	Microtubule lesions in neurons	Yes
Niu et al. 2015b	68 mg/L	68 mg/L	Alterations in protein expression	No
Niu et al. 2018a	4.5, 23, and 45 mg/L	4.5 mg/L	Endoplasmic reticulum stress	Yes
Niu et al. 2018b	11, 23, and 45 mg/L	11 mg/L	Myelin damage, and alteration to synaptic structure	Yes

Table continued next page

Table A-1. Summary of animal studies that have investigated neuroanatomical and neurochemical endpoints of fluoride toxicity – *Continued*

Paper	Animal	Sex	Maturity at Start of Exposure	Length of Exposure	Animals per group
Pal and Sarkar 2014	Wistar Rats	Male	Post-weaning[f]	30 days	6 to 8
Pan et al. 2015	Sprague-Dawley Rats	Male	3 weeks after weaning	30 days	15
Pereira et al. 2011	Wistar Rats	Male	30 days old	30 days	4-10 (of 15)
Pulungan et al. 2018	Wistar Rats	Male	12-16 weeks old	30 days	8
Qian et al. 2013	Sprague-Dawley Rats	Male	Newly weaned	6 months	2-20 (of 20)
Reddy et al. 2009	Swiss Albino Mice	Female	Adults	14 days	6
Reddy et al. 2014	Wistar Rats	Male	4 months old	90 days	6
Rogalska et al. 2017	Wistar Rats	Both	8 weeks old	4 weeks	6-8
Samanta et al. 2016	Sprague-Dawley Rats	Female	Post-weaning[f]	16 weeks	5
Sarkar et al. 2014	Wistar Rats	Male	Post-weaning[f]	30 days	6
Shalini and Sharma 2015	Wistar Albino Rats	Female	Adults	60 days	10
Sharma et al. 2014	Swiss Albino Mice	Male	1.5 months old	30 days	7
Sharma et al. 2018	Swiss Albino Mice	Both	1 month old	30 days	7
Shen et al. 2019	Wistar Rats	Both	1 month old	12 & 24 weeks	30
Sun et al. 2017	Sprague-Dawley Rats	Both	Pre-Pregnancy	Prenatal + 14 or 28 days	10
Sun et al. 2018	Kumming Mice	Female	Prenatal	Prenatal + 21 days	6 (of 12)
Teng et al. 2018	Sprague-Dawley Rats	Male	Recently weaned	18 months	6-7 (of 13)
Trivedi et al. 2007	Swiss Albino Rats	Male	Young adults	30 days	10
Wang et al. 2018a	ICR Mice	Female	Prenatal	Prenatal (7th day) + 21 days	6 (of 15)
Wang et al. 2018b	Wistar Albino Rats	Male	12-weeks old	8 weeks	10 (of 24)
Wei et al. 2018	Sprague-Dawley Rats	Both	1 month old	>6 months	15
Wei et al. 2018	Sprague-Dawley Rats	Both	Pre-Pregnancy	Prenatal + 28 days	6-10 (of 10)
Yan et al. 2016	Wistar Rats	Both	5 weeks old	10 weeks	20
Yang et al. 2018a	Wistar Rats	Male	6 weeks old	4 & 12 weeks	4-6 (of 10)
Yu et al. 2019	ICR Mice	Male	Newly weaned	3 & 6 months	20
Yuan et al. 2019	Kumming Mice	Male	7 weeks old	90 days	12 (of 24)
Zhang et al. 2013a	Wistar Rats	Male	6 weeks old	3 months	3 (of 10)
Zhang et al. 2015a	Sprague-Dawley Rats	Both	2 months old	3 months & 6 months	10 (of 20)

Table continued next page

Table A-1. Summary of animal studies that have investigated neuroanatomical and neurochemical endpoints of fluoride toxicity – *Continued*

Paper	Treatment groups	LOAEL	Specific Effect	Hippocampus?
Pal and Sarkar 2014	9 mg/kg/day	9 mg/kg/day	Oxidative stress, inhibited enzymes, altered neurotransmitters, reduced protein content	No
Pan et al. 2015	9 mg/kg/day	N/A[d]	Altered protein expression	Yes
Pereira et al. 2011	45 mg/L	45 mg/L	Alterations in neurotransmitters	Yes
Pulungan et al. 2018	2.3, 4.5 & 9 mg/kg/day	none	No reduction in number of pyramidal cells in medial prefrontal cortex	No
Qian et al. 2013	23 mg/L	23 mg/L	Impaired synaptic plasticity, oxidative stress, altered protein expression	Yes
Reddy et al. 2009	9 mg/kg/day	9 mg/kg/day	Oxidative stress & altered enzyme activity	No
Reddy et al. 2014	9, 27, & 45 mg/L	9 mg/L	Oxidative stress, alterations in neurotransmitters, and immunosuppression	No
Rogalska et al. 2017	4.5 & 23 mg/L	23 mg/L[c]	Increased glucose uptake	Yes
Samanta et al. 2016	5.9 mg/kg/day	5.9 mg/kg/day	Oxidative stress, cellular degeneration, apoptosis	No
Sarkar et al. 2014	9 mg/kg/day	9 mg/kg/day	Oxidative stress, inhibited enzymes, & reduced protein content	No
Shalini and Sharma 2015	10 mg/L	10 mg/L	Oxidative stress, reduced protein content & AChE activity	No
Sharma et al. 2014	120 mg/L	120 mg/L	Oxidative stress & cellular degeneration	Yes
Sharma et al. 2018	54 mg/L	54 mg/L	Oxidative stress and neuronal damage	Yes
Shen et al. 2019	200 mg/L	200 mg/L	Apoptosis and degeneration of nerve cells in spinal cord	No
Sun et al. 2017	45 mg/L	45 mg/L	Altered gene expression & apoptosis	Yes
Sun et al. 2018	11, 23, and 45 mg/L	11 mg/L (Fig 3b)	Altered mRNA expression	Yes
Teng et al. 2018	8.25, 16.5, & 33 mg/L	16.5 mg/L[c]	Elevated calcium in hippocampus	Yes
Trivedi et al. 2007	2.7 & 5.4 mg/kg/day	2.7 mg/kg/day	Reduced protein content	No
Wang et al. 2018a	11, 23, and 45 mg/L	11 mg/L (Fig 4b)	Altered expression of mi-RNAs	No
Wang et al. 2018b	45 mg/L	45 mg/L	Cellular degeneration, DNA damage	Yes
Wei et al. 2018	50 mg/L (adults)	50 mg/L	Neuronal injury (as evident by damage to Nissl bodies)	No
Wei et al. 2018	50 mg/L (offspring)	50 mg/L	Neuronal injury (as evident by damage to Nissl bodies)	No
Yan et al. 2016	60 & 120 mg/L	60 mg/L	Increased apoptosis & inflammation	Yes
Yang et al. 2018a	60 & 120 mg/L	60 mg/L	Apoptosis, altered protein expression, increased inflammation	Yes
Yu et al. 2019	2.3 & 13.6 mg/L	2.3 mg/L	Alterations of L-type calcium channels	Yes
Yuan et al. 2019	23, 45, 68 mg/L	23 mg/L	Reduced brain protein content, impaired insulin signaling pathway, reduced brain organ coefficient	Yes
Zhang et al. 2013a	45 mg/L	45 mg/L	Oxidative stress, neuronal loss, altered protein expression	Yes
Zhang et al. 2015a	5 & 50 mg/L	5 mg/L	Increased oxidative stress & activation of AGE/RAGE Pathway	Yes

Table continued next page

Table A-1. Summary of animal studies that have investigated neuroanatomical and neurochemical endpoints of fluoride toxicity – *Continued*

Paper	Animal	Sex	Maturity at Start of Exposure	Length of Exposure	Animals per group
Zhang et al. 2017a	Sprague-Dawley Rats	Both	Pre-Pregnancy	Prenatal + 14 or 28 days	15-20 (of 20)
Zhang et al. 2019	Wistar Rats	Both	4 weeks old	3 months	2-3 (of 20)
Zhao et al. 2019	Sprague-Dawley Rats	Both	Pre-Pregnancy	Prenatal + 60 days	2-5 (of 15)
Zheng et al. 2016	Sprague-Dawley Rats	Male	Newly weaned	3 months	20
Zhou et al. 2019	Sprague-Dawley Rats	Female	Pre-Pregnancy	Prenatal + 6 months	6
Zhu et al. 2011 & Zhang et al. 2011	Sprague-Dawley Rats	Male	Just weaned	9 months	6 (of 12)
Zhu et al. 2017	Sprague-Dawley Rats	Both	Prenatal	Prenatal + 21 or 42 days	6 (of 8)

Table continued next page

Table A-1. Summary of animal studies that have investigated neuroanatomical and neurochemical endpoints of fluoride toxicity – *Continued*

Paper	Treatment groups	LOAEL	Specific Effect	Hippocampus?
Zhang et al. 2017a	45 mg/L	45 mg/L	Impaired synaptic plasticity	No
Zhang et al. 2019	25, 50, 100 mg/L	50 mg/L[e]	Autophagy in hippocampus	Yes
Zhao et al. 2019	4.5, 23, 45 mg/L	4.5 mg/L [Fig 6e]	Mitochondrial disturbances	Yes
Zheng et al. 2016	45 mg/L	45 mg/L	Increased apoptosis	Yes
Zhou et al. 2019	4.5, 23, 50 mg/L	23 mg/L[c]	Decreased neurons, suppressed autophagy, and enhanced apoptosis in hippocampus	Yes
Zhu et al. 2011 & Zhang et al. 2011	7, 13.6, & 27 mg/L	13.6 mg/L[c]	Decrease in synaptic membrane fluidity & increased calcium	Yes
Zhu et al. 2017	34 mg/L	34 mg/L	Altered protein expression in ERK/CREB signaling pathway	Yes

[a] Where the study does not identify the sex of the animals, it is assumed that both sexes were studied.

[b] A LOAEL refers to the lowest observed adverse effect level where a statistically significant result was observed.

[c] At least one effect was seen at lower treatment doses (as reflected by a visually apparent dose-related trend), but the effect(s) at the lower treatment levels did not reach statistical significance.

[d] The authors did not perform a statistical analysis to determine if the observed changes were statistically significant.

[e] Ultrastructural observations of the rat hippocampal CA1 cells identified changes in the 25 mg/L group (i.e., increased lipofuscin content), but a statistical analysis of these changes was not performed.

[f] Where the study does not identify the age of the animal at the start of the experiment, it is assumed that the animals had already completed weaning.

Table A-2. Summary of animal studies that have investigated toxic effects of fluoride on learning and memory

Paper	Strain	Sex[a]	Maturity at Start of Exposure	Length of Exposure	Animals per group
Banala and Karnati 2015	Wistar Rats	Both	Prenatal	Prenatal + 30 days	5
Bartos et al. 2018	Wistar Rats	Female	Prenatal (day 0)	Prenatal + 21 days	9-10
Bartos et al. 2019	Wistar Rats	Both	Prenatal (day 0)	Prenatal + 21 days	9-10
Basha et al. 2011b	Wistar Albino Rats	Both	Prenatal/Multigenerational	Prenatal + 30 days	6
Basha & Sujitha 2012b	Wistar Rats	Male	3 months old	1 month	6
Bera et al. 2007	Wistar Rats	Both	Prenatal (day 1)	Prenatal (day 1) + 9 days	6-12
Chen et al. 2018a	Sprague-Dawley Rats	Female	2 months pre-gestation	Prenatal + 6 months	6
Chioca et al. 2008	Wistar Rats	Male	Adult	30 days	15 (of 18)
Cui et al. 2017	Sprague-Dawley Rats	Both	Pre-Pregnancy	Prenatal + 60 days	12
Dong et al. 2015	Sprague-Dawley Rats	Both	One month old	10 months	30
Dong et al. 2015	Sprague-Dawley Rats	Both	10 months pre-birth	Prenatal + 1 to 28 days	10
Ge et al. 2018	ICR Mice	Both	Pre-Pregnancy	Prenatal + 60 days	6
Han et al. 2014	Kunming Mice	Male	Sexually matured mice	180 days	15
Jetti et al. 2016	Wistar Rats	Male	Adult	30 days	6
Jiang et al. 2014a	Sprague-Dawley Rats	Male	Weaned	3 months	8
Jiang et al. 2014b	Sprague-Dawley Rats	Both	Pre-pregnancy	Prenatal + 2 months	12
Liu et al. 2010	Sprague-Dawley Rats	Both	Adult	6 months	10 (of 24)
Liu et al. 2014	BaB/C Mice	Male	4 weeks old	4 weeks	11-12 (of 12)

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Table A-2. Summary of animal studies that have investigated toxic effects of fluoride on learning and memory - *Continued*

Paper	Strain	Sex[a]	Maturity at Start of Exposure	Length of Exposure	Animals per group
McPherson et al. 2018	Long-Evans Hooded Rats	Male	Prenatal (day 6)	Prenatal (day 6) + 90 days	11-23 (of ~23)
Niu et al. 2009	Wistar Albino Rats	Both	Postnatal (day 0)	6 to 12 weeks	8
Niu et al. 2014	Kunming Mice	Male	Prenatal	Prenatal + 56 days	15
Niu et al. 2018a	Sprague Dawley Rats	Female	Post-weaning[g]	2 months	6 (of 10)
Pereira et al. 2011	Wistar Rats	Male	30 days old	30 days	14-15
Pulungan et al. 2018	Wistar Rats	Male	12 to 16 weeks old	30 days	8
Raghu et al. 2013	Wistar Rats	Male	1 month old	30 days	6
Shalini and Sharma 2015	Wistar Albino Rats	Female	Adults	60 days	10
Sharma et al. 2018	Swiss Albino Mice	Male	1 month old	30 days	7
Sun et al. 2018	Kunming Mice	Both	Prenatal	Prenatal + 21 days	6 (of 12)
Wang et al. 2018a	ICR Mice	Female	Prenatal	Prenatal (day 7) + 21 days	15
Whitford et al. 2009	Sprague-Dawley Rats	Female	8 days after weaning	8 months	8
Yang et al. 2018a	Wistar Rats	Male	6 weeks old	4 to 12 weeks	10
Yuan et al. 2019	Kunming Mice	Male	7 weeks old	12 weeks	12 (of 24)
Zhang et al. 2013a	Wistar Rats	Male	6 weeks old	3 months	3 (of 10)
Zhang et al. 2019	Wistar Rats	Both	4 weeks old	3 months	15 (of 20)
Zhao et al. 2019	Sprague-Dawley Rats	Both	Pre-Pregnancy	Prenatal + 60 days	5 (of 15)
Zheng et al. 2016	Sprague-Dawley Rats	Male	Newly weaned	3 months	20
Zhou et al. 2019	Sprague-Dawley Rats	Female	Pre-Pregnancy	Prenatal + 6 months	6
Zhu et al. 2017	Sprague-Dawley Rats	Both	Prenatal	Prenatal + 42 days	8

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Table A-2. Summary of animal studies that have investigated toxic effects of fluoride on learning and memory - *Continued*

Paper	Treatment groups	Selected Tests	LOAEL[b]
Banala and Karnati 2015	20 mg/L	Maze Learning	20 mg/L
Bartos et al. 2018	5 & 10 mg/L	Step Down Inhibitory Avoidance	5 mg/L
Bartos et al. 2019	5 & 10 mg/L	Step Down Inhibitory Avoidance	5 mg/L
Basha et al. 2011b	100 & 200 mg/L	T Maze	100 mg/L
Basha & Sujitha 2012b	270 mg/L	T Maze	270 mg/L
Bera et al. 2007	1.13 & 2.3 mg/kg/day	Active Avoidance / Novel Object Recognition	2.3 mg/kg
Chen et al. 2018a	4.5, 23, & 45 mg/L	Morris Water Maze	23 mg/L[c]
Chioca et al. 2008	23 & 45 mg/L (5.15 & 10.77 mg/kg/day)	Open Field / Two-Way Active Avoidance	23 mg/L
Cui et al. 2017	4.5, 23, & 45 mg/L	Morris Water Maze	4.5 mg/L
Dong et al. 2015	50 mg/L	Morris Water Maze	50 mg/L (adults)
Dong et al. 2015	50 mg/L	Morris Water Maze	50 mg/L (pups)
Ge et al. 2018	50 & 100 mg/L	Morris Water Maze	50 mg/L
Han et al. 2014	11, 23, and 45 mg/L	Novel Object Recognition / Open Field	45 mg/L[d]
Jetti et al. 2016	100 mg/L	T Maze / Passive Avoidance	100 mg/L
Jiang et al. 2014a	55 mg/L	Morris Water Maze	55 mg/L
Jiang et al. 2014b	11, 23, & 45 mg/L	Morris Water Maze	11 mg/L
Liu et al. 2010	2.3 & 23 mg/L	Morris Water Maze	2.3 mg/L
Liu et al. 2014	0.9, 2.3, and 4.5 mg/L	Morris Water Maze / Novel Object Recognition / Elevated-Plus Maze	2.3 mg/L[c]

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Table A-2. Summary of animal studies that have investigated toxic effects of fluoride on learning and memory - *Continued*

Paper	Treatment groups	Selected Tests	LOAEL[b]
McPherson et al. 2018	10 & 20 mg/L (+food exposure group)	Open Field / Elevated Plus Maze / Passive Avoidance / Morris Water Maze / Y Maze	None
Niu et al. 2009	68 mg/L	Y Maze	68 mg/L
Niu et al. 2014	68 mg/L	Novel Object Recognition	68 mg/L[e]
Niu et al. 2018a	4.5, 23, & 45 mg/L	Morris Water Maze	23 mg/L[c]
Pereira et al. 2011	45 mg/L	Open Field	45 mg/L
Pulungan et al. 2018	2.3, 4.5 & 9 mg/kg/day	Y Maze	None[f]
Raghu et al. 2013	100 mg/L	T Maze / Passive Avoidance	100 mg/L
Shalini and Sharma 2015	10 mg/L	Maze Test	10 mg/L
Sharma et al. 2018	68 mg/L	Morris Water Maze / Classic Maze	68 mg/L
Sun et al. 2018	11, 23, & 45 mg/L	Radial Arm Maze / Open Field	23 mg/L[c]
Wang et al. 2018a	11, 23, & 45 mg/L	Open Field / Eight-Arm Maze	23 mg/L[c]
Whitford et al. 2009	2.9, 5.7, & 11.5 mg/kg/day	Appetitive Based Learning	None
Yang et al. 2018a	60 & 120 mg/L	Morris Water Maze / Open Field	60 mg/L
Yuan et al. 2019	23, 45, & 68 mg/L	Y Maze	23 mg/L
Zhang et al. 2013a	45 mg/L	Y Maze	45 mg/L
Zhang et al. 2019	25, 50, & 100 mg/L	Morris Water Maze	100 mg/L[c]
Zhao et al. 2019	4.5, 23, & 45 mg/L	Morris Water Maze	23 mg/L
Zheng et al. 2016	45 mg/L	Morris Water Maze / Open Field	45 mg/L
Zhou et al. 2019	4.5, 23, & 45 mg/L	Morris Water Maze	23 mg/L[c]
Zhu et al. 2017	45 mg/L (8 to 11 mg/kg/day)	Morris Water Maze	45 mg/L

[a] Where the study does not identify the sex of the animals, it is assumed that both sexes were studied.

[b] A LOAEL refers to the lowest observed adverse effect level where a statistically significant result was observed.

[c] At least one effect was seen at lower treatment doses (as reflected by a visually apparent dose-related trend), but the effect(s) at the lower treatment levels did not reach statistical significance.

[d] At least one statistically significant effect was seen at lower treatment doses but for a neurological endpoint that is not specific to learning or memory impairments.

[e] The effect in the fluoride + lead treatment group was statistically significant, but the effect in the fluoride-only treatment group did not reach statistical significance.

[f] A statistically significant effect was observed in the low treatment dose group (5 mg/kg/day) when compared to the control, but there were no significant differences between the control and mid/high dose treatment groups (10 mg/kg/day & 20 mg/kg/day).

[g] Where the study does not identify the age of the animal at the start of the experiment, it is assumed that the animals had already completed weaning

Appendix B

KATHLEEN M. THIESSEN, Ph.D.
Senior Scientist
Oak Ridge Center for Risk Analysis, Inc.

Education

Ph.D.	1986	Genetics, University of Tennessee-Oak Ridge, Graduate School of Biomedical Sciences, Oak Ridge, TN
B.A.	1981	Biology and Chemistry (*Summa cum laude*), Covenant College, GA

Capabilities

Health Effects Assessment
Dose and Risk Assessment
Analysis of Environmental Transport and Exposure Pathways
Uncertainty and Sensitivity Analysis
Technical Writing/Editing, Technical and Public Presentations

Experience Summary

Dr. Thiessen is experienced in the evaluation of exposures, doses, and risks to human health from trace levels of contaminants in the environment and in the use of uncertainty analysis for environmental and health risk assessment. She has served on two National Research Council subcommittees, one charged with the review of fluoride exposure and toxicology, and one dealing with guidance levels for air contaminants (including hydrogen fluoride) in submarines. Dr. Thiessen has also written two reports for the U.S. Environmental Protection Agency, one on the health effects of hydrogen fluoride and related compounds, and one on the health effects of mercuric chloride. Dr. Thiessen has led several working groups on urban contamination and dose reconstruction for the International Atomic Energy Agency's programs on environmental transport modeling and has served on the coordinating committees of the programs; she currently leads a working group on assessment of exposures and countermeasures in urban environments. She also serves on a committee for the preparation of a new International Atomic Energy Agency report on modeling the impacts of planned discharges or radioactivity, and she is involved in the preparation of an IAEA guidance document on implementation of remediation strategies following accidental releases of radioactivity. Dr. Thiessen participated in two symposia on reconstruction of internal doses from Fukushima releases organized by Japan's National Institute of Radiological Sciences, and she has served as a consultant on environmental modeling issues to the Korea Atomic Energy Research Institute and on uncertainty analysis to the National Council on Radiation Protection and Measurements. Dr. Thiessen contributed to the development of a risk-based screening approach to prioritize further investigation of contaminants and exposure situations in various assessment contexts, and she led in the application of risk-based screening techniques for the reconstruction of doses and health risks associated with releases of chemicals and radionuclides from the U.S. Department of Energy's Oak Ridge (Tennessee) facilities. Dr. Thiessen also led an analysis of human exposures, doses, and health risks to off-site individuals associated with historic releases of radionuclides to the Clinch River from the Oak Ridge facilities.

