The finding's of the NTP's 6-year fluoride neurotoxicity evaluation

Chris Neurath
Science Director
American Environmental Health Studies Project

May 4, 2023

What did the NTP find?

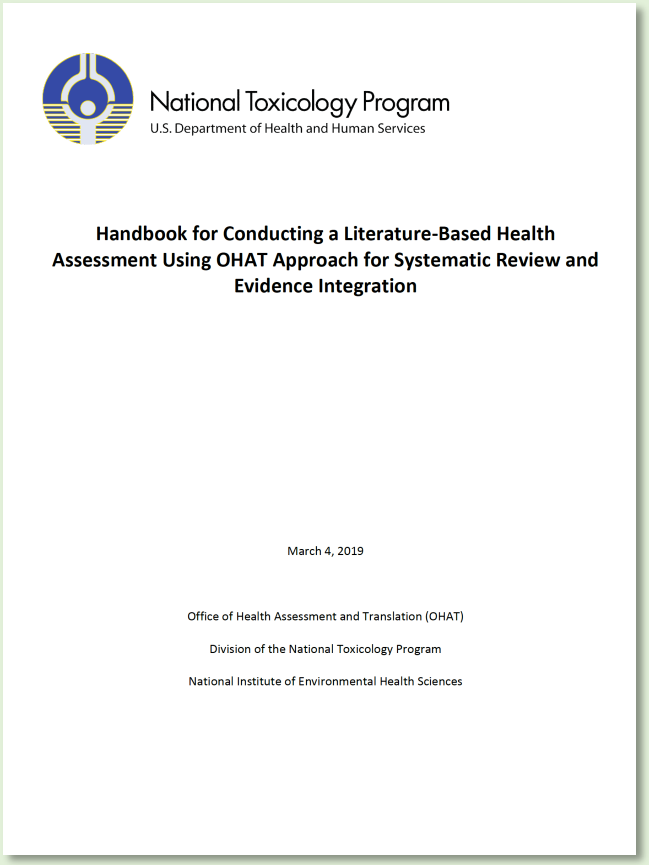
The NTP's

"moderate confidence"

conclusion for developmental neurotoxicity in human studies supports a

"presumed hazard"

conclusion when applying NTP's OHAT methodology.


National Toxicology Program
U.S. Department of Health and Human Services

Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration

March 4, 2019

Office of Health Assessment and Translation (OHAT)

Division of the National Toxicology Program

National Institute of Environmental Health Sciences

"Moderate confidence" is the 2nd highest OHAT confidence conclusion.

"Presumed hazard" is the 2nd highest OHAT hazard conclusion and is applied when human studies give "moderate confidence" and there is a "relatively large and consistent body of evidence"

Did NTP find a "relatively large and consistent body of evidence"?

"Moderate confidence" is the 2nd highest OHAT confidence conclusion.

"Presumed hazard" is the 2nd highest OHAT hazard conclusion and is applied when human studies give "moderate confidence" and there is a "relatively large and consistent body of evidence"

Latest NTP 2022 monograph

- **52 of 55 human studies found reduction in IQ from fluoride**

- **18 of 19 human studies rated low Risk of Bias by NTP found reduction in IQ from fluoride**

"The pattern of results across the 55 studies was consistent; 52 (95%) reported an inverse association"

"Subgroup analyses by sex, age group, study location, outcome assessment type, and exposure assessment type further support the consistent and robust pattern of an inverse association between fluoride exposure and children's IQ"

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When NTP was still making hazard assessments in 2020, how large and consistent was the body of evidence needed to support a "presumed hazard" conclusion?

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The body of evidence has strengthened

Earlier NTP 2020 monograph

- **44 of 46 human studies found reduction in IQ from fluoride**
- **8 of 9 human studies rated low Risk of Bias by NTP found reduction in IQ from fluoride**

NTP 2020 monograph concluded fluoride posed a "presumed hazard" of developmental neurotoxicity

Dose-Response

Did NTP find a safe threshold?

Dose-Response

Did NTP find a safe threshold?