Experience

1992-present Senior Scientist and Director, Oak Ridge Center for Risk Analysis, Inc. (Formerly *SENES* Oak Ridge, Inc., Center for Risk Analysis), Oak Ridge, TN.

- Review of data on contaminant exposure and toxicology.
- Analysis of environmental transport and exposure pathways.
- Screening techniques for environmental assessment.
- Dose reconstruction.
- Uncertainty analysis for environmental assessment.
- International model validation using Chernobyl data sets.
- Working Group Leader for International Atomic Energy Agency research programs.
- Project coordination.
- Technical review.

1991-1992 Consultant and Technical Writer. Environmental Sciences Division, Oak Ridge National Laboratory, Oak Ridge, TN.

1987-1992 Lecturer in Genetics. University of Tennessee, Oak Ridge Graduate School of Biomedical Sciences.

1986-1989 Oak Ridge National Laboratory, Health and Safety Research Division, Chemical Hazard Evaluation Program.

- Assessment of health effects from chemicals.
- Risk assessment.
- Technical review.

Publications and Technical Reports

Periáñez, R., Thiessen, K.M., Chouhan, S.L., Mancini, F., Navarro, E., Sdouz, G., and Trifunović, D. 2016. Mid-range atmospheric dispersion modelling. Intercomparison of simple models in EMRAS-2 project. *Journal of Environmental Radioactivity* 162-163:225-234.

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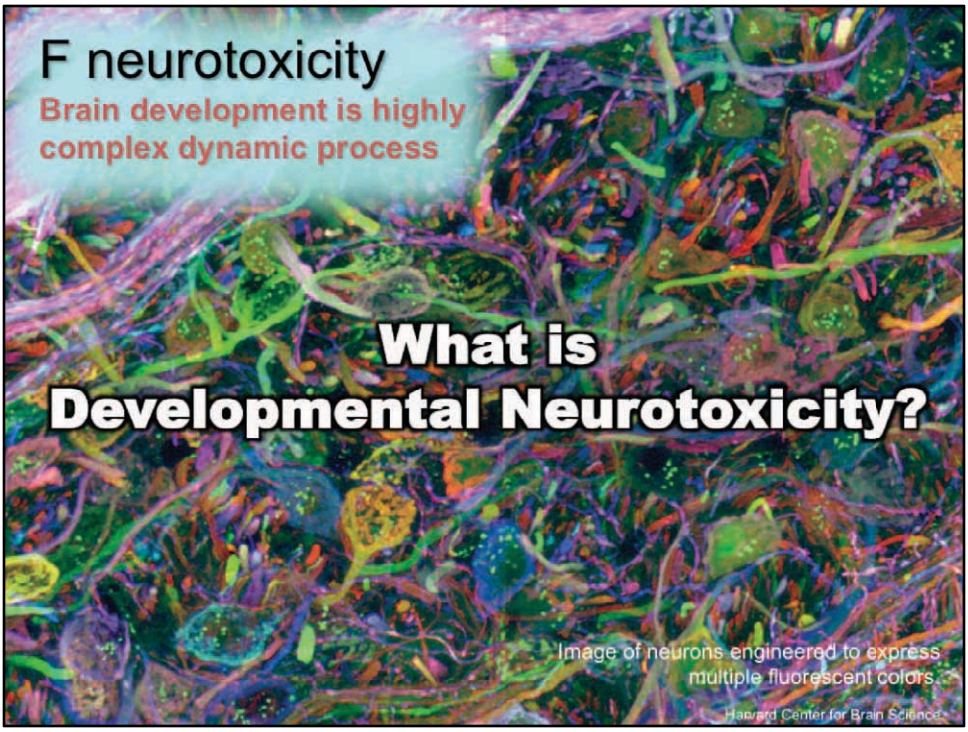
The Scientific Evidence for Fluoride's Developmental Neurotoxicity

February 10, 2020

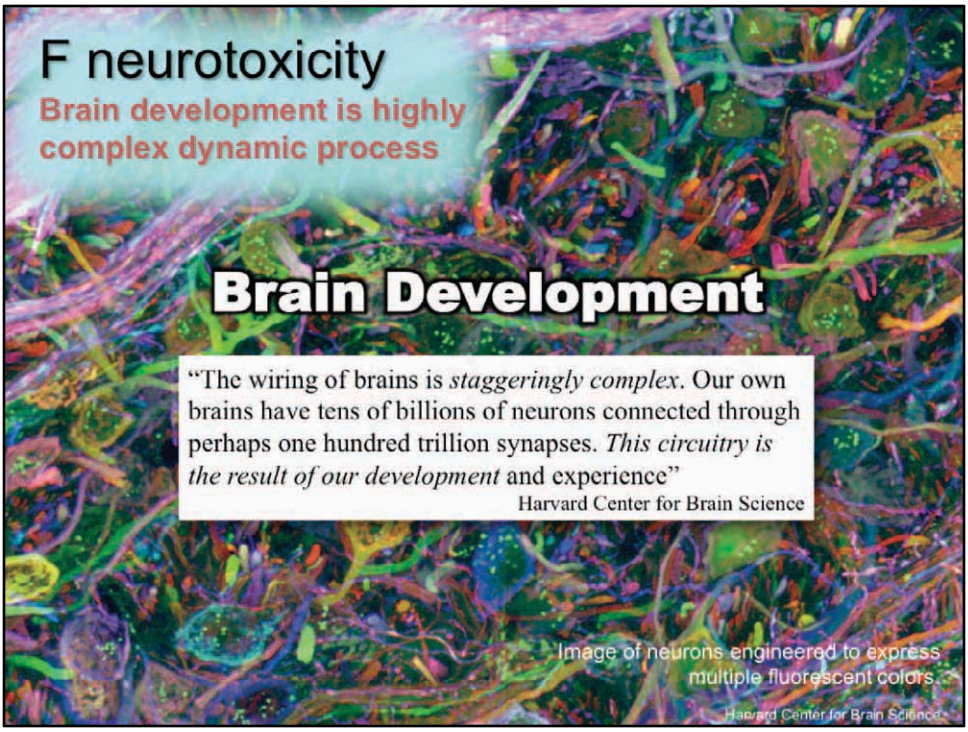
Chris Neurath
Research Director
American Environmental Health Studies Project
FLUORIDEALERT.ORG
Fluoride Action Network

1

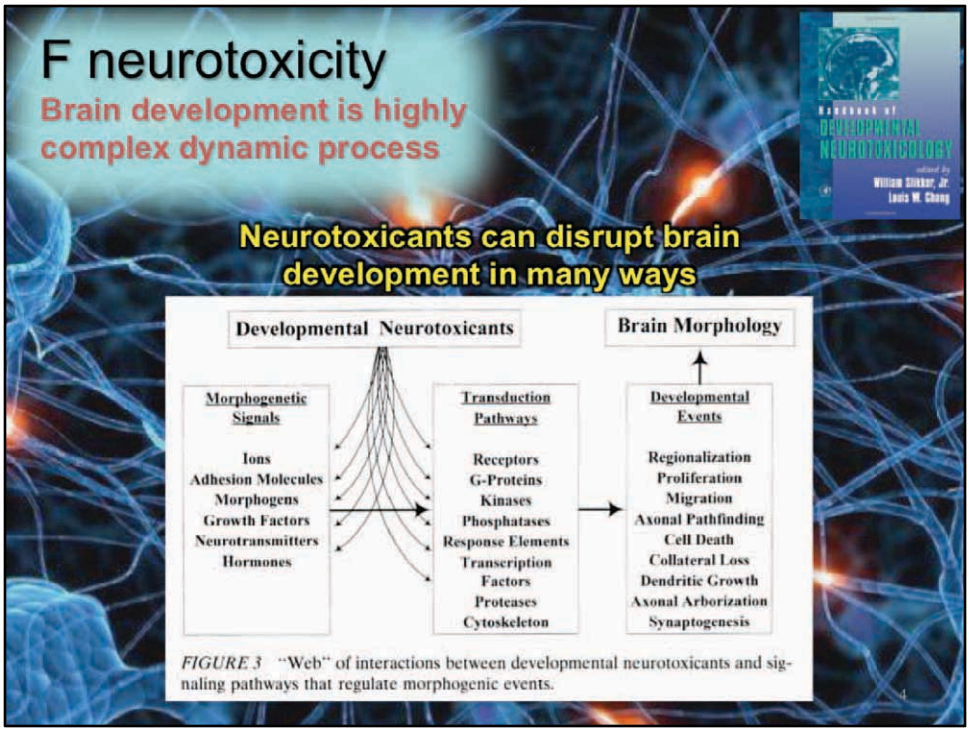
I'm Chris Neurath and I'm the Research Director for the American Environmental Health Studies Project. I'm going to give an overview of the scientific evidence for fluoride's developmental neurotoxicity.



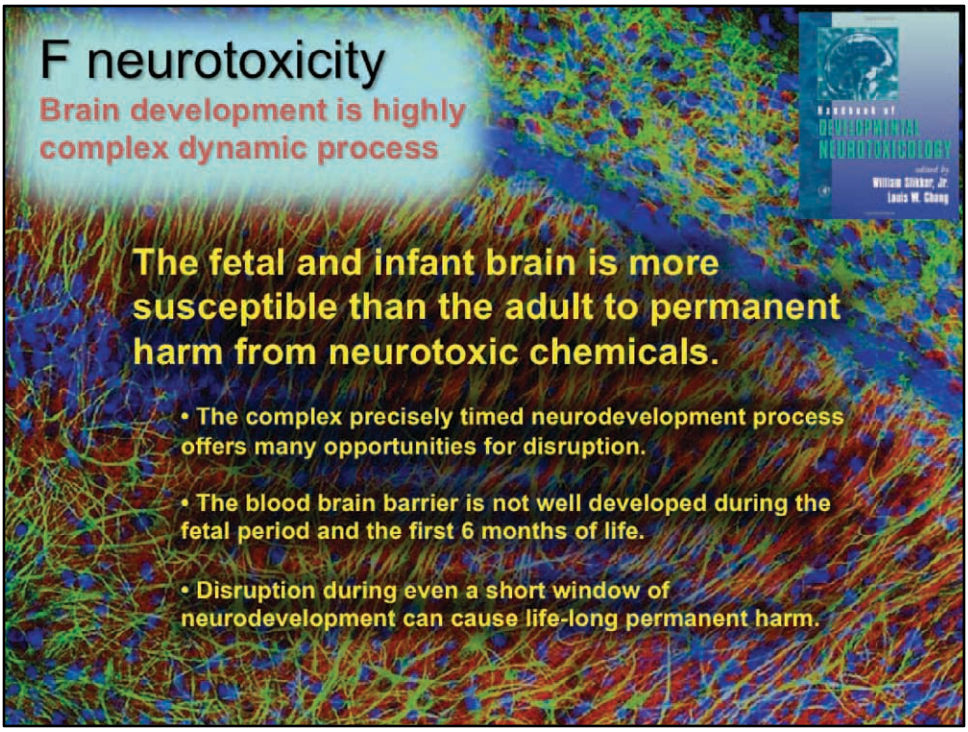
I’m going to start with some amazing and beautiful pictures ... and the question: What exactly is developmental neurotoxicity ... and why is it such a focus of current research on fluoride?



Brain development starts with a few cells in the early fetus and continues rapidly in a highly complex dynamic process through infancy. Indeed the rate of neurodevelopment in humans is extremely rapid in utero, but is even faster in the first months after birth. This formation of the wiring of our brains is "staggeringly complex" as described by the Harvard Center for Brain Science. "Our own brains have tens of billions of neurons connected through perhaps one hundred trillion synapses."



There are many critical processes during neurodevelopment, which all have to take place with precise timing and coordination with the other processes. A disruption from a toxic chemical to any process, even during a brief window of time, can cause permanent harm. Reduced IQ is one symptom of such harm.



The fetal brain and the infant brain is more susceptible to disruption than the adult brain because of this complex neurodevelopment process but also because the blood-brain barrier, which can limit access of toxic chemicals to the brain in adults, is not well developed until after age 6 months. Disruptions to neurodevelopment can cause life-long harm which often can not be repaired.

The best place to start is with the recently released National Toxicology Program, or NTP, a systematic review of fluoride's neurotoxicity. This was a very thorough review that has been 5 years in the making. They concluded that fluoride is a presumed neurotoxin.

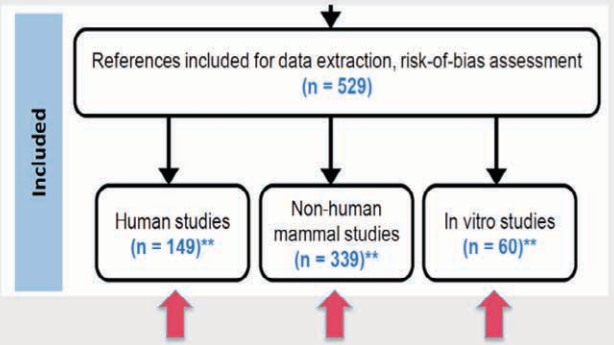
F neurotoxicity

Large number of studies

National Toxicology Program
U.S. Department of Health and Human Services

Systematic Review of Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects

Figure 4. Study Selection Diagram



7

Their conclusion is based on a very large amount of evidence that would probably surprise most people who have not studied fluoride's adverse effects. The NTP identified 149 human studies and 339 laboratory animal studies.

F neurotoxicity

Large number of studies

National Toxicology Program
U.S. Department of Health and Human Services

Systematic Review of Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects

Figure 5. Number of Epidemiological Studies by Outcome and Age Categories*

Outcome Category	Age Category: Child	Adult	Child/Adult Combined	Infant	Fetus
Intelligence (IQ)	60	3			
Learning/Memory	4	3		1	
Cognitive Development	2			1	
Cognitive Impairment		5			
Attention/Hyperactivity/Behavioral Issues	5				
Motor/Sensory Function or Development	2	4		1	
Mood/Affect		1			
Visual-Spatial/Visual-Motor Function	2	2			
Brain Activity		1			
Brain Structure					2
Neurological Biochemical	2	1	1		1
Neurological Complications of Fluorosis		3			
Neurological Symptoms	1	3			
Birth Defects				3	
Thyroid Gland Function	12	5	2		
Thyroid Disease		2			

8

Of the human studies, there was a wide variety of developmental neurotoxic endpoints, with the largest number being studies of IQ in children with 60 such studies.

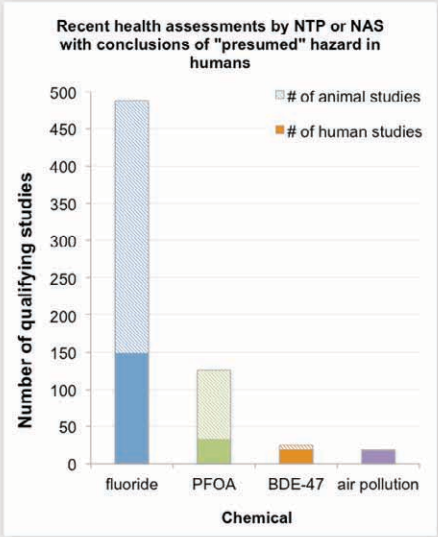
F neurotoxicity

Large number of studies

National Toxicology Program
U.S. Department of Health and Human Services

Systematic Review of Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects

NTP found many more studies of F neurotoxicity compared to what it has found for other toxins in its recent reviews



9

It is worth comparing this NTP review of fluoride neurotoxicity to NTP reviews of other toxic chemicals. The NTP's main purpose is to assess the toxicity of chemicals and they have issued several recent reports on other chemicals that concluded they were "presumed" hazards. But fluoride turns out to have many more studies than any of these other chemicals. The other chemicals shown are PFOA which is a perfluorinated chemical, BDE-47 is a brominated fire retardant, and "air pollution" which includes PM 2.5.

F neurotoxicity

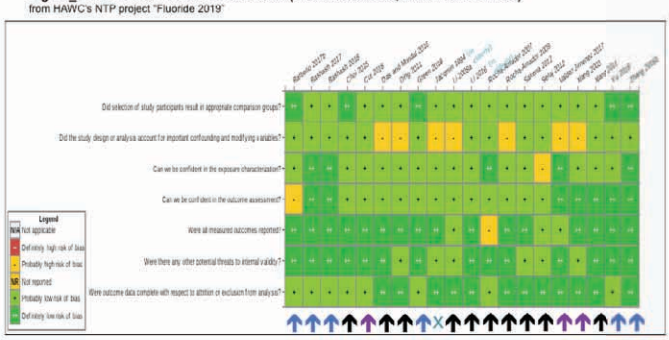
Large number of studies

National Toxicology Program
U.S. Department of Health and Human Services

Systematic Review of Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects

20 of the studies were considered high quality (low Risk of Bias).

Figure_A3-01 Human Risk of Bias scores (neurobehavioral, lower RoB studies)
from HAWC's NTP project "Fluoride 2019"



All studies except one found significant adverse effects

↑= Study found adverse effects at exposure levels of **0.7 mg/L** water F or equivalent

↑= Study found adverse effects at exposure levels **below 1.5 mg/L** water F or equivalent

↑= Study found adverse effects at exposure levels **above 1.5 mg/L** water F or equivalent

X= did not find statistically significant adverse effect

10

The NTP carefully assessed every study and gave them scores for several domains. Of the 149 human studies, they determined that 20 were high quality, or in their terminology, at "low Risk of Bias". When comparing this number of high quality human studies to the number available for other developmental neurotoxins, or for toxins of any type, this is a very large number. The EPA, for example, has determined that some chemicals are neurotoxins without a single high quality human study available.

The green in the graphic essentially means "good" and low Risk of Bias for that domain. Yellow and red indicate higher Risk of Bias. Of the 20 high quality studies, 18 were in children and all 18 found statistically significant adverse effects. This is the high level of consistency cited by the NTP in their conclusion of "presumed" neurotoxic in humans.

The graphic is from the NTP report but I have added the colored arrows that are **blue**, **purple**, and **black**. They indicate the exposure levels at which harm was found and are related to the exposure levels found in the USA, due largely to artificially fluoridated water. The **blue arrows** indicate studies that found adverse effects at 0.7 mg/L water fluoride concentrations or the equivalent in urine fluoride. 0.7 mg/L is currently the most common level of fluoridation in the USA. The NTP also considered that levels below 1.5 mg/L are relevant to exposures in the USA. I've marked those in **purple**. Half of the high quality studies found that exposures common in the USA were associated with harm, mostly lowered IQ.

F neurotoxicity

Pre-conceptions

JAMA Editor's Podcast excerpts, on Green 2019:

Pre-conceptions that people who claimed that fluoridation is harmful were "nuts".

Frederick P. Rivara, MD, MPH
Editor, *JAMA Networks Open*

Dimitri A. Christakis, MD, MPH
Editor, *JAMA Pediatrics*

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I now want to discuss the reaction to the rapidly emerging evidence that fluoride is neurotoxic and can lower IQ of children. The single study which has received by far the most attention is the Green 2019 study published in *JAMA Pediatrics* in August 2019. You've probably heard about it and may have read it. I found the *JAMA* editors reactions to it to be very revealing of where most people, including health professionals, beliefs about fluoride have been ... and where they can move to when they have an open mind. I'm going to give excerpts from their Podcast discussion of the paper.

F neurotoxicity
Pre-conceptions

Dr Rivara- "The paper is about fluoride, and maternal fluoride exposure during pregnancy, and its effects upon IQ scores of children at ages 3 and 4, which in itself is like a shocking title, because I had never known that there was even any concern that maternal fluoride use might affect children's IQ."

Dr Christakis- "… the traditional teaching when I was going through residency in my early professional career was that fluoride was completely safe, all these people that are trying to take it out of the water are nuts, its the best thing that's ever happened for children's dental health, and we just need to push back and get it into every water system."
"So when I first saw this title my initial inclination was **'What the hell?'**"

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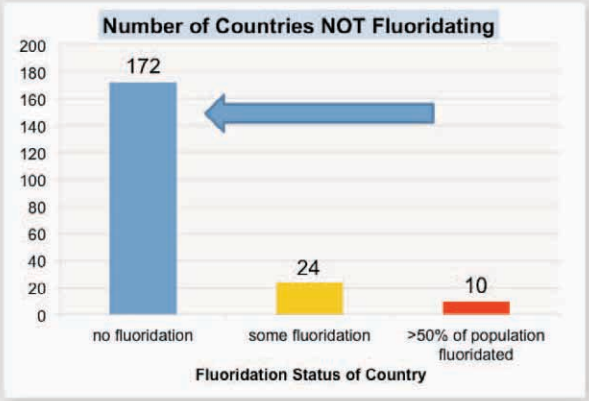
Excerpts from their Podcast: audio clip A.

Open "JAMAPed clip A" to play

F neurotoxicity

"in Europe only 3% of municipal water supplies are fluoridated"

Editors surprised by just how much of the world does *NOT* fluoridate.



13

The editors were surprised at how many cities and countries do not fluoridate their water. In fact, the large majority of the world does not fluoridate.

F neurotoxicity

"in Europe only 3% of municipal water supplies are fluoridated"

Editors surprised by just how much of the world does *NOT* fluoridate.

Dr Rivara- "… this was from Canada and they picked some large cities in Canada; these were Montreal, Vancouver, Kingston, Toronto, Hamilton and Halifax; so I'm a little surprised that those places did not [all] have fluoridated water supplies."

Dr Rivara- "And the other interesting thing that came out, like in the editorial and in this paper, was that in Europe only 3% of municipal water supplies are fluoridated."

Dr Christakis- "Right, so again this was to me sort of eye-opening, that you known, I sort-of thought that 'everyone did it'; certainly all developed countries, everyone that was at any level of sophistication was putting fluoride in the water."

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Excerpts from Podcast: audio clip B.

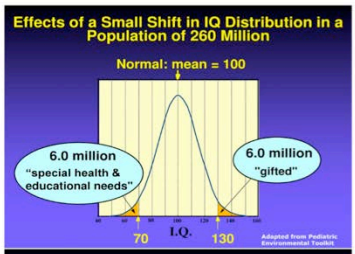
Open "JAMAPed clip B" to play

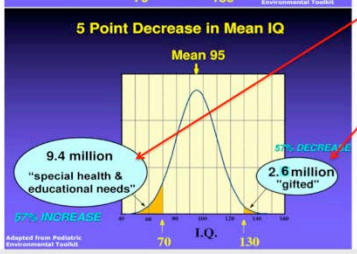
F neurotoxicity

A sizable effect "on par with lead"
"that's a real concern"

Editors "really startled" at size of effect.

For an increase of 1 mg/L in maternal urine fluoride concentration, boys lost 5 IQ points.





How 5 IQ point average loss shifts the IQ distribution and dramatically changes numbers of children at each "tail".

3.4 Million MORE special needs people

3.4 million FEWER gifted people (geniuses)

Steven Rosenberg, M.D., M.P.H.
Everything You Always Wanted to Know About Childhood Lead Poisoning (but Were Afraid to Ask)
SlideShare-June 21, 2007

The editors noted with concern that the loss of IQ from fluoridation is "on par with lead". They also point out that even a small average drop of IQ of a few points, can produce a large increase in those on the lower tail of the distribution who need special education, and a halving of the number of gifted children on the high end distribution tail.

F neurotoxicity

A sizable effect "on par with lead"
"that's a real concern"

Dr Rivara- "… a 1 mg/L increase in the maternal urinary fluoride concentration was associated with a 5 point lower score on the boys' IQ."
Dr Christakis- "Right. An effect size which is sizable, on a par with lead"
Dr Rivara- "Right, it is."

Dr Rivara- "The effect size is really quite large, because when you think about it really in terms of not the individual child so much as the shift in the curve … the shift in the curve, now, being shifted to the left, for boys, that's a real concern …."

Dr Rivara- "the results are really startling"

Dr Christakis- "… there have been other observational studies that have shown this, and there have been animal models as well, that have shown this idea that fluoride could be a neurotoxin; which again was totally news to me because I thought it was junk science, anyone would ever say such a thing."

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Excerpts from Podcast: audio clip C.

Open "JAMAPed clip C" to play

F neurotoxicity

Editor's advice: Pregnant mothers should avoid fluoridated water

The editors concluded with the advice that pregnant mothers should not drink fluoridated water.

F neurotoxicity

Editor's advice: Pregnant mothers should avoid fluoridated water

Dr Rivara- "So, if mothers now come into their doctor's offices and ask the pediatrician what to do, what are you going to say?"

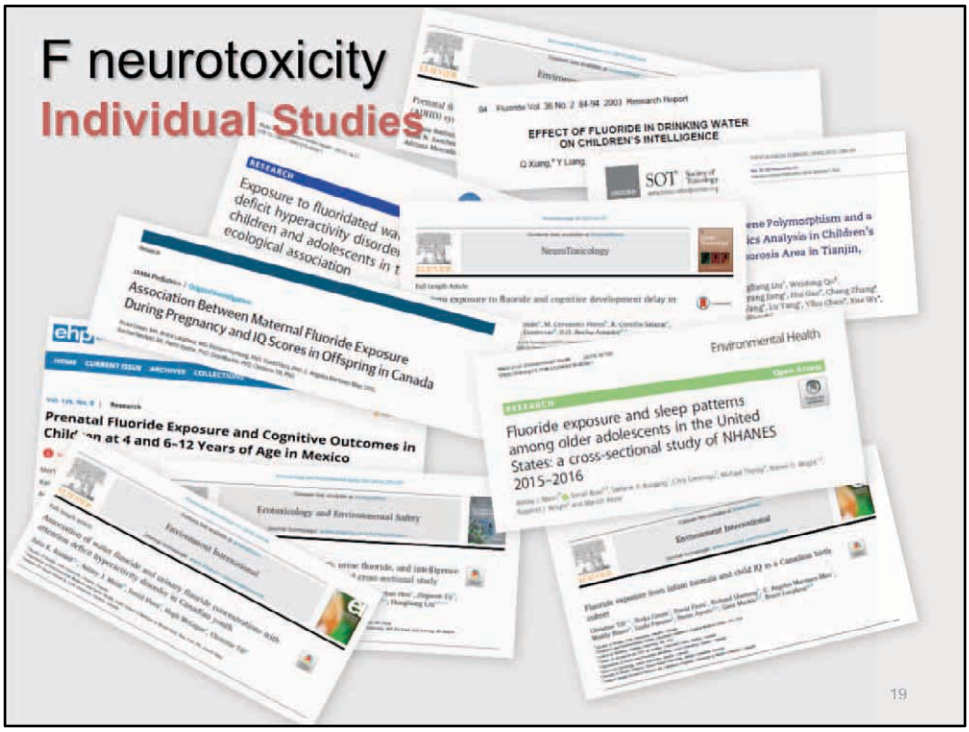
Dr Christakis- "I think I would advise them to drink bottled water, or filtered water, because its not a particularly odious thing to do, and potentially does reduce the risk."

Dr Rivara- "Yea, you know the other thing is that some people may not be able to afford bottled water, it could be a financial burden to some low-income families, and we need to think about that as well."

"Well, its going to get a lot of attention, and I'm very proud that you published it." 18

Excerpts from Podcast: audio clip D.

Open "JAMAPed clip D" to play



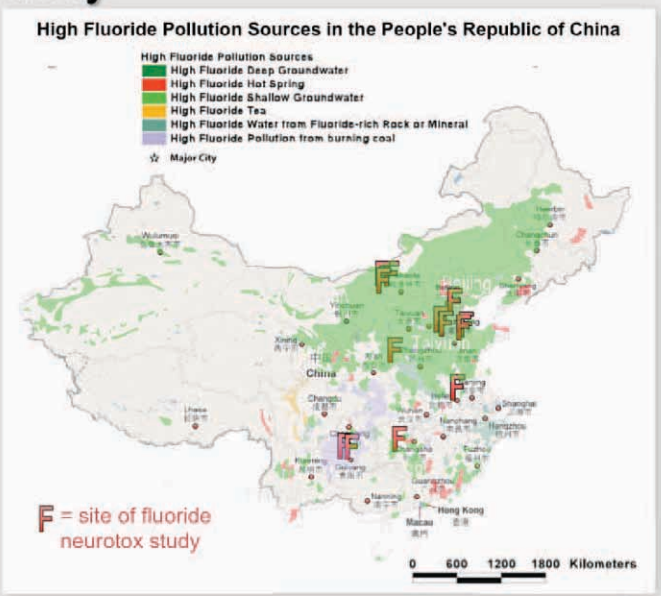
I'm now going to briefly go over some of the most important individual studies. These will just be ones that the NTP rates high quality and low risk of bias.

F neurotoxicity

First studies from China

In the 1980s China started investigating F neurotoxicity because it had 100 million people living in endemic fluorosis areas due to natural F in groundwater.

No artificial fluoridation in China.



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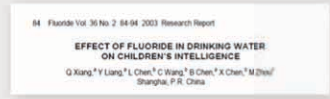
Studies of fluoride's developmental neurotoxicity started in China in the 1980s. That's because large areas of China with a population of about 100 million used groundwater for drinking that had elevated fluoride levels. China and WHO consider water fluoride concentrations above 1.5 mg/L elevated. The map shows the large areas with elevated groundwater fluoride as light green. It shows other sources of fluoride exposure in other colors. Purple shaded areas are a special localized situation where people cook indoors using coal briquettes that are made from a mix of clay and coal. The clay is the source of the high indoor fluoride levels. Normal coal combustion, such as from power plants, is not a significant source of fluoride exposure. The large red "F" markers show the locations of neurotox studies, which are spread throughout China in many different populations. Almost all of the studies found reduced IQ in the children with higher fluoride exposure.

F neurotoxicity

Xiang 2003


84 Fluoride Vol. 36 No. 2 84-94 2003 Research Report

EFFECT OF FLUORIDE IN DRINKING WATER ON CHILDREN'S INTELLIGENCE

Q.Xiang,[a] Y.Liang,[a] L.Chen,[b] C.Wang,[a] B.Chen,[a] X.Chen,[a] M.Zhou[c]
Shanghai, P.R. China

High quality study with individual level data; China.

F and IQ

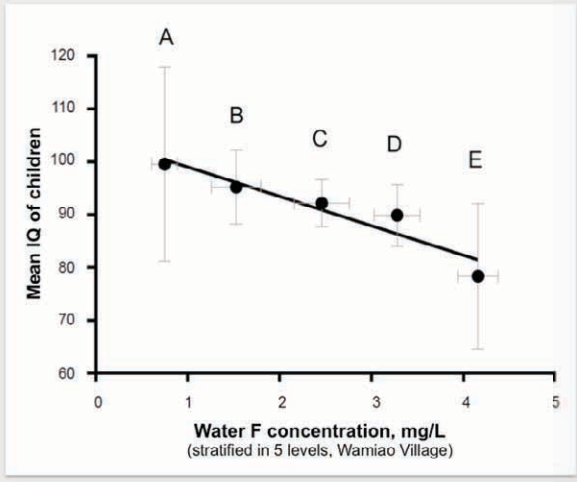


Figure adapted from Hirzy 2016 based on data reported in Xiang 2003.

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The earliest studies in China were often of relatively unsophisticated design, but by about 2000, stronger study designs were being used. The Xiang 2003 study is the earliest study to be rated high quality in NTP's review. As shown in the graph, as the water fluoride increased, IQ steadily decreased. Loss of IQ is even apparent at concentrations below 1.5 mg/L.

F neurotoxicity

Xiang 2003

High quality study with individual level data; China.

F and % IQ below 80

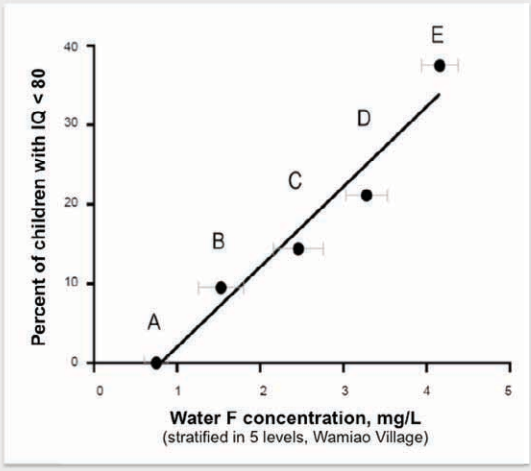

Figure adapted from Hirzy 2016 based on data reported in Xiang 2003.

22

But Xiang 2003 also found an even more worrying effect by looking at the percentage of children with IQ below 80, as shown in this graph. At the lowest water fluoride level of about 0.8 mg/L, shown as group "A", no children had IQ below 80. At the next higher level, group "B", at about 1.5 mg/L, 10% of children had IQs below 80, and at the highest exposure level almost 40% of children had IQ below 80.

F neurotoxicity

Zhang 2015

High quality study; first with gene-F interaction; China.

Found 5x greater loss of IQ for those with specific genotype

Genotype	*N*	IQ points lost per 1 mg/L urine F	*p*-value
combined	108	–2.42	0.030
val/val	28	–9.67	0.003

F and IQ

all genotypes combined

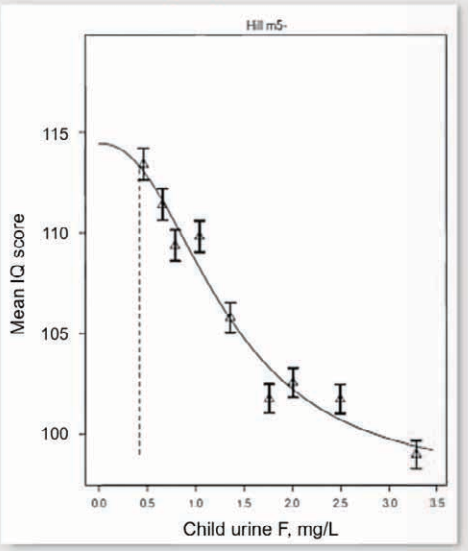

Figure based on Zhang 2015, Figure 1, with Benchmark Dose analysis using PROAST method.

Of the 18 studies in children that NTP considers to be of high quality, I'm only going to discuss those that have some special feature. All 18 found statistically significant adverse effects. The Zhang 2015 study shown here was the first study to look at interactions between fluoride and genes. That is, it looked to see whether individuals with particular genetic variants were more susceptible to loss of IQ from fluoride than more common genetic variants. It found a 5-fold greater loss of IQ for a specific gene variant. The table on the lower left shows that for all children with all variants the loss of IQ was 2.42 points per 1 mg/L increase in urine fluoride, but for the val/val variant, the loss was 9.67 IQ points. About a quarter of the population had the val/val variant. The figure on the right shows how IQ drops in the susceptible group as urine fluoride increases. There is a substantial drop in IQ even at the lowest urine fluoride levels which are well below 1.5 mg/L.

F neurotoxicity

Valdez-Jimenez 2017

High quality study; first mother-offspring longitudinal cohort; Mexico.

F and IQ

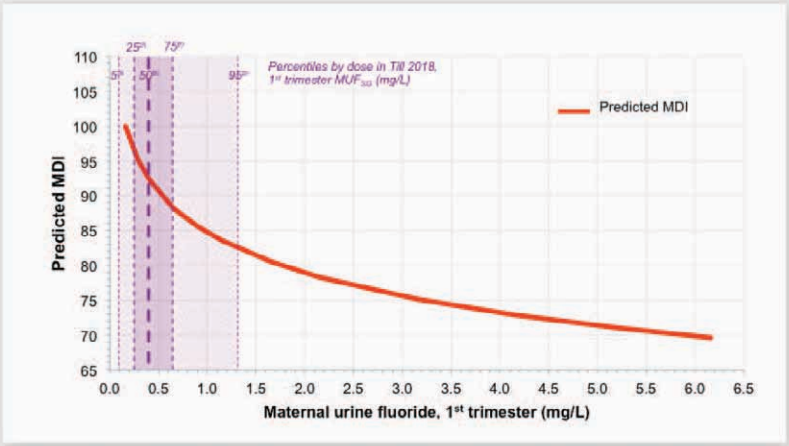

Figure based on Valdez-Jimenez 2017, Table 4, with overlay of Till 2018 exposure levels in Canada.

This study is noteworthy because it is the first mother-offspring longitudinal cohort study. It measured fluoride in the mothers during pregnancy and then assessed the neurodevelopment of the infants. There was a steep drop in infant's neurodevelopment score, especially in the range of maternal urine fluoride below 1.5 mg/L. This study was in Mexico, but the exposure levels can be related to those in Canadian pregnant women or pregnant women in the USA, for that matter. The purple shading indicates urine fluoride levels found in a Canadian study. Much of the loss of IQ occurs within the shaded purple range.

F neurotoxicity

Bashash 2017

High quality, mother-offspring longitudinal cohort study; Mexico City.

First NIH-funded study of F developmental neurotoxicity.

Found large, statistically significant effects on IQ.

Average IQ losses of 4-6 points for each 1 mg/L increase in mother's urine F.

F and IQ

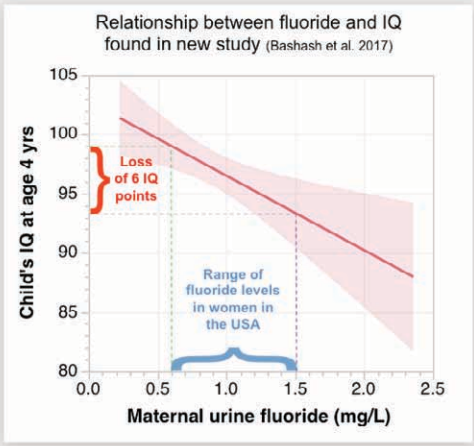

Figure based on Bashash 2017, Figure 2.

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This study, Bashash 2017, was the first funded by the US National Institutes of Health, or NIH, with a grants totaling about $3 million. It is a very high quality study and found a large, statistically significant effect of fluoride on IQ. The average loss was 4 to 6 IQ points for each 1 mg/L increase in mother's urine fluoride. The graph shows the dose-response relationship found for children tested at age 4 years. It also shows in the blue bracketed region the range of fluoride levels expected in the USA and the resulting loss of IQ of 6 IQ points is shown in the red bracketed region.

To date, there have not been any published studies of maternal urine fluoride levels in the USA so the range sown here is based on studies in artificially fluoridated areas of Canada and New Zealand.

F neurotoxicity

Bashash 2017

Many potential confounders considered and/or adjusted for:

Child characteristics:

1. gestational age
2. weight at birth
3. sex
4. parity (being the first child)
5. age at outcome measurement

Maternal characteristics:

6. smoking history (ever smoked vs. nonsmoker)
7. marital status (married vs. others)
8. age at delivery
9. maternal IQ
10. education,
11. cohort (Cohort 3-Ca, Cohort 3-placebo and Cohort 2A)
12. HOME score (Home Observation for the Measurement of the Environment)
13. child's urine F at outcome assessment
14. SES (Socio-Economic Status)
15. maternal bone lead
16. maternal blood mercury
17. calcium supplement

Excluded from study if:

18. history of psychiatric disorders
19. high-risk pregnancies
20. gestational diabetes

or reported current use of:

21. daily alcohol
22. illegal drugs
23. continuous prescription drugs

or were diagnosed with:

24. preeclampsia
25. renal disease
26. circulatory diseases
27. hypertension
28. seizures during the index pregnancy

As just one indication of the high quality and rigor of the Bashash 2017 study, this is a listing of all the potential confounders that were considered and adjusted for if necessary.

F neurotoxicity

Bashash 2017

High quality, mother-offspring longitudinal cohort study; Mexico City.

"**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."

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The study concluded: "higher levels of maternal urinary fluoride during pregnancy ... in the range of levels of exposure in other general populations ... were associated with lower scores on tests of cognitive function ... in offspring". The phrase "in the range of levels of exposure in other general populations" is important, because it means this study in Mexico had fluoride exposures in the same range that women experience in the USA from artificially fluoridated drinking water. There is no artificial water fluoridation in Mexico, and instead salt is fluoridated, but the total intake of fluoride covers the same range as in the USA.

F neurotoxicity

Cui 2018

High quality study; with gene-F interaction; China.

F and IQ

- **Second study to ever look at gene-F interaction. Also found much greater susceptibility to IQ loss for those children with a gene variant:**

10 IQ point loss for 1 mg/L increase in urine F.

- **4x greater loss than for all children combined.**
- **14% of children had susceptible TT gene variant.**

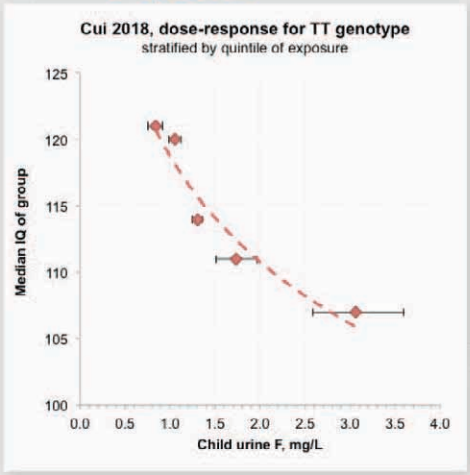


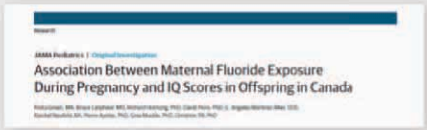
Figure based on Cui 2018, Table 1 and Table 4.

28

This study, Cui 2018, is noteworthy because it is the second to examine gene-fluoride interactions. Just as the first such study by Zhang 2015, it found a much greater loss of IQ in those children with a particular gene variant, although in this study they looked at a different gene. For the genetically susceptible children, this study found a 10 IQ point loss for each 1 mg/L increase in urine fluoride. This was a 4-fold greater loss than in all children combined. 14% of the children had this susceptible gene variant. The graph shows that this large loss of IQ was found even below 1.5 mg/L urine fluoride.

F neurotoxicity

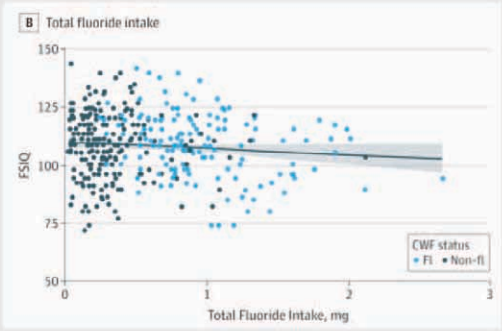
Green 2019


Association Between Maternal Fluoride Exposure During Pregnancy and IQ Scores in Offspring in Canada

High quality, mother-offspring longitudinal cohort study; Canada.

- **Second NIH-funded study of F developmental neurotoxicity.**
- **Found large, statistically significant effects on IQ.**
- **Average IQ loss of 4.5 points in boys for each 1 mg/L increase in mother's urine.**
- **Average IQ loss of 3.7 points for each 1 mg/day increase in mother's F ingestion.**

F and IQ



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The Green 2019 paper is the highly cited study in *JAMA Pediatrics*, which the editors commented about in their Podcast that I gave excerpts from earlier. This study was also NIH funded, and is important not just because of its very high quality, but because it was done in Canada. Canada is about as similar to the USA in socioeconomic and fluoride exposure conditions as anywhere. Fluoride exposure in both countries comes mainly from artificial water fluoridation, with the average level in Canada being about 0.6 mg/L and in the USA, somewhat higher, at 0.7 mg/L. Although no study of fluoride and IQ has yet been done in the USA, this study in Canada can be considered very applicable to the USA.

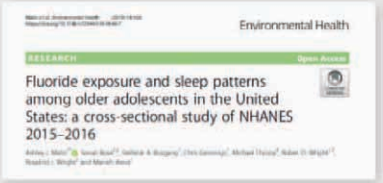
It found large statistically significant effects on IQ. For boys, the average IQ loss was 4.5 points for each 1 mg/L increase in mother's urine. The study also estimated total daily fluoride intake in the mothers and found an average 3.7 IQ points loss for both boys and girls for each 1 mg/day increase in mother's fluoride ingestion.

Defenders of water fluoridation have tried to criticize this Green 2019 study. I won't get into a detailed discussion of this, other than to point out that the authors themselves have rebutted virtually all the criticisms in a letter published in *JAMA Pediatrics* in December 2019. If you are interested in the discussions about the validity and relevance of the Green 2019 study that response letter is a good place to start.

F neurotoxicity

Malin 2019

1st study of F and sleep patterns; adolescents in USA.



- **Altered sleep patterns in adolescents linked to levels of fluoride in the drinking water in the USA.**
- **Study used nationally representative NHANES data collected by CDC.**
- **Animal studies suggest F may impair melatonin production in pineal gland.**

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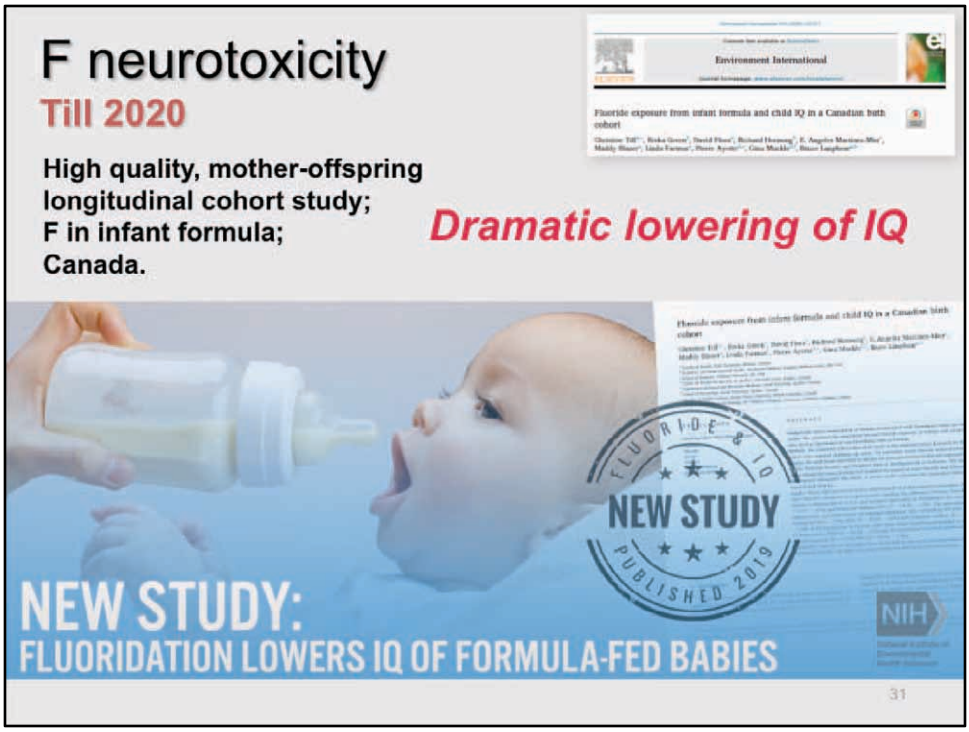
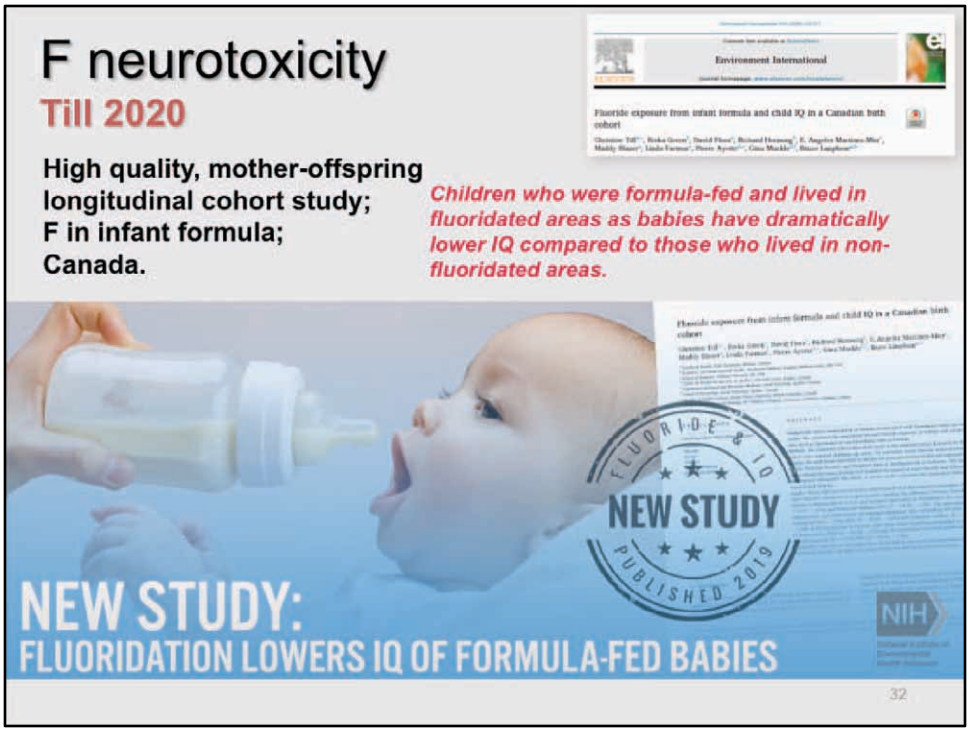
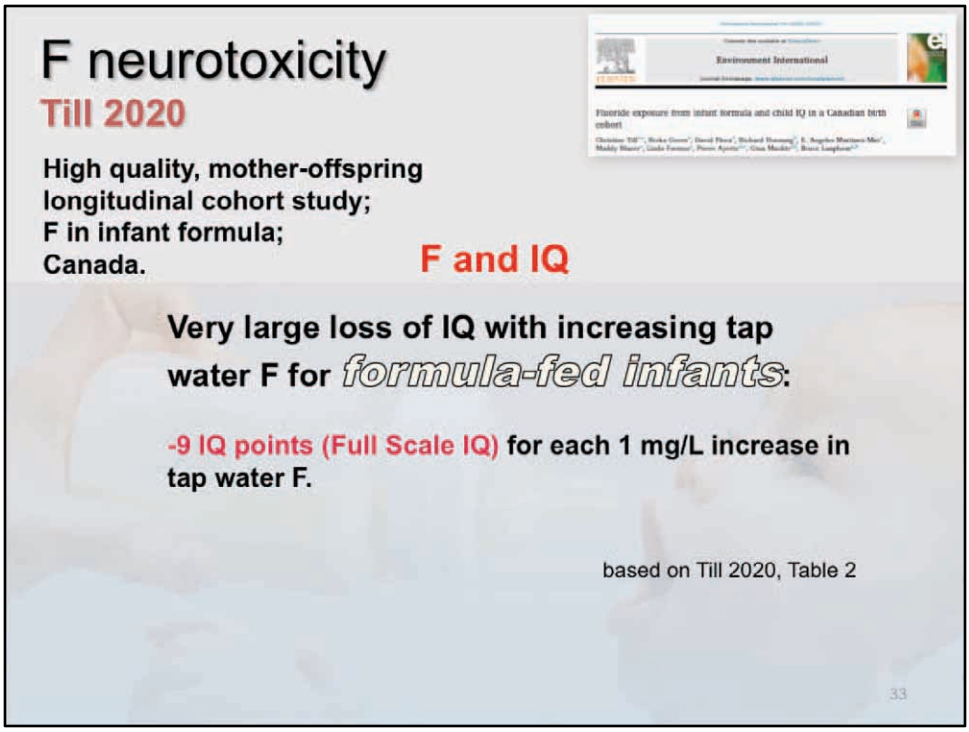
The NTP review of fluoride neurotoxicity studies only included studies published up until August 2019. There have been 3 more high quality studies published in just the last 6 months, and they both reinforce and extend the evidence compiled in the NTP review. This study, Malin 2019, was the first to ever examine sleep patterns in relationship to fluoride exposure. Furthermore, it used data from the USA in the nationally representative sample of the NHANES survey conducted by the CDC. It found altered sleep patterns in adolescents with higher drinking water fluoride levels. Altered sleep patterns can be considered a neurologic effect. Animal studies suggest fluoride may impair melatonin production in the pineal gland, so that might be the mechanism for altering sleep patterns.



This is the most recently published study, and in my opinion, is the most concerning study yet. It was done in the same Canadian cohort as the Green 2019 paper in *JAMA Pediatrics*. But, instead of estimating prenatal exposure to fluoride it measured exposure to the infants between birth and age 6 months, with comes largely through infant formula when it is made up with fluoridated water.

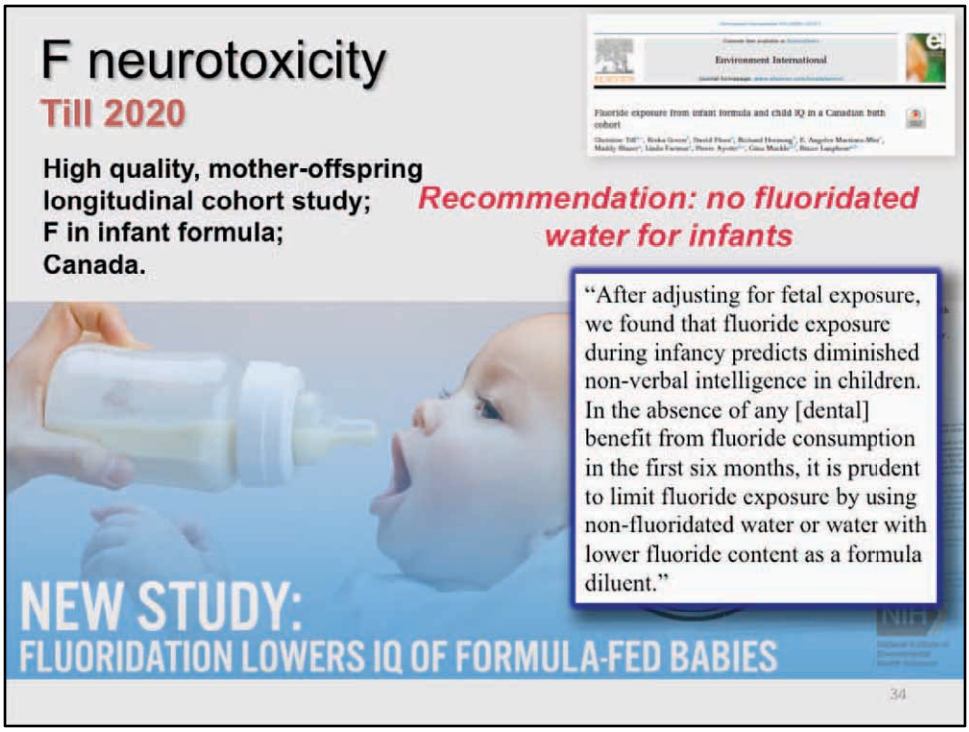


The study found that children who were formula-fed and lived in fluoridated areas as babies have dramatically lower IQ compared to those who lived in non-fluoridated areas.



Children given formula as infants **lost 9 IQ points** for each 1 mg/L increase in tap water fluoride. For the so-called Performance Scale IQ score, also known as "non-verbal IQ score", **the children lost 19 points** for each 1 mg/L increase in tap water fluoride. These are dramatic and very concerning reductions in IQ that are even larger than the losses from prenatal exposure.

Two possible factors may explain this greater loss from infant period exposure than from prenatal. First: Brain development is actually more rapid during early infancy than prenatally, so may be more sensitive to disruption by neurotoxic agents. Second: Infant exposures to fluoride are much simpler and are less subject to random error than are maternal urine fluoride measurements. Maternal urine fluoride can vary by whether the mother ingested any fluoride in the hour or so before the urine sample was taken. Random error in estimating the prenatal exposures can lead to what is called "bias toward the null" which is an underestimate of the true effect. Therefore, the studies of prenatal fluoride exposure may be underestimating the size of the effect. In contrast, this study of fluoride from infant formula is not underestimating the effect, so this larger effect may be closer to the true effect.



The authors conclude that for infants: **"in the absence of any [dental] benefit from fluoride consumption in the first six months, it is prudent to limit fluoride exposure by using non-fluoridated water"** to make formula.

F neurotoxicity

Fluoride and ADHD

Three studies of Fluoride and ADHD

While most studies of fluoride neurotoxicity have looked at IQ loss, there have also been several that have looked at the association with ADHD, or Attention Deficit Hyperactivity Disorder. I'll discuss three such studies.

F neurotoxicity

Malin 2015

F and ADHD

1st study of F and ADHD; ecological; USA.

Dramatic rise in ADHD prevalence as percent of state fluoridated increased.

About 50% higher ADHD rate in states with most fluoridation compared to those with least.

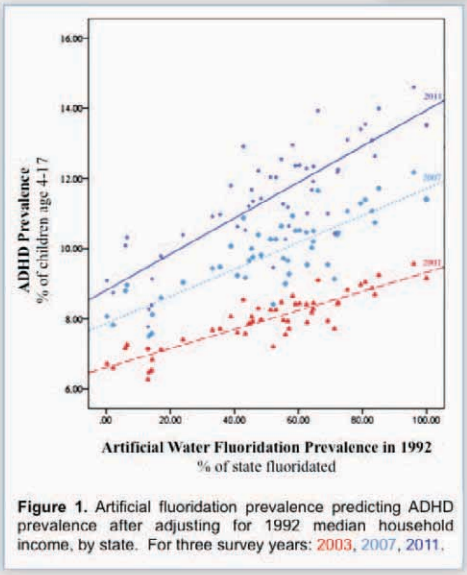


Figure 1. Artificial fluoridation prevalence predicting ADHD prevalence after adjusting for 1992 median household income, by state. For three survey years: 2003, 2007, 2011.

36

The first study to ever look at fluoride and ADHD was by Malin in 2015. It found a dramatic increase of ADHD prevalence with increasing percent of state-level fluoridation. States with high proportions of their population fluoridated had significantly higher rates of ADHD than states with less fluoridation. The effect is large, with the most fluoridated states having about 50% higher rates of ADHD than the least fluoridated states.

The study also looked at secular trends in ADHD rates by comparing surveys conducted in three different years: 2003, 2007, and 2011. In the graph, the red is the earliest survey in 2003, the light blue is the middle survey in 2007, and the most recent survey in 2011 is shown in dark blue. ADHD diagnoses have been increasing over time, and the association between fluoridation and ADHD has continued and even grown between 2003 and 2011.

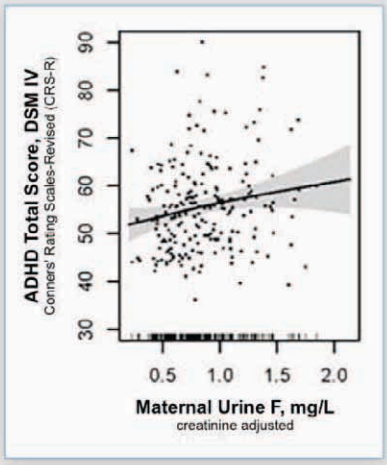
F neurotoxicity

Bashash 2018

1st high quality study of F and ADHD; Mexico.

Statistically significant increase in ADHD Total Score (inattentive and hyperactive-impulsive behaviors combined) with higher maternal urine F.

F and ADHD



37

The next study of fluoride and ADHD was the first using a high quality longitudinal mother-child cohort design. It found a statistically significant increase in child ADHD score with increasing prenatal exposure, as estimated by the maternal urine fluoride level.

F neurotoxicity

Riddell 2019

High quality study of F and ADHD; Canada.


Environment International

Full length article

Association of water fluoride and urinary fluoride concentrations with attention deficit hyperactivity disorder in Canadian youth

Julia K. Riddell, Ashley J. Malin, David Flora, Hugh McGague, Christine Till

F and ADHD

Found almost 300% higher risk of ADHD for those living in fluoridated areas in national sample of Canadian children.

Found 600% higher risk of ADHD for every 1 mg/L increase in tap water F.

> "In conclusion, we found that higher tap water fluoride levels and fluoridation of municipal water supplies were associated with a higher risk of an ADHD diagnosis as well as increased symptoms of hyperactivity and inattention, especially among adolescents."

38

The latest fluoride ADHD study was published just a few months ago, and found a dramatically higher risk of ADHD in children living in fluoridated areas of Canada compared to those living in unfluoridated areas. The risk of having a diagnosis of ADHD was **300% higher** in fluoridated areas. The study used a sample of children from throughout Canada from the CHMS survey or Canadian Health Measures Survey. This survey is conducted by Health Canada and is similar to the NHANES survey in the USA.

The increased risk of ADHD, when stated in terms of a 1 mg/L increase in the tap water fluoride concentration, was **600% higher**.

An implication of these findings is that the majority of ADHD cases may be attributable to water fluoridation.

Summarizing the overall body of evidence, with particular focus on the strong studies discussed here, the scientific evidence for Fluoride's developmental neurotoxicity ...

is Overwhelming.

F neurotoxicity

Should we care?

What are the implications of a few IQ points lost per person?

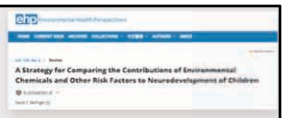
Should we care?

40

But what are the implications of a few IQ points lost per person, on average? Should we care?

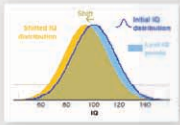
F neurotoxicity

Population-wide IQ loss



Estimate of total IQ points lost in the USA due to fluoridated water

Using similar methods as Bellinger 2012 used for other risk factors.
Assume steady-state conditions of exposure.
Loss of IQ for infants fed formula made up with fluoridated tap water:
8.8 IQ points loss per 1.0 mg/L increase in tap water F (Till 2020)
0.46 mg/L difference in water F between fluoridated and non-fluoridated areas (Till 2020)
8.8 X 0.46 = 4.1 IQ point average loss in fluoridated areas
50% of infants formula-fed in first 6 months (Till 2020)
70% of USA has fluoridated tap water
50% X 70% = 35% formula-fed and have fluoridated water
3.8 million children born in USA each year

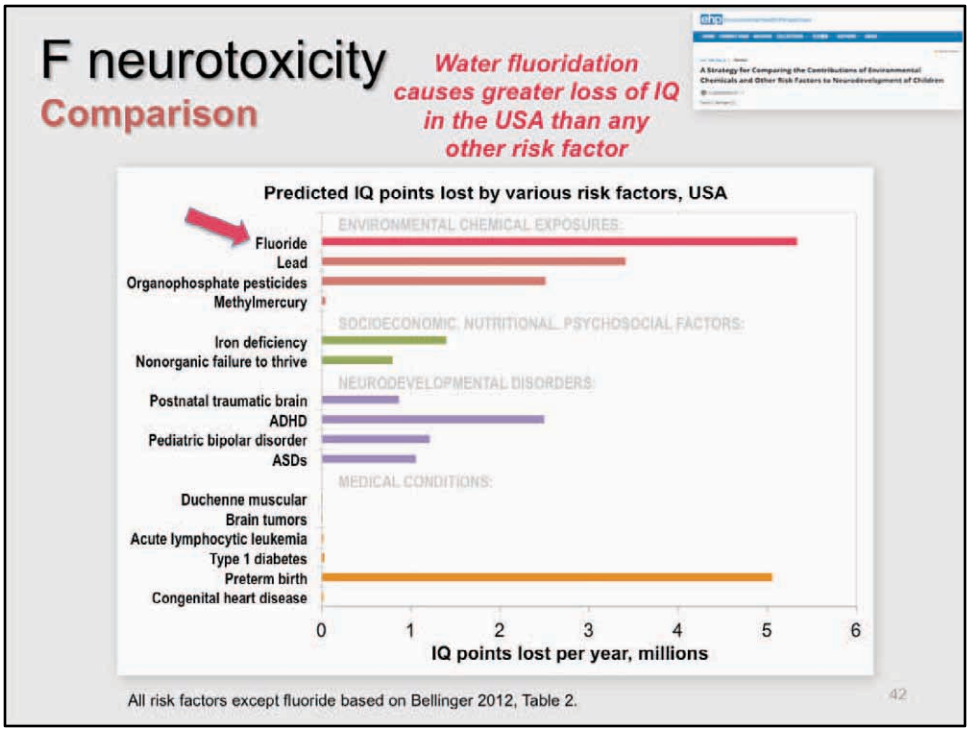


3.8 million children X 35% who are formula-fed and have fluoridated tap water X 4.1 IQ points loss =

5.4 million IQ points lost per year in the USA
due to water fluoridation

41

As the *JAMA Pediatrics* editors noted in their Podcast, even a small shift downward in the distribution of IQ scores can represent a large population-wide loss of IQ. In order to compare the total harm to the population of the USA from fluoridation to that from other causes of IQ loss, we have calculated the total IQ points lost per year. Since infant formula made with fluoridated water appears to represent the greatest effect on IQ, we used the results from the Till 2020 study in Canada to estimate the total number of IQ points lost in the USA, assuming the same dose-response and infant feeding practices as in Canada but accounting for the much larger population of the USA with fluoridated water. We estimated that 5.4 million IQ points are lost per year. It is likely that a certain fraction of the population who are genetically more susceptible will bear the majority of the burden, although considering the large magnitude of the effect found in the Till 2020 study amongst all children, it is plausible that even those who are genetically less susceptible will suffer loss of IQ.



A loss of 5.4 million IQ points per year can be put into context by comparing it to the estimated losses from a variety of other risk factors, including the best known developmental neurotoxic chemicals lead, mercury, and organophosphate pesticides. Bellinger 2012 estimated the total USA-wide IQ loss for 16 other well-established risk factors and I have graphed them here. My estimate shows that fluoridated water is responsible for a greater total IQ points loss than any of the other risk factors, including lead, organophosphate pesticides, and preterm birth.

F neurotoxicity

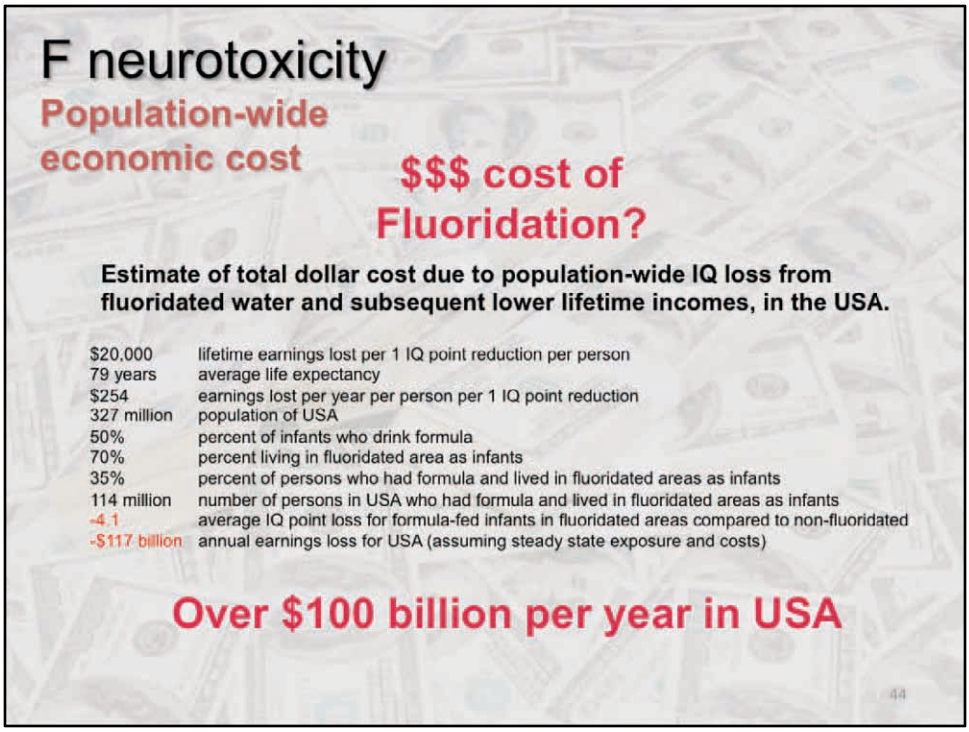
Population-wide economic cost

$$$ cost of Fluoridation?

Estimate of total dollar cost due to IQ loss from fluoridated water and subsequent lower lifetime incomes, in the USA.

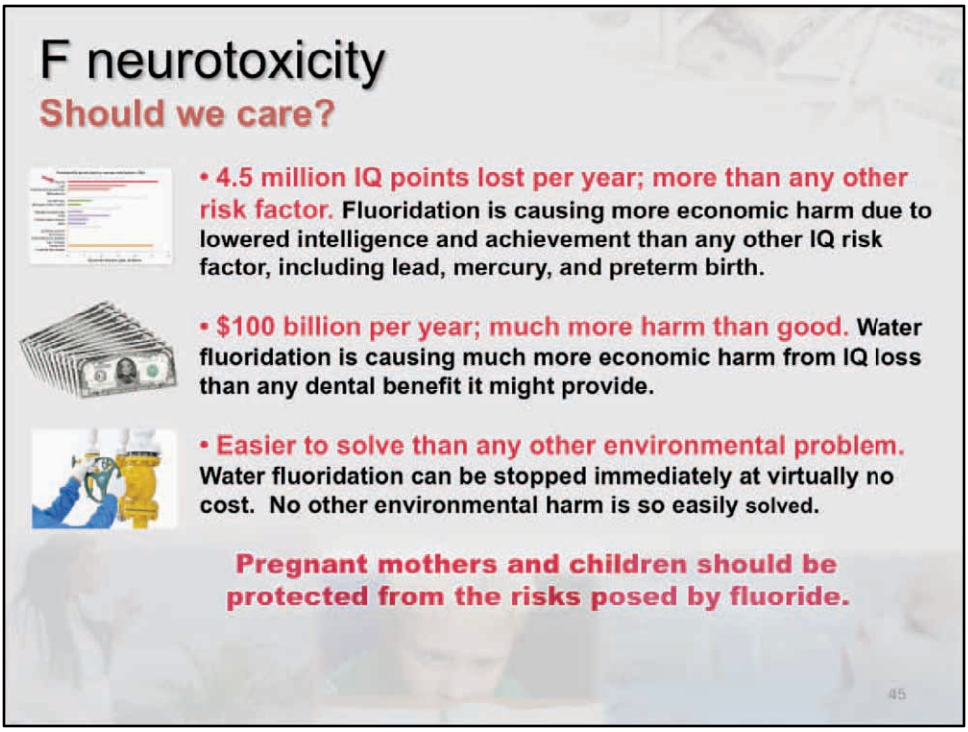
43

It may seem crass, but there are standard methods for estimating the total economic cost to society from IQ loss. The main economic harm arises from the reduced lifetime earnings which have been found associated with lowered IQ.



We have calculated the annual dollar cost of water fluoridation, from earnings lost due to lower IQ. We have used standard methods of health economists that have been applied to other developmental neurotoxins, like mercury. It is worth noting that the US EPA considers that a population-wide average loss of just 1 IQ point is an adverse effect to be avoided.

A standard estimate for lifetime earnings lost per person for a 1 IQ point lowering is about $20,000. When applied to the population of the USA who are formula-fed as infants and live in fluoridated areas, it works out to a cost of over $100 billion a year. This assumes steady-state exposure and costs. This is a huge economic cost.



So, should we care about the scientific evidence showing water fluoridation lowers IQ by a few points? **Absolutely!** Fluoridation is doing much more economic harm than good.

• The dollar cost of IQ loss far exceeds any dental benefit water fluoridation may provide. Furthermore, there is no dental benefit from fluoride prenatally and in infancy. It is well established that the dominant dental benefit of fluoride comes from topical contact on the teeth and not from swallowing the fluoride.
• Fluoride may be causing more neurocognitive harm than any other risk factor, including lead, mercury, and preterm birth.
• The environmental health harm from fluoridation is easier to solve than any other environmental problem. Simply stop adding fluoridation chemicals to public drinking water. I'm not aware of any other environmental harm that is so easily and inexpensively solved.
• **Pregnant mothers and children should be protected from the risks posed by fluoride.**

So ... Should we care?

I’d be happy to answer any questions about the science and individual studies.

FLUORIDATION'S NEUROTOXICITY

There is now **no question** that fluoride is neurotoxic, damaging the brain and central nervous system, as documented by hundreds of recent studies. ***It can not be declared safe.***

2006: The National Research Council published Fluoride in Drinking Water,[1] the most authoritative review of fluoride's toxicity. It stated unequivocally that "***fluorides have the ability to interfere with the functions of the brain and the body."***

2012: A Harvard-funded meta-analysis[2] found that children ingesting higher levels of fluoride tested an average 7 IQ points lower in **26 out of 27 studies**. Most had higher fluoride concentrations than in U.S. water, but many had total exposures to fluoride no more than what millions of Americans receive.

"Fluoride seems to fit in with lead, mercury, and other poisons that cause chemical brain drain."
Philippe Grandjean, MD, PhD, Harvard study co-author, Danish National Board of Health consultant, co-editor of Environmental Health, author of over 500 scientific papers

2017: A National Institutes of Health (NIH) - funded study[3] in Mexico covering 13 years found that every one half milligram per liter (mg/L) increase in fluoride in pregnant women's urine – approximately the difference caused by ingestion of fluoridated water[4] - was associated with a reduction of their children's IQ by about 3 points. Leonardo Trasande, a leading physician unaffiliated with the study, said it "**raises serious concerns about fluoride supplementation in water**."[5]

2018: A Canadian study[6] found iodine-deficient adults (nearly 18% of the population) with higher fluoride levels had a greater risk of hypothyroidism (known to be linked to lower IQs). Author Ashley Malin said "**I have grave concerns about the health effects of fluoride exposure.**"[7]

2019: Another NIH-funded study[8] in the Journal of the American Medical Association Pediatrics found every 1 mg/L increase in fluoride in Canadian pregnant women's urine was linked to a 4.5 decrease in IQ in their male children. The physician editor of JAMA Pediatrics said "**I would not have my wife drink fluoridated water**"[9] if she was pregnant.

2019: A Canadian study[10] found a nearly **300% higher risk of ADHD** for children living in fluoridated areas. This reinforced earlier studies linking fluoride to ADHD in Mexico (2018)[11] and the U.S. (2015).[12]

2019: Another NIH-funded study[13] in Canada found that babies fed formula mixed with fluoridated water averaged 4 IQ points less than those mixed with non-fluoridated water. Losses of non-verbal IQ were even more serious, an average of 9 points.

2019: A systematic review of 149 human studies and 339 animal studies by the U.S. National Toxicology Program[14] concluded that "**fluoride is presumed to be a cognitive neurodevelopmental hazard to humans**." The report is still in draft form, but NTP also said there is little chance they will change their finding.

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3/10/20

FLUORIDEALERT.ORG
Fluoride Action Network

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Pediatric RESEARCH

www.nature.com/pr

PERSPECTIVE

Controversy: The evolving science of fluoride: when new evidence doesn't conform with existing beliefs

Christine Till[1] and Rivka Green[1]

Over the past 75 years, health authorities have declared that community water fluoridation—a practice that reaches over 400 million worldwide—is safe. Yet, studies conducted in North America examining the safety of fluoride exposure in pregnancy were nonexistent. When a Canadian study reported that higher fluoride exposure in pregnant women was associated with lower IQ scores in young children, critics attacked the methodology of the study and discounted the significance of the results. Health authorities continued to conclude that fluoride is unequivocally safe, despite four well-conducted studies over the last 3 years consistently linking fluoride exposure in pregnancy with adverse neurodevelopmental effects in offspring. We describe the challenges of conducting fluoride research and the overt cognitive biases we have witnessed in the polarized fluoride debate. The tendency to ignore new evidence that does not conform to widespread beliefs impedes the response to early warnings about fluoride as a potential developmental neurotoxin. Evolving evidence should inspire scientists and health authorities to re-evaluate claims about the safety of fluoride, especially for the fetus and infant for whom there is no benefit.

Pediatric Research _####################_; https://doi.org/10.1038/s41390-020-0973-8

> Do not avoid difficult areas of investigation. Take risks. If scientists exclusively choose the safe routes, avoid controversial research problems and play only minor variations of someone else's themes, they voluntarily turn themselves into technicians. Our craft will indeed be in peril.[1] Herbert Needleman, MD

Most people assume that community water fluoridation (CWF)—adding fluoride to public drinking water supplies—is a safe and effective way to prevent cavities. After all, it has been endorsed by public health, dental and medical organizations since it was introduced 75 years ago.[2,3] Today, about three-fourths of people in the United States and one-third of Canadians have fluoride added to their drinking water.

After reviewing the scientific literature, it became clear that there were growing concerns about fluoride as a developmental neurotoxin.[4,5] In 2006, a report by the National Research Council (NRC)[6] acknowledged that fluoride exposure may be associated with adverse cognitive and endocrine outcomes, and recommended further study, especially for vulnerable populations. One NRC panel member, Dr. Isaacson, said the report "should be a wake-up call". Yet, nearly 10 years later, not a single study had directly examined fetal exposure to fluoride in humans.

In many academic circles, it is a taboo to study fluoride. Dr. Phyllis Mullenix,[7] former Head of the Toxicology Department at the Forsyth Dental Centre in Boston, was heavily criticized for publishing her study showing that sodium fluoride was neurotoxic to developing rats. People who questioned the safety of water fluoridation are quickly dismissed as zealots or anti-science fanatics. Indeed, some scientists dismissed our funding application with comments such as, "This study is not needed. We know that fluoride is safe". But we forged ahead; shouldn't claims about safety be based on evidence?

In 2015, we sought funding to investigate the safety of fluoride exposure in pregnancy. We assembled an interdisciplinary team of scientists from complementary fields including epidemiology, environmental health, neuropsychology, and dentistry—knowing that diverse perspectives would be critical for minimizing conscious or unconscious biases in our investigative process. We naively expected that the public health and medical community would trust the scientific process.

THE SCIENTIFIC PROCESS

We studied 512 mother–child pairs enrolled in the MIREC (Maternal Infant Research on Environmental Contaminants) study. The families lived in six Canadian cities; 40% lived in cities with CWF. To our astonishment, we found that higher levels of fluoride in pregnant women and water concentrations were associated with a 3- to 5-point lower IQ score in their 3- to 4-year-old children.[8] We thought there may be other factors at play, but this association held up after accounting for important characteristics of the study population and looking at the relationship in many different ways.

> In August 2018, we presented our findings at an international meeting held in Ottawa. We were nervous how the results would be received by the audience, which included members from Health Canada and other public health agencies. Afterwards, someone approached me and said, "Congratulations – you have just sabotaged your career before it even started". Rivka Green

As part of our agreement, our manuscript required approval by the MIREC Biobank before we submitted it for publication.

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Considering the sensitive nature of the topic, the manuscript was sent to reviewers from various divisions of public health. In over 60 pages, we responded to over 200 specific critiques. The upshot of addressing each critique was that we were able to do better science by refining our methods.

We submitted the manuscript to three top medical journals; two did not send it for peer review because it was "of low research relevance". As we waited, we hired an independent data analyst to rerun all of the analyses for the third time. In April 2019, *JAMA Pediatrics* accepted our paper. We responded to several additional rounds of review by the *JAMA* editors until we eventually reached a compromise that reflected the strength of the evidence, as well as their implications for public health.

One year after that conference in Ottawa, our article was published on August 19, 2019. In only 2 months, it was viewed over 100,000 times and ranked among the top 0.0005% of research output scored by Altmetric. We expected our study would reignite the debate about the safety of fluoridation, but we didn't expect we would be at the crossfire of this political and polarized debate.

THE BACKLASH

Outside of our colleagues in environmental epidemiology, who were initially skeptical, the results were met with resistance. Attempts to debunk the data were especially apparent from "experts" who held strong beliefs about the benefits and safety of fluoridation.

> There are thousands of articles pointing to the safety of community water fluoridation … this study doesn't change the benefits of optimally fluoridated water and exposure to fluoride.[9] Dr. Braun, chair of the AAP Section on Oral Health Executive Committee

Yet, there are no other prospective studies with biomarkers of fluoride in pregnant women living in regions with CWF. Canada's national newspaper rang with the headline, "Fluoride won't make you dumber, but the 'debate' about its safety might".[10] Didn't the NRC deliberately call for more studies to address this "debate"?[6]

Vitriolic comments and claims with little scientific basis, such as the results are driven by outliers, were made by the American Council on Science and Health[11] and the UK-based Science Media Centre,[12] both heavily funded by the pharmaceutical and food and beverage industries. In reality, we presented our models with and without outliers and the effect remained. These types of vacuous claims exemplify attempts to manipulate the scientific evidence and manufacture doubt.

> So what this study found was just an association. And we know from other areas … they are inherently problematic and inherently complex.[13] Timothy Caulfield, University of Alberta

This was not a scholarly debate on the neurotoxicity of fluoride; it was an attack on IQ scores, statistical methodology, and observational studies. Ironically, the evidence showing that CWF protects against tooth decay was largely based on observational or "association" studies, most of which were conducted prior to the introduction of fluoridated toothpaste in the early 1970s.[14] Moreover, most landmark studies in public health–including those linking smoking with lung cancer, air pollution with coronary heart disease, and asbestos with mesothelioma—were observational. Indeed, this design is optimal to study many important public health problems, usually in conjunction with toxicological studies.

> There is no sensible biochemical reason why fluoride would harm the brains of boys but not those of girls. So, are the authors wrong? Probably.[15] Alex Berezow, Ph.D., Vice President of Scientific Affairs, American Council on Science and Health

Our paper continued to be attacked in scientific and public arenas, many of them drawing upon critiques made by the industry-funded groups. Accusations that our data did not support our conclusions spread quickly and were propagated by social media. "Experts" wrote that the association between maternal urinary fluoride and lower IQ in males, but not females, defied plausibility. However, as we noted in our original proposal, males are often more susceptible to toxicants and failure to examine sex-specific effects of fluoride exposure may result in missing a potentially vulnerable group. Further, the NTP in 2016 specifically called for more studies on fluoride exposure with an emphasis on sex-specific associations.[16]

> I'm confused as to why the authors would want to withhold the data.[17] Stuart Ritchey, Ph.D.

On October 23, 2019, a letter signed by 30 health-care professionals and scientists from six countries was sent to the Acting Director and Acting Deputy Director of the NIEHS. The letter cited concerns about the replicability of scientific research in general and the need for transparency. Our research team was accused of "refusing to release data", but we had not refused to release the data. The policies that govern access to the MIREC Biobank and procedures to access it are sent to anyone who requests the data.

RISK AND BENEFITS

Some critics maintained that our conclusion—that pregnant women should reduce their fluoride intake—overstated the implication of the findings and was "dangerous". Other critics said that we should not change our actions based on "one study". We agree that no one study is definitive; we should carefully evaluate the collective evidence from multiple studies, as well as the risks and benefits of fluoridation.

Four high-quality, prospective birth cohort studies[5,8,18,19] show that fetal exposure to fluoride is associated with diminished cognitive abilities. In November 2019, the National Toxicology Program released a draft report on fluoride concluding that fluoride is presumed to be a cognitive neurodevelopmental hazard. This report was largely ignored by the critics of our study.[17,20]

Fluoride offers no benefits to the fetus. The beneficial effects of fluoride predominantly occur at the tooth surface, after the teeth have erupted.[21–23] Accordingly, the Canadian Pediatric Society and the American Academy of Pediatrics advise against fluoride supplements during the first 6 months of life.[24]

Exposure to fluoride comes from a variety of sources, but for people who live in cities with fluoridated water, the main source of ingestion is drinking water. Importantly, pregnant women and formula-fed babies may not be able to access nonfluoridated water.

CONCLUSION

Did our article shift the needle? Perhaps for those who are willing to integrate new knowledge with their existing beliefs. To understand why many questions about the safety of CWF are still not settled after 75 years, we need to recognize how entrenched beliefs can lead to biases and blind spots, even among highly trained clinicians and scientists. Science advances by continuously challenging old ideas and adjusting our beliefs as new knowledge emerges, even if this new evidence conflicts with conventional wisdom or is inconvenient.

Dr. Lanphear, a senior scientist on our team who conducted many of the pivotal lead toxicity studies that helped confirm Dr. Needleman's work, reminded us that it took two decades of research before the CDC declared, "there is no safe level of lead in children's blood". Dr. Lanphear wrote, "The critics—who were often paid by industry or simply ignorant about lead toxicity but

still willing to offer their 'expert' opinion—delayed efforts to prevent lead poisoning by decades".

We typically fret about subtle biases, like recall bias and unmeasured confounding, but confirmation bias, the tendency to ignore or debunk data that does not conform to what we believe, is arguably a much larger problem. Failure to act on consistent evidence that indicates safety risks could amount to enormous costs at the population level.

ACKNOWLEDGEMENTS

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ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

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Fluoride Action Network
The Toxic Substances Control Act (TSCA) Fluoride Trial
June 8 – June 17, 2020
For more information click here

PLAINTIFFS' CLOSING ARGUMENT (Wed June 17,2020)

MR. CONNETT: Thank you, Your Honor.

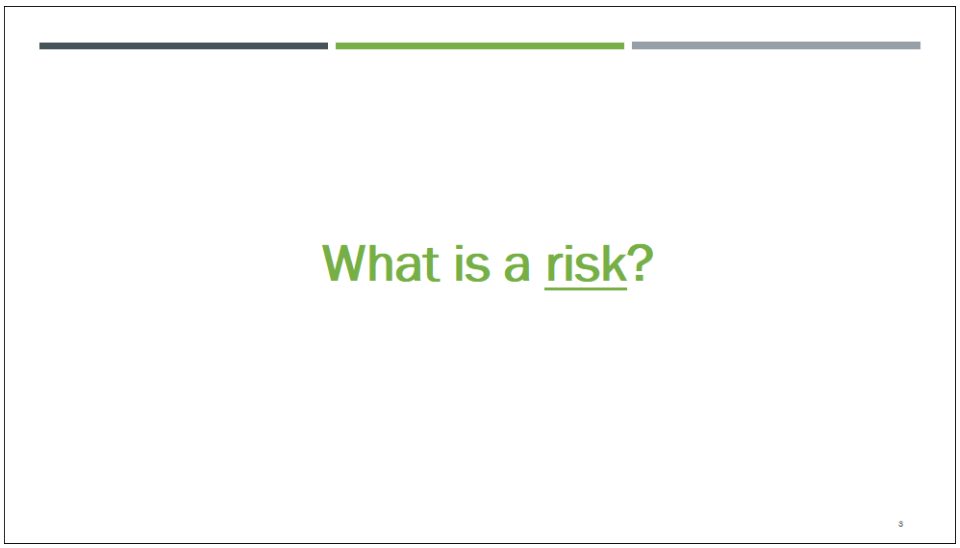
May it please the Court. On behalf of the plaintiffs I wish to begin today by expressing our immense gratitude for having had an opportunity to present our case in court, and in so doing to give voice to those who have too often been voiceless, and to hold accountable an agency that, at least on this particular issue, has failed to responsibly carry out its duties to protect this nation from harm.

In most cases closings are about argument, but today, Your Honor, I'm not going to argue that much. Because the undisputed facts in this case speak for themselves.

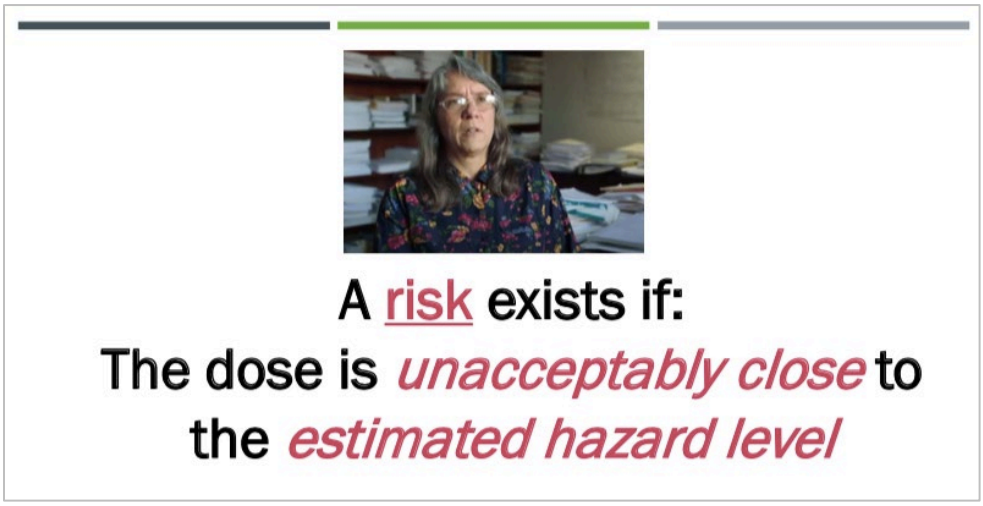
So I begin, Your Honor, by addressing a simple fundamental question to this case. What is a risk? What is the standard that EPA uses to determine when a risk exists?

First off, we know that TSCA commands that the EPA protect not just the general public, but susceptible subpopulations as well, including pregnant mothers and bottle-fed infants.

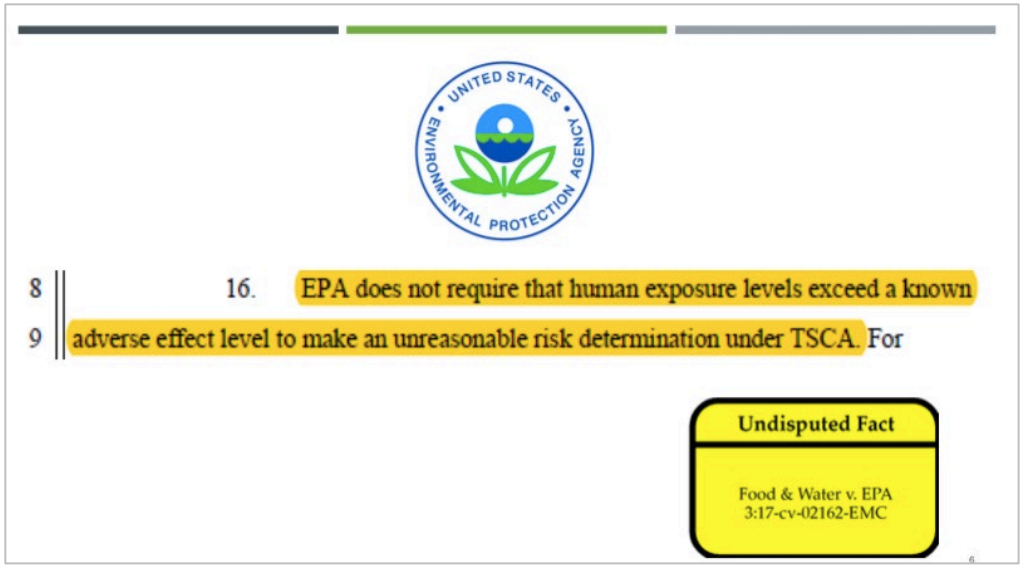
The statute makes clear that if there is one unreasonable risk to one susceptible subpopulation, EPA must take regulatory action to protect from harm.



So what is a risk? As Dr. Thiessen explained to Your Honor, a risk exists if the human exposure level is unacceptably close to the estimated hazard level. EPA has not and does not require data demonstrating that human exposures under the condition of use cause the hazard.

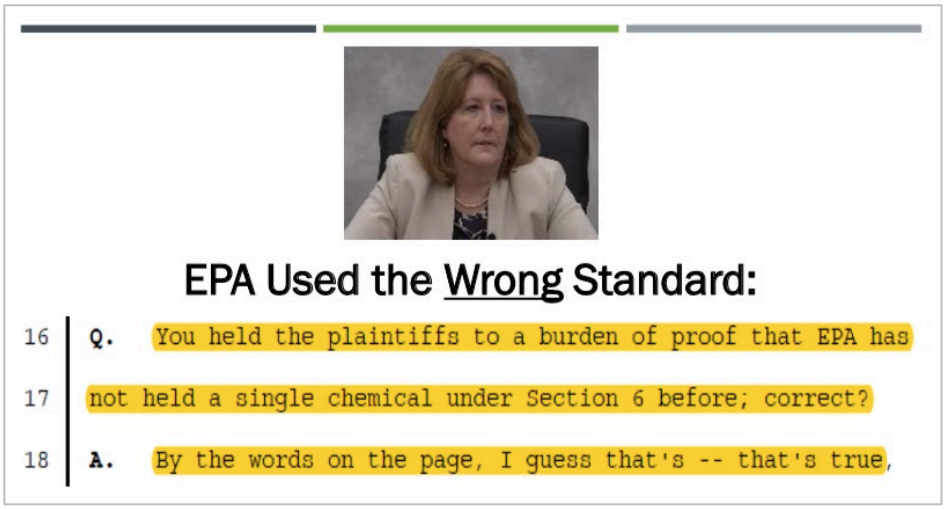


Now, Your Honor, this standard is not in dispute. Indeed, it is an undisputed fact in this case, undisputed fact No. 16, that EPA does not require that human exposure levels exceed a known adverse effect level to make a finding of risk.



But despite this, Dr. Tala Henry admitted yesterday in no uncertain terms that EPA has from day one of this litigation used the wrong standard. They used the wrong standard of risk to assess the plaintiff's evidence.

As Dr. Tala Henry talked about yesterday, each and every one of EPA's experts in this case used a *causation* standard to assess the evidence, not a *risk* standard.



Now, causation is relevant, your Honor, to a risk finding, but it is not and never has been a pre-requisite to a finding of risk.

So now I'll talk about the experts that your Honor has heard from in this case. The three experts that EPA called to the stand to discuss fluoride were not actually experts on fluoride prior to this litigation. But as you heard, Your Honor, EPA does have experts on fluoride at the agency, including Dr. Kristina Thayer.

Now, EPA did call Dr. Thayer as a fact witness to discuss the process of systematic review, but EPA avoided asking Dr. Thayer the obvious. They avoided asking Dr. Thayer for her assessment of the fluoride literature.

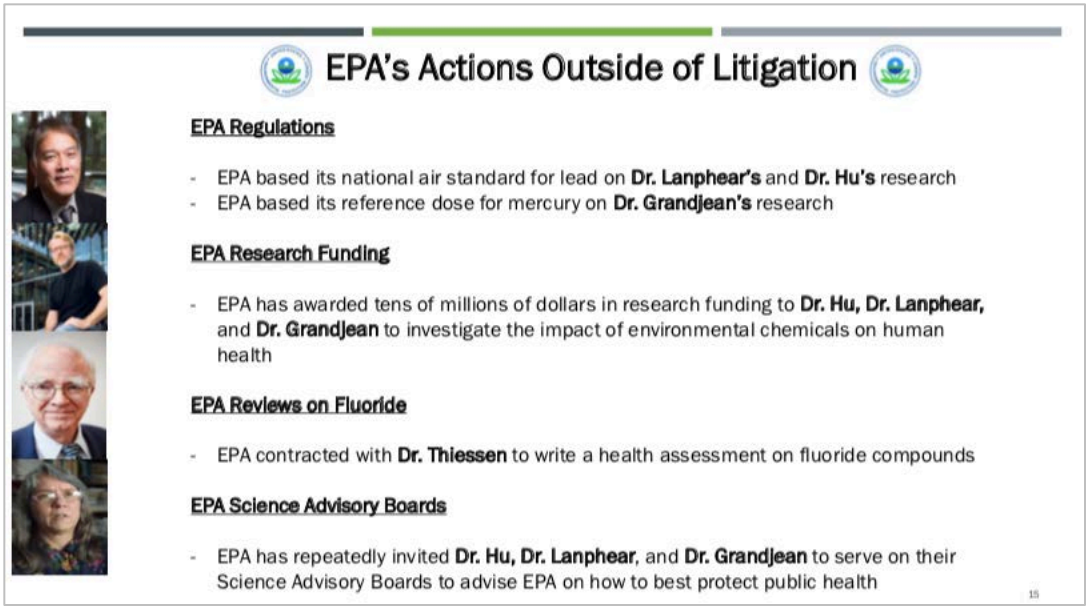
It was the plaintiffs, Your Honor, not the EPA, who asked this question. And Dr. Thayer agreed that fluoride damages the brain and that the animal data supports the biological plausibility of fluoride causing neurotoxic effects in animals.

So why did EPA go outside the agency and hire experts from Exponent? I submit, Your Honor that the answer to this question is obvious and needs no further comment from me.

Although plaintiffs are citizen groups and without the resources of the EPA, we brought before your Honor world-class experts of the highest caliber. Experts who have devoted their professional lives to understanding the impact of environmental chemicals on human health. Experts who EPA has consistently relied upon for protecting this nation from harm. This includes Dr. Howard Hu. This includes Dr. Bruce Lanphear. And Phillipe Grandjean. And Dr. Kathleen Thiessen.

And as you heard, Your Honor, there is no substitute for expert judgment. No matter how many thousands of pages a systematic review may be, at the end of the day the determination of risk will always come down to expert judgment.

And as you have heard throughout this trial, EPA's own actions show that the agency trusts the expert judgment of plaintiff's experts.



EPA has based its regulations on the major neurotoxicants, lead and mercury, on the research of plaintiffs' experts. EPA has awarded plaintiffs' experts tens of millions of dollars in research funding.

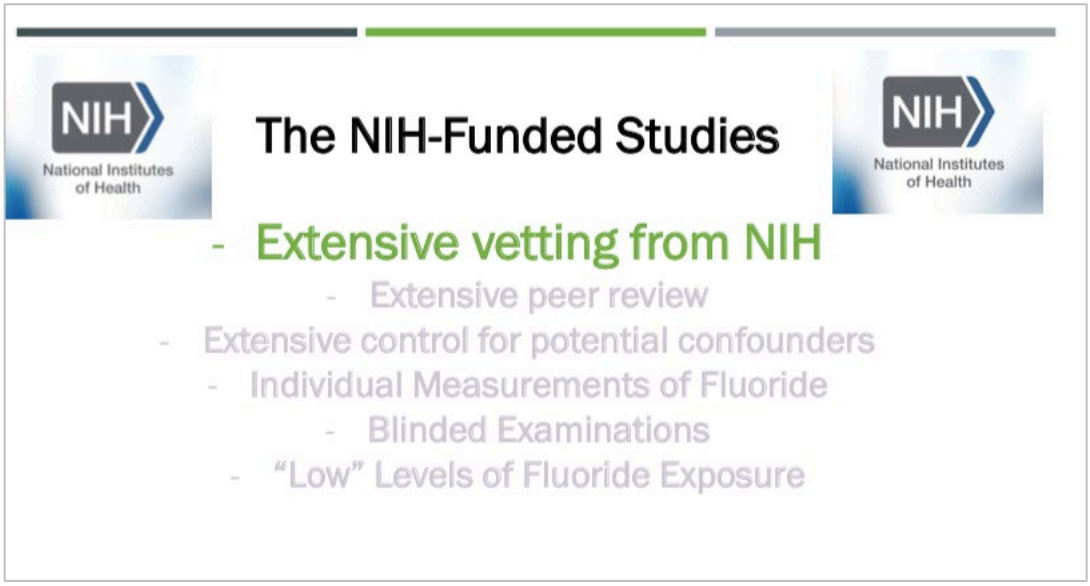
EPA contracted with Dr. Thiessen to write the agency's health assessment on fluorides.

And EPA has repeatedly invited plaintiffs' experts to serve on its science advisory boards, including as recently as two weeks ago.

By contrast, Your Honor, the record in this case is devoid of any evidence showing EPA has ever once relied on the expert judgment of the Exponent scientists it retained. Not a single solitary example.

So I'll talk now about the methods, the methods that plaintiffs' experts used to assess the evidence in this case. The TSCA statute commands that EPA base its decisions on the best available science, and we brought that science before your Honor. Dr. Hu and Dr. Lanphear explained how their NIH funded cohort studies easily satisfied EPA's definition of best available science. This is not even in dispute.

Dr. Chang has admitted that these studies are the best, most rigorous studies ever done on fluoride and neurodevelopment.

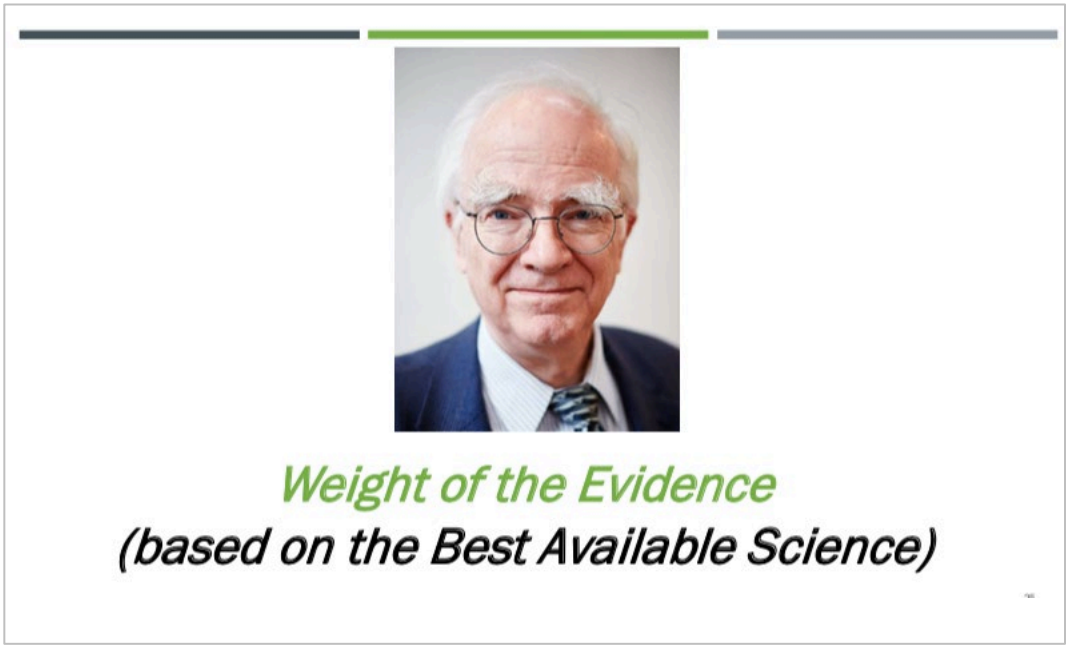


The methodology used by Drs. Hu and Lanphear underwent extensive vetting. Before they even did the studies, they underwent extensive vetting by the NIH specialist committees. And then after they did the studies and got the results, you heard testimony that they

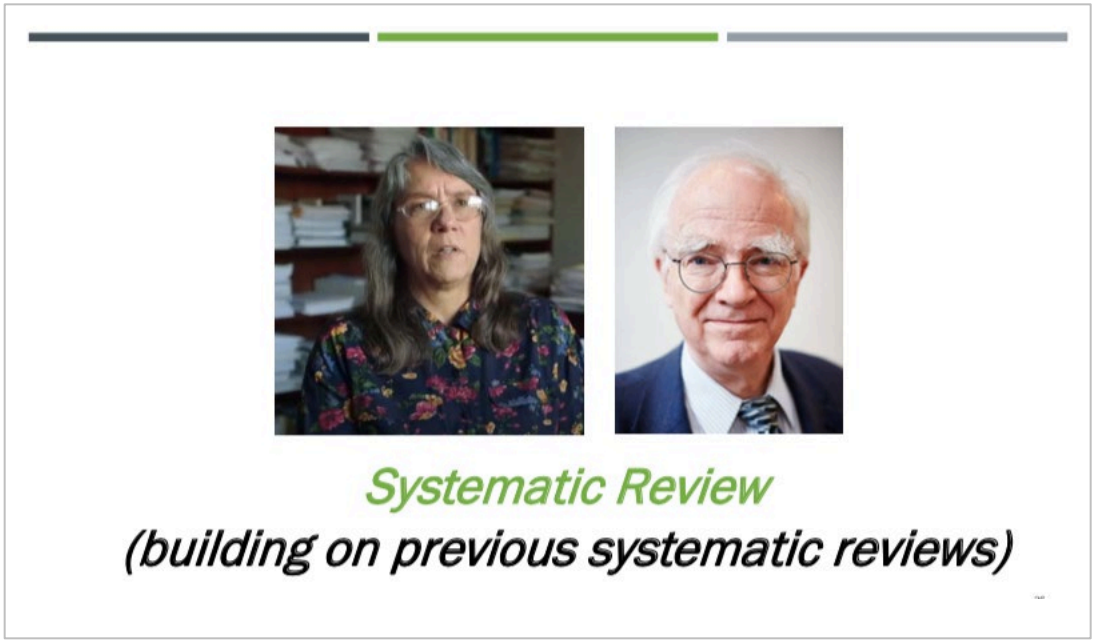
submitted these studies to world-class leading scientific journals, who then did another round of extensive peer review.

And as you heard, Your Honor, the MIREC and ELEMENT studies had extensive control for potential confounders. And unlike the much cruder studies from New Zealand, the NIH studies had individual measurements of fluoride during the critical window of development, the prenatal period, just as recommended by the Faroes statement back in 2007.

In addition, the examinations were fully blinded, eliminating the potential for examiner bias, and the studies investigated so-called optimal levels of fluoride exposure that are added to drinking water here in the United States.



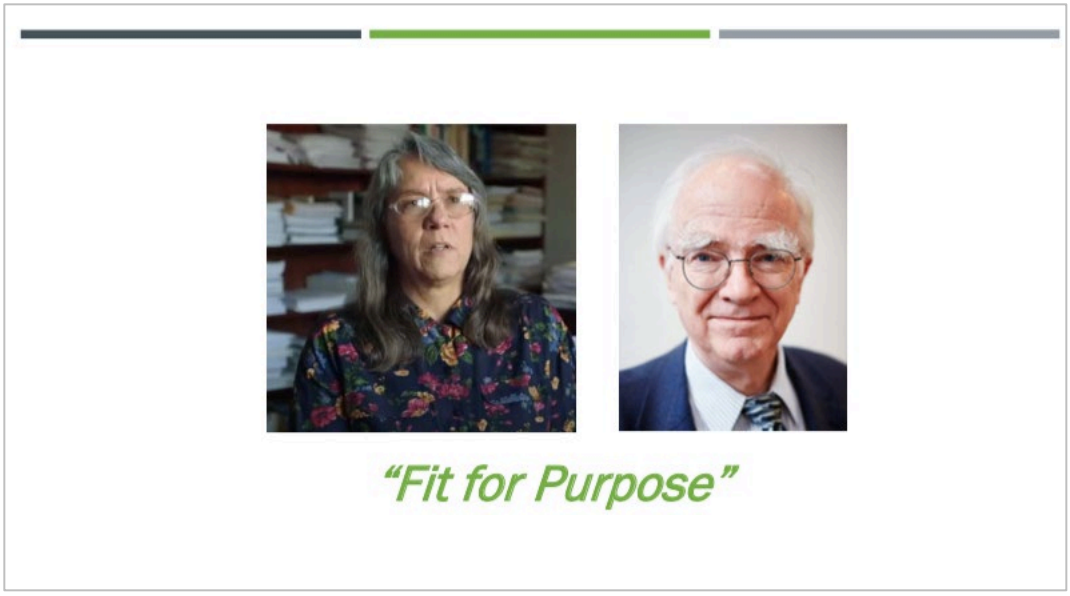
In addition to providing the best available science, Dr. Grandjean conducted an extensive weight of the evidence analysis in which he focused and he gave greatest weight to the best available science. And as Dr. Thayer explained on Friday, this is the approach that EPA has used since its inception to assess the risk of environmental chemicals, a weight of the evidence analysis that focuses on the best available science.



Additionally, both Dr. Grandjean and Dr. Thiessen conducted the functional equivalent of a systematic review. For Dr. Grandjean, he built upon the systematic review that he had published in 2012. In addition, he fully considered the systematic review conducted by Dr. Chang in this case.

And as Dr. Thayer explained on Friday, it is now a recommended practice that even EPA agrees with that when you are doing a systematic review, you can and should build upon existing systematic reviews.

Dr. Thiessen, meanwhile, conducted a risk assessment under the Guidelines for Neurotoxicity Risk Assessment, which Dr. Henry explained yesterday is the effective equivalent of a systematic review.



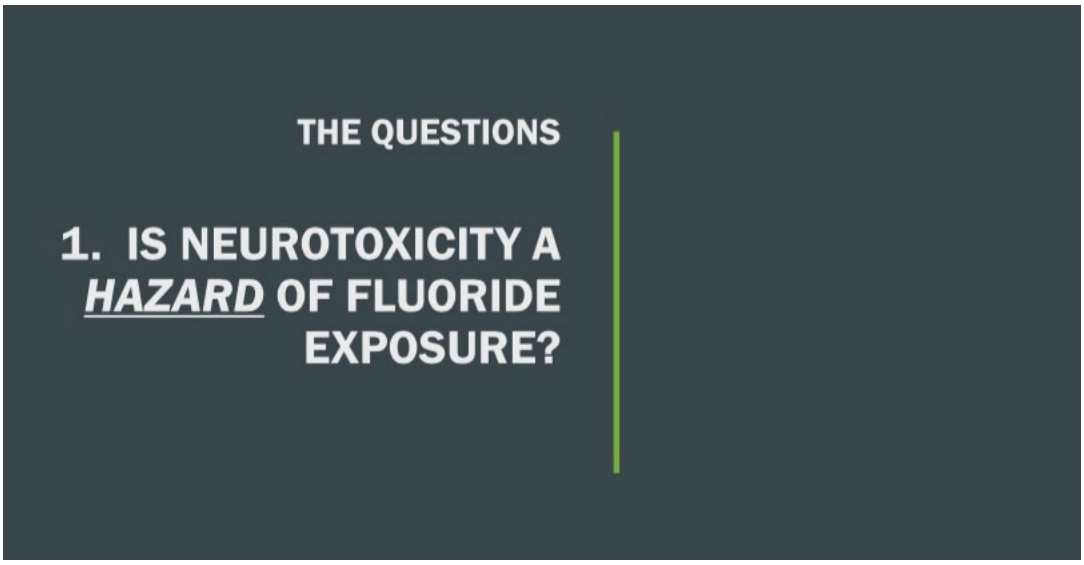
Your Honor, you've heard this concept at points throughout this case of "fit for purpose." This is a concept that EPA specifically discusses in the risk evaluation rule. It's a concept that recognizes that a risk evaluation under TSCA is not a straightjacket. EPA recognizes that there is room for practicality. There is room for flexibility. There is room for common sense.

This recognition is embodied in this concept of fit for purpose. And both Dr. Grandjean and Dr. Thiessen conducted fit for purpose assessments in this case, and there has been no demonstration to the contrary.

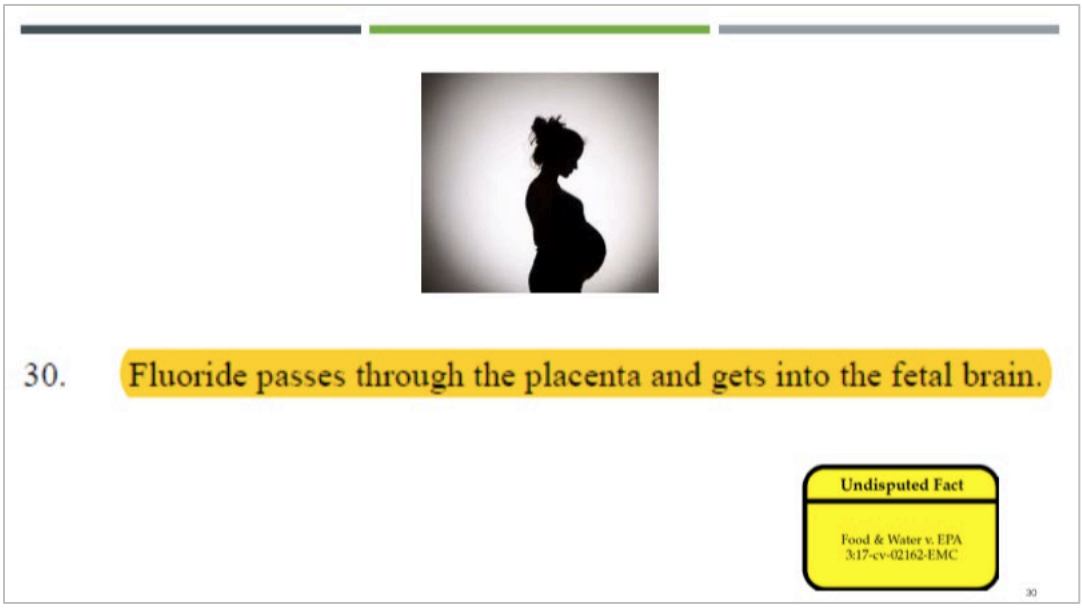
So now, Your Honor, I will turn to the evidence.

At the beginning of this case I said that there were three key questions that need to be answered: is there a hazard? Is there a risk? And is the risk unreasonable?

The undisputed evidence in this case, we submit, demonstrates that the answer to all three of these questions is yes.

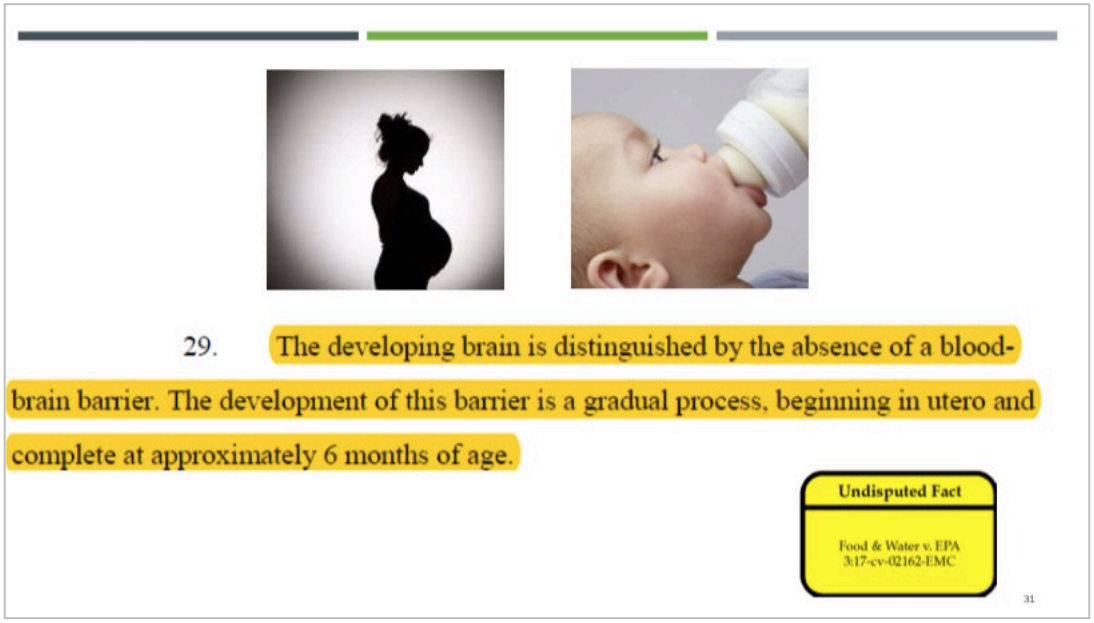


First, it is undisputed that fluoride passes through the placenta and gets into the fetal brain. This means that when a pregnant mother drinks a glass of fluoridated water, the fluoride in the water will have access to the child, including the brain.

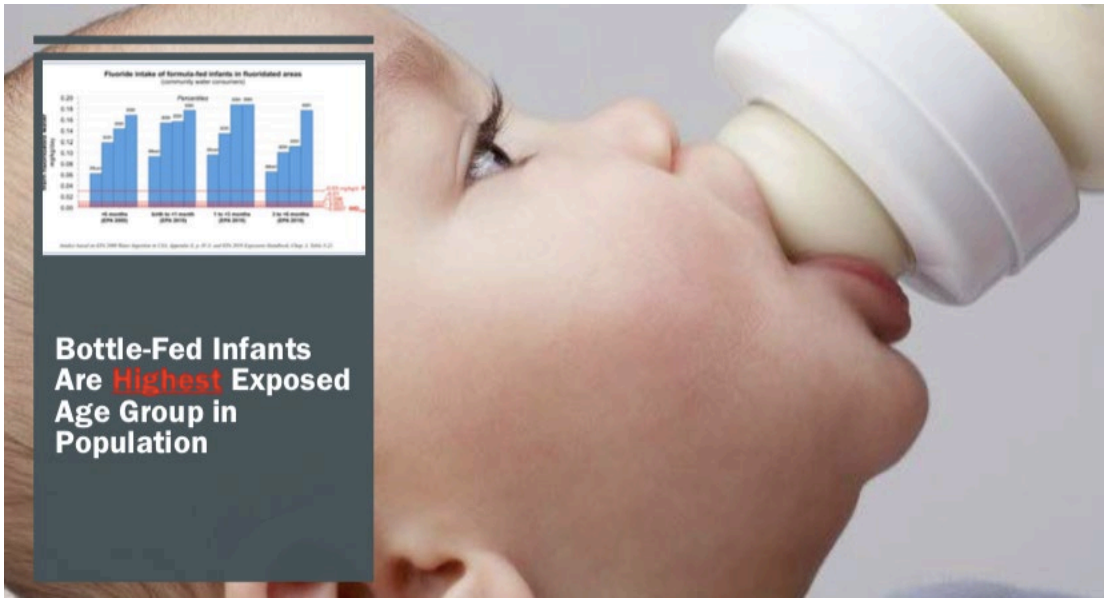


It is also undisputed that, unlike older children and healthy adults, a young child does not have the protection of the blood-brain barrier in utero and in early infancy. In fact, as you can see in this undisputed fact in the case, the blood-brain barrier is not fully developed

until six months after birth. And because of this, Dr. Thayer explained on Wednesday that the EPA recognizes we need to pay special attention to chemical exposures that occur during the first six months of life.



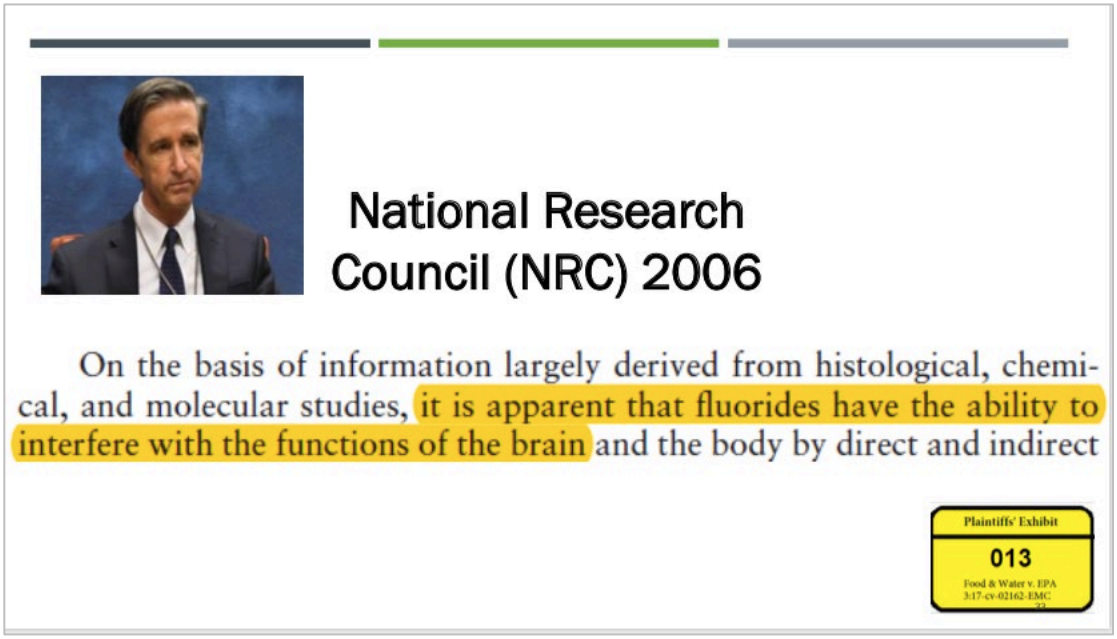
Yet, Your Honor, that is precisely what happens when we add fluoridation chemicals to drinking water. It is undisputed – undisputed -- that babies who are bottle fed with fluoridated water receive the highest doses by far of any age group in the population. At the moment of their greatest vulnerability, we are exposing infants, often from the poorest and most disadvantaged communities, to a very high burden of fluoride.



Now, there is no dispute in this case, Your Honor, that fluoride damages the brain. The NRC made this finding as far back as 2006. And the CDC representative in this case, Casey Hannan, who you heard from, testified that the CDC agrees with the NRC's summary of the hazard, including the NRC's summary of the neurotoxic hazard.

And here you can see, Your Honor, the finding of the NRC, that:

"It is apparent that fluorides have the ability to interfere with the functions of the brain."



Now, at that point, Your Honor, they were focusing on the neurochemical and neuroanatomical effects because there was not many learning and memory studies then available, but many such studies have since become available.

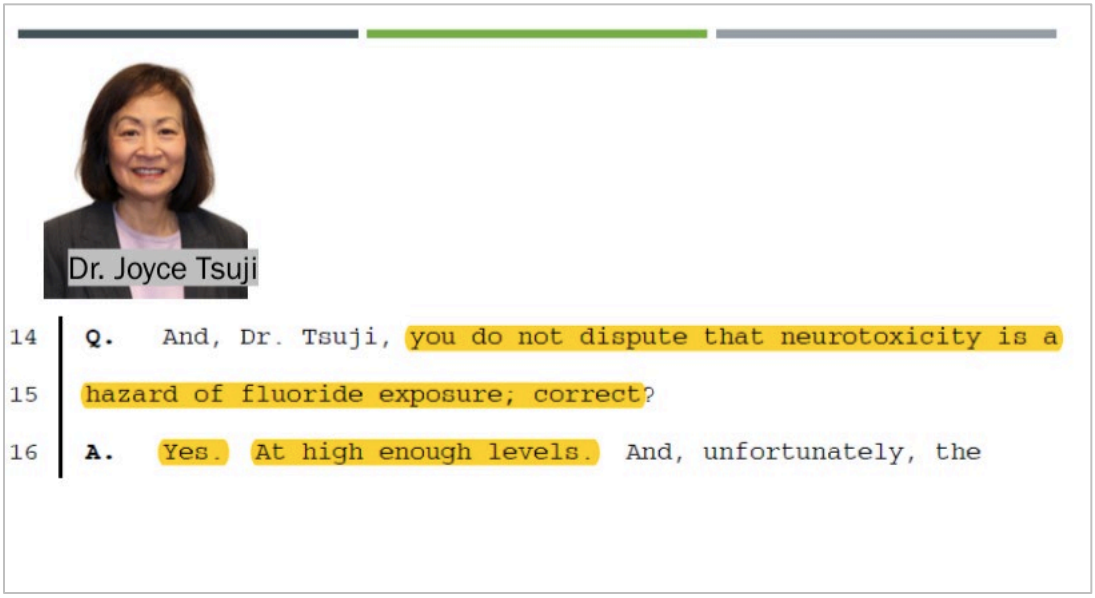
Now, while EPA's experts in this case have criticized the methods of many of the studies, it is important to keep in mind what they do *not* dispute. No one came before your Honor to say that fluoride is not a neurotoxicant. So the question of hazard really is not in dispute in this case.

Here you can see testimony from Dr. Joyce Tsuji. I asked her:

"QUESTION: You do not dispute that neurotoxicity is a hazard of fluoride exposure; correct?"

And her answer was:

"ANSWER: Yes, at high enough levels."



But what EPA didn't do is they never even attempted, never once attempted to determine, but what are those levels? They never attempted to provide to Your Honor an estimate as to what the levels are that are causing these neurotoxic effects.

The record is devoid of any EPA expert in this case making any attempt to do that. But importantly, they do not dispute that fluoride will damage the brain at a certain dose.

THE COURT: And my understanding is that they didn't do so because the levels that -- that all of these studies that you're talking about show involve levels well above the exposure levels of humans in the United States. I think that's the EPA's position; right?

MR. CONNETT: Well, the problem with that position, Your Honor, is even -- Dr. Joyce Tsuji testified on Monday that she accepts that 20 parts per million in the water of rats is effectively the equivalent of 1.3 parts per million in the water of humans.

And Your Honor, as Dr. Thiessen explains in her declaration, it's absolutely standard practice for EPA, when interpreting animal data, to do an analysis for calculating the human equivalent dose.

And for fluoride, specifically, we know that rats need more fluoride in their water to obtain the same level of fluoride in their blood. That's a toxicokinetic difference.

THE COURT: I understand that, but 1.3 is still well above -- isn't that well above the exposure levels in the United States?

MR. CONNETT: Not at all, your Honor. And that is only -- just to put this in context. That 1.3 figure, Your Honor, that's just providing for interspecies differences. Under EPA risk assessment you still need to provide a factor to assess, to account for human-to-human differences.

So going from 20 to 1.3, Your Honor, all that is doing is adjusting for interspecies differences.

Then you also need to do an adjustment for human-to-human differences. And as we've talked about throughout this case, EPA almost always uses an adjustment of 10. So if you put the adjustment of 10 to that 1.3 figure, you're down to .13.

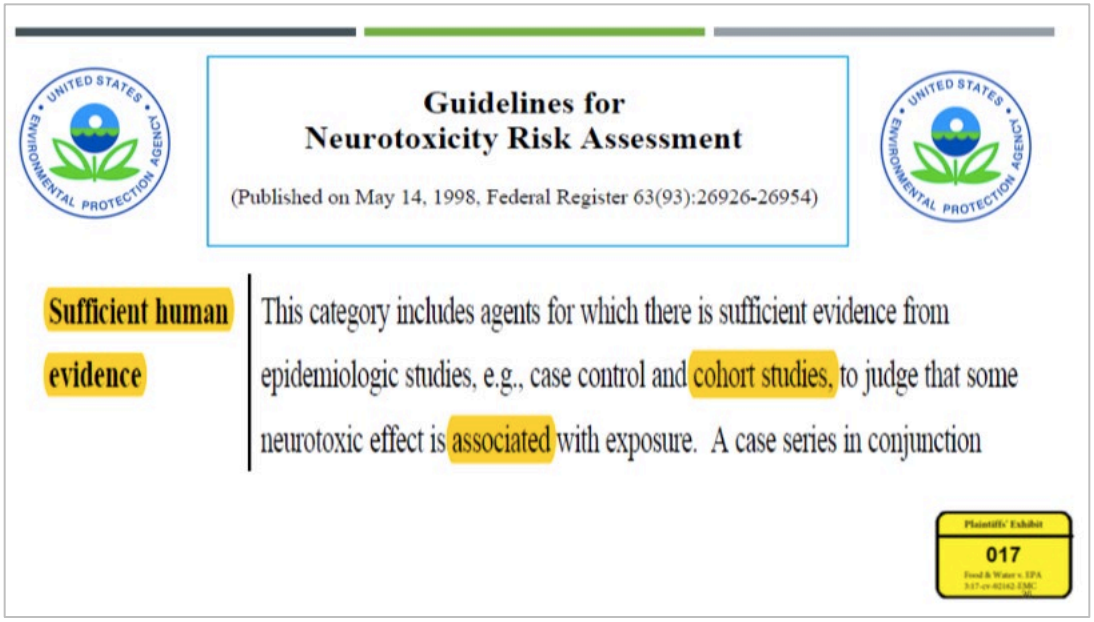
So it's important when looking at animal data, we can't treat the water fluoride level in rats as equivalent to the water fluoride levels in humans. You need to dose the animals at substantially higher levels.

And, also, you need to account for the fact that you have much fewer rats, much fewer animals. You know, with fluoridated water you have 200 million people drinking it.

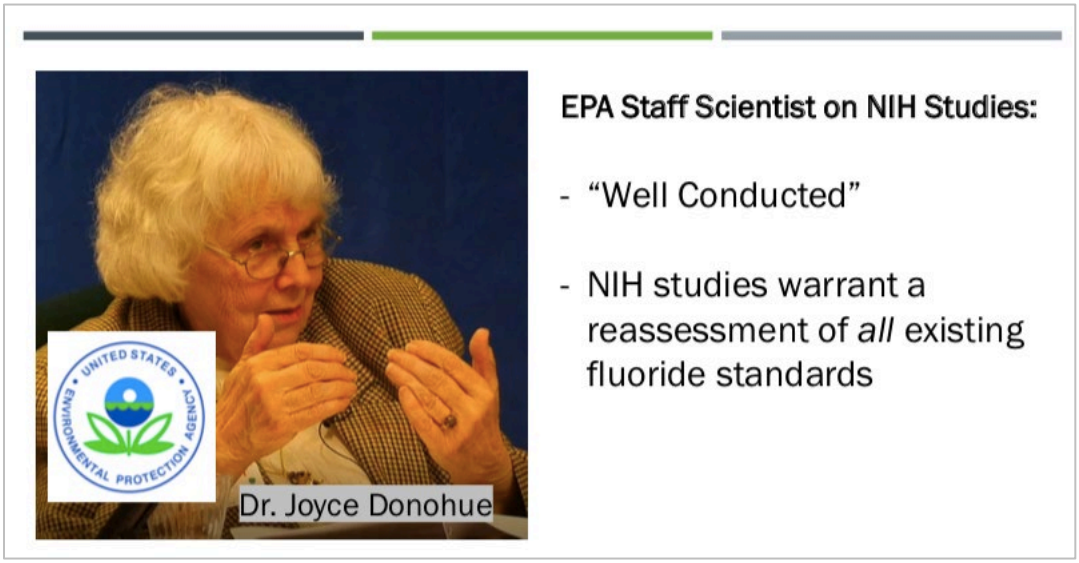
So, Your Honor, it is standard practice for the EPA to make adjustments to the animal data to account for the differences in susceptibility between rodents and humans.

And so in terms of this hazard assessment, Your Honor, we have, as you've heard throughout this case, four high quality prospective cohort studies. Each of them have found significant associations between early life fluoride exposures and large reductions in IQ on the magnitude of up to five points, when you go from zero to one milligram per liter of fluoride in the urine. That's a very large effect size that rivals the effect of lead.

And under EPA's Guidelines for Neurotoxicity Risk Assessment, the NIH studies are actually sufficient, Your Honor, by themselves. And, clearly, we have a lot of other data besides the NIH studies, but the EPA's guidelines recognize that sufficient evidence of a neurotoxic hazard can be demonstrated by cohort studies which associate the chemical with a neurotoxic effect. And we certainly have that here in the fluoride database.

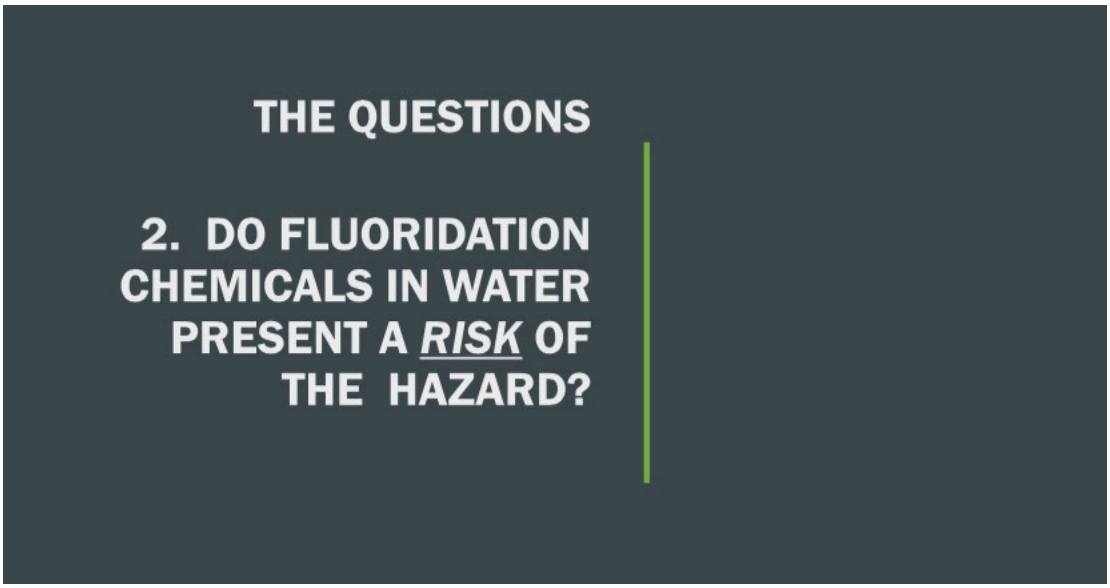


And you heard from EPA staff scientist Dr. Joyce Donohue from the Office of Water. She confirmed the obvious, that these are well-conducted studies, but she also said that these studies warrant a reassessment of all existing fluoride standards.

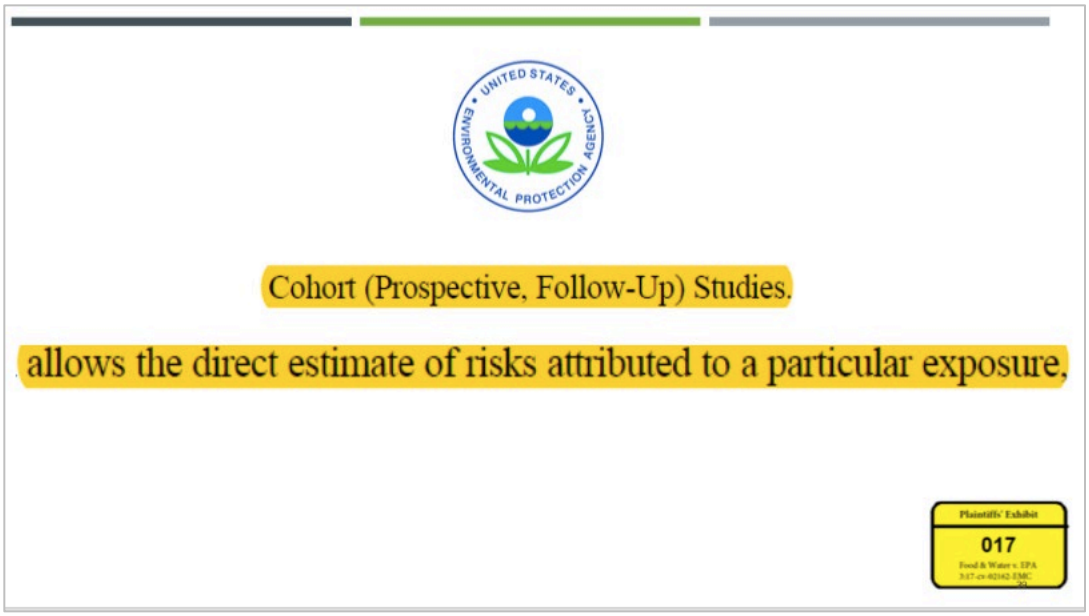


And, you know, Dr. Donohue has focused her work at EPA on the dental and skeletal effects. So the neurotoxicity subject is a bit beyond what she has focused on, but she recognizes that these are high quality studies that warrant a reassessment of the current framework for regulating fluoride.

So that brings us to the second question, Your Honor, is the risk question. Do fluoridation chemicals in water present a risk of this hazard?



And to answer this, I think we again should look for guidance from EPA's Guidelines for Neurotoxicity Risk Assessment. And these guidelines specifically state that:



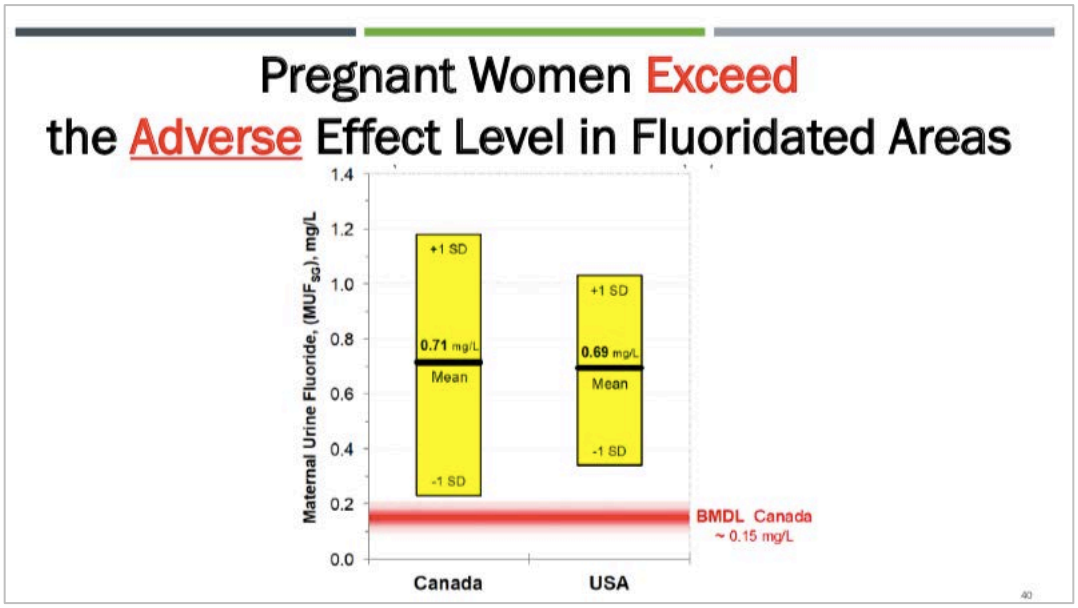
"Prospective cohort studies allow the direct estimate of risks attributed to a particular exposure."

Again: "Allows the direct estimate of risks attributed to a particular exposure."

So we have the proper studies, Your Honor, to make a finding of risk according to EPA's own guidelines.

And Dr. Grandjean, as you've heard, he did a BMD analysis to take those prospective cohort studies and to assess the risk from those studies.

And this figure, which was discussed during Dr. Grandjean's testimony, shows that pregnant women living in fluoridated areas of both the United States and Canada substantially exceed -- if you just look at the mean levels, Your Honor, the average levels, these average levels substantially exceed the BMDL for a one-point loss of IQ.

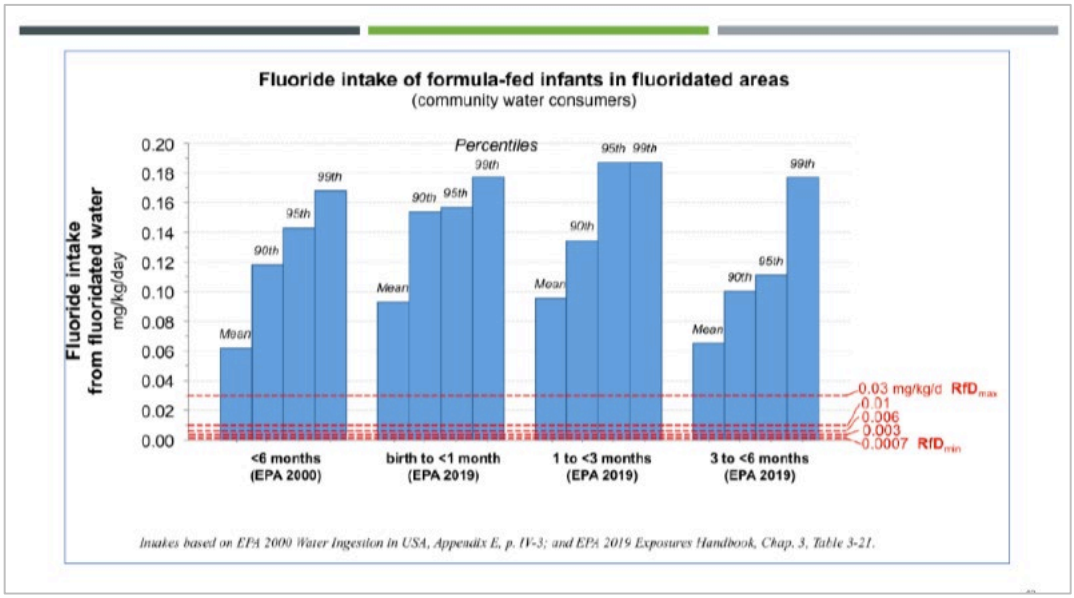


And when you start to consider the upper range of exposures, which TSCA commands that we do -- TSCA commands that we don't just look at the average. TSCA commands that we look at highly exposed people. If you look at the highly exposed people in fluoridated areas, you are going to see a very large differential there.

There is no dispute in this case, Your Honor, that the human data is the appropriate data to derive the point of departure. To derive the reference dose. To derive your risk calculations. But that does not mean that the animal data is irrelevant.

EPA has recognized that even where you have high quality human studies, it's still relevant to consider the animal data, to derive references doses from the animal data because if it's consistent with what the human data shows, it adds robustness and confidence to the conclusions.

And as Dr. Thiessen explains, Your Honor, the animal data, when you calculate the full range of RfDs that can be justified from the data, human exposures from fluoridated water exceed the entire range. Even the least protective reference dose.



Dr. Thiessen, as one of her points of departure, used the McPherson study. And when you use the McPherson study as the point of departure and apply standard EPA adjustments, you get a reference dose that is well exceeded by the exposures to fluoridated water.

So the animal data and the human data are consistent in indicating and showing a risk.

And that brings us lastly, Your Honor, to the question of whether this risk is unreasonable. And as I noted at the beginning of this case --

THE COURT: Before you get to that, let me ask you about the McPherson study, because a lot was made by the EPA that the negative findings of the McPherson study post the -- you know, the systematic review.

Why shouldn't -- why isn't that significant? That is -- you would agree, just as they would agree, that the best studies are the MIREC and the ELEMENT studies on the human side.

Wouldn't you agree that the McPherson study is the best available evidence on the animal side?

MR. CONNETT: I think it is a -- it is a well-done study. It has significant limitations.

But I think, Your Honor, a key point here is this. They max their dose at 20 parts per million. And I asked Dr. Tsuji: Shouldn't they have dosed the animals at 40 parts per million or 45 parts per million?

And Dr. Tsuji said it wasn't necessary because we know you see effects up in that range.

And so I think that's an important context to put it in. It had a lower dose. And in this case there is no dispute: If you start going beyond 20 parts per million, you're seeing effects.

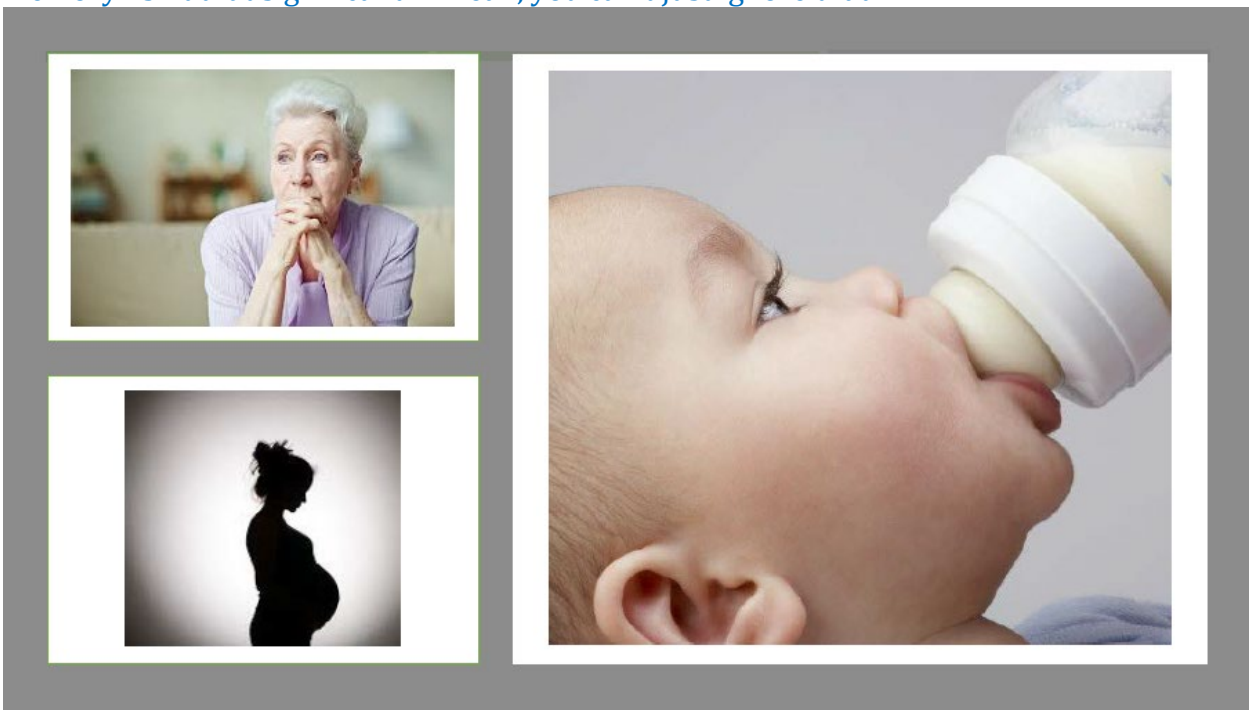
So McPherson doesn't do anything to contradict that. And, also --

THE COURT: I thought McPherson found at the maximum they tested, which was 20 parts per million, there were no associations except for pain sensitivity.

MR. CONNETT: Yes, Your Honor. At 20 parts per million in the McPherson study there was an increase in pain sensitivity, which is a neurotoxic effect. So 20 ppm would be a LOAEL for pain sensitivity.

They also found that the rats swam faster. And while it's not dispositive of hyperactivity, it's certainly not a clean result. It's not a -- this is not a clean bill of health study. You have increase in pain sensitivity. You have rats swimming faster. So it's not a clean bill of health from the McPherson study.

THE COURT: Well, but no association with respect to the critical endpoints of learning and memory. Isn't that significant? I mean, you can't just ignore that.



I know it's not a clean bill of health, but you're looking at an indicator that may not have much association or effect with respect to learning and memory, which is the key here.

MR. CONNETT: Well, a few things, Your Honor, about this.

First is, the McPherson study, as with all animal studies to date, did not expose the neonates to fluoride. Okay? So there is not a single animal study, as we sit here today, that has ever attempted to assess the neurological effects of a critical window of development.

In humans we have -- we have many -- we have many infants who are drinking fluoridated water from day one all the way through infancy. That is a critical window of development. EPA recognizes that. But we have no animal data to assess the neurological effects of that, including McPherson.

Secondly, the McPherson study did not have any exposure during the first six days of gestation. Your Honor, that's about one-third of the gestational period.

And the OECD guidelines say, if you can expose the rats from day zero, do it if you can. They are not saying don't. They are saying if you don't have pre-implantation loss at day zero, dose them at day zero. But McPherson did not do that.

THE COURT: But exposure at day six is also an accepted protocol; is it not?

MR. CONNETT: It is an accepted protocol, Your Honor. It's not as sensitive a protocol as you could have.

So what's important here, Your Honor, is that the study is ultimately not reflecting the full range of susceptibility.

So you can't take from McPherson, you can't have any confident conclusion that the study is capturing what we see in humans, which is full pregnancy exposure, full infancy exposures. It's not there in McPherson.

And, Your Honor in Dr. Thiessen's risk calculations, she treated the 45 part per million concentration, which Dr. Tsuji accepts is a neurotoxic level. She treated that concentration as a lowest observed adverse effect level.

And even if you treat 45 parts per million as a lowest observed adverse effect level, your reference dose is still well below human exposures.

THE COURT: When you apply the uncertainty factors, et cetera, et cetera?

MR. CONNETT: Correct.

THE COURT: But you would agree that you start with the NTP -- was it the NTP study that gave only low level of -- I forget the term, confidence about effect with respect to infant animals, young animals? And then you add to that McPherson, at least when you look at it on that basis, it appears to me that the animal studies are not very helpful.

MR. CONNETT: Your Honor, I think what's – as Dr. Thayer testified last week, she said: It's a reasonable hypothesis if you're seeing learning impairments in the adult treated rats, it's a reasonable hypothesis that you would also see the learning impairments in the developmental studies.

So we can take from the moderate confidence finding that the NTP had in the adult studies, you can impute from that into the developmental studies that if you had the well-conducted studies, you're going to find an effect as well.

THE COURT: Well, that's what I found sort of curious. Why did they have different confidence levels? I mean, based on the -- their review of the literature, you have kind of an inverse relationship.

MR. CONNETT: Right. And I think the reason that Dr. Thayer has provided is that at the time that the NTP did its review in 2016, there were very few developmental studies available. Certainly, few at the -- in the dose range of greatest interest.

So in part, Your Honor, that was why the NTP had lower confidence in the developmental studies, as well as the issue of not controlling for litter effects, which is, as you have noted, a methodological limitation.

But I don't think we can or should divorce the moderate confidence in the adult studies from our assessment of the developmental studies. It makes no biological sense that you would find learning impairments in adult animals, but not find it in the developmental studies.

THE COURT: So the low level of confidence is due to the nature of the number of studies and the quality of studies and the limitations, not necessarily reflective of the real world.

MR. CONNETT: I believe so, Your Honor. I believe that's what the evidence suggests.

Again, Dr. Thayer said on Wednesday that it's a reasonable hypothesis that if you're seeing the effects in the adults, you're going to see it in the fetal and neonatal exposures.

And there is no dispute in this case that the developing brain is the most susceptible to environmental toxicants. It would be the a priori expectation that an animal exposed in early life will suffer greater effects than animals exposed during adulthood.

THE COURT: Okay.

MR. CONNETT: So now to this question of unreasonable risk.

And I believe the evidence, Your Honor, in this case -- and you've heard from Dr. Hu, you've heard from Dr. Lanphear and Dr. Grandjean -- is that the situation with fluoridated water today is analogous to the situation this nation once faced with leaded gasoline. There, as here, we have a widespread dispersal of a neurotoxicant, which results in exposure to an enormous amount of people, including the most vulnerable.

It's an undisputed fact in this case that approximately 200 million people live in communities where fluoridation chemicals are added to water, and many more drink processed beverages that have been contaminated with fluoridation chemicals.

To put this number in context, Your Honor, the EPA has found unreasonable risks under Section 6 where the conditions of use impact less than 2,000 people.

Because of the widespread reach of fluoridation, you have millions of susceptible people being exposed on a daily basis, including 2 million pregnant mothers and over 400,000 exclusively formula-fed babies.

Your Honor, these are children -- and most of them are in lower income, more disadvantaged communities -- who from day one of their life, their only sustenance is infant formula, and that infant formula is reconstituted with the tap water. These are children who are being placed at a much higher risk of harm, and their interests should be considered by the EPA.

Now, plaintiffs do not need to prove causation at .7 parts per million to prevail in this case. That's not the standard that EPA has ever used, as Dr. Tala Henry admitted yesterday. But what makes this case so compelling, Your Honor, is that the evidence actually supports this conclusion.

Dr. Grandjean explained this in his testimony. The Bradford Hill factors support a finding of causation, rather than detract from it.

And all risk assessments, Your Honor, have uncertainties. Every single one. I don't think there is a single risk assessment in the history of this world where you don't have some uncertainties.

These are not the exception. They are the rule. Uncertainties do not preclude a finding of risk. If they did, I don't think the EPA would have made many risk determinations with the chemicals it has assessed so far under Section 6.

Exponent scientists in this litigation have identified for Your Honor a long list of possible reasons to possibly explain the findings.

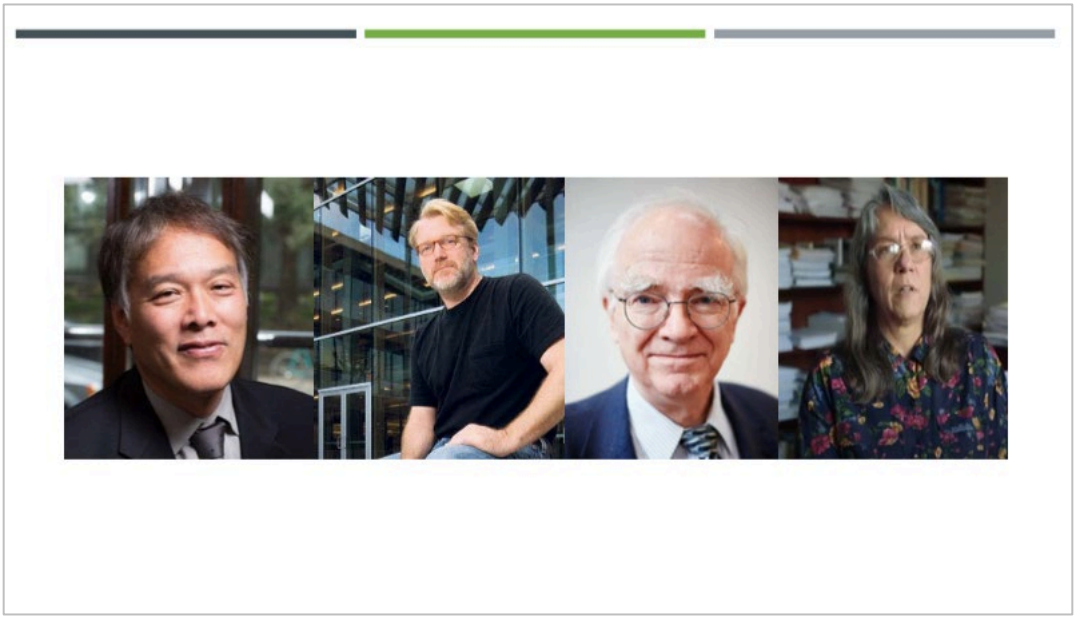
But I think Your Honor's exchange with Dr. Ellen Chang yesterday was notable and important. Dr. Chang was unable to identify for this Court any reason why the MIREC or ELEMENT studies would have been biased towards showing an effect.

The EPA, Your Honor, has not identified for you any cogent explanation that can explain the consistent results that we see across the human studies, across multiple populations, multiple study designs, both strong and weak.

Your Honor, we would submit what we submitted at the beginning of this case. The most likely explanation for the consistent results in both animal and human studies is that fluoride is a neurotoxicant that reduces IQ, including at the levels added to community water supplies in the United States. And this effect is strong enough to be detected, even in studies with weak study designs.

So, Your Honor, I believe the preponderance of evidence in this case has demonstrated that fluoridation chemicals present an unreasonable risk of harm.

And we thank you again for giving us an opportunity to present the evidence in this case.



THE COURT: Thank you Mr. Connett. If I can hear from the government please.

THE WORLD-WIDE MOVEMENT AGAINST WATER FLUORIDATION

In stark contrast to the Center for Disease Control's claim that fluoridation is one of the top ten public health achievements of the 20th century, it is **one of the most widely rejected health interventions in the world.**

Out of 196 nations, only 24 have any fluoridation, and only 10, like the U.S., for more than half their population. Over 95% of the world's population is fluoridation-free. The U.S. fluoridates as many people as the rest of the world combined.

None of the largest Asian nations, including China, India and Japan, fluoridate. Out of 54 countries in Africa, only one fluoridates – Libya, and only for a small percent of its population. In Europe, only four out of 48 countries fluoridate (less than 2% of the population). A few have fluoridated salt, but only as a consumer choice.

France, Germany, Belgium, the Netherlands, Denmark, Norway and Sweden have all prohibited fluoridation, many citing the ethical problem of putting any drug in drinking water.

For dozens of nations that haven't banned it, thousands of major cities and smaller towns don't fluoridate, including **Athens, Barcelona, Budapest, Geneva, Helsinki, London, Madrid, Prague, Rome, Vienna and Warsaw**. Ireland is the only European nation mandating fluoridation. But despite the mandate, 13 town and county councils, including Dublin and Cork, have voted for its immediate cessation.

Many organizations still support fluoridation, but **those opposing it grows year by year**. They include:

• American Academy of Environmental Medicine • Center for Health, Environment and Justice
• Children's Health Defense • Eau Secours (Canadian coalition of 234 groups promoting clean, safe water)
• Council of Canadians • Environmental Working Group • Food and Water Watch
* Institute of Neurotoxicology & Neurological Disorders • International Academy of Biological Dentistry and Medicine
• International Academy of Oral Medicine and Toxicology • League of United Latin American Citizens
• Moms Against Fluoridation • Organic Consumers Association

In addition, **many organizations once endorsing fluoridation have pulled back**, no longer taking a position. They include the Alzheimer's Association, American Academy of Allergy, Asthma and Immunology, Center for Science in the Public Interest, Consumers Union (Consumer Reports), National Association of Social Workers, National Down Syndrome Congress, National Down Syndrome Society and National Kidney Foundation.

The trend is clear. And as the scientific data accumulate, more and more nations, cities and organizations are challenging the safety, efficacy, costs and ethics of fluoridation.

References at fluoridealert.org/references1

FLUORIDEALERT.ORG
Fluoride Action Network