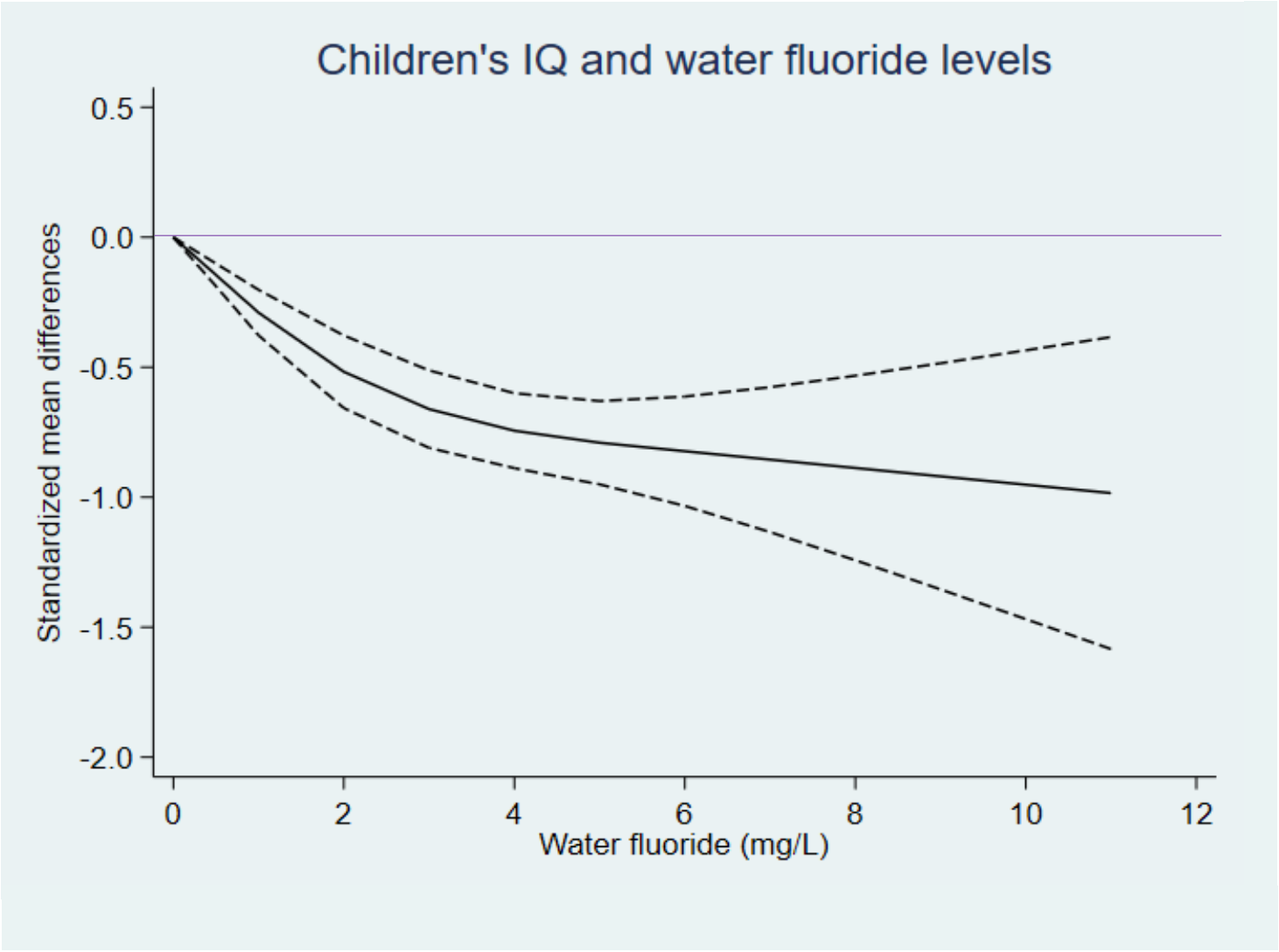
"there was no obvious threshold as illustrated by the figure …"

[BSC WG report page 326]

July 2022

Dose-Response Meta-Analysis

eFigure 17



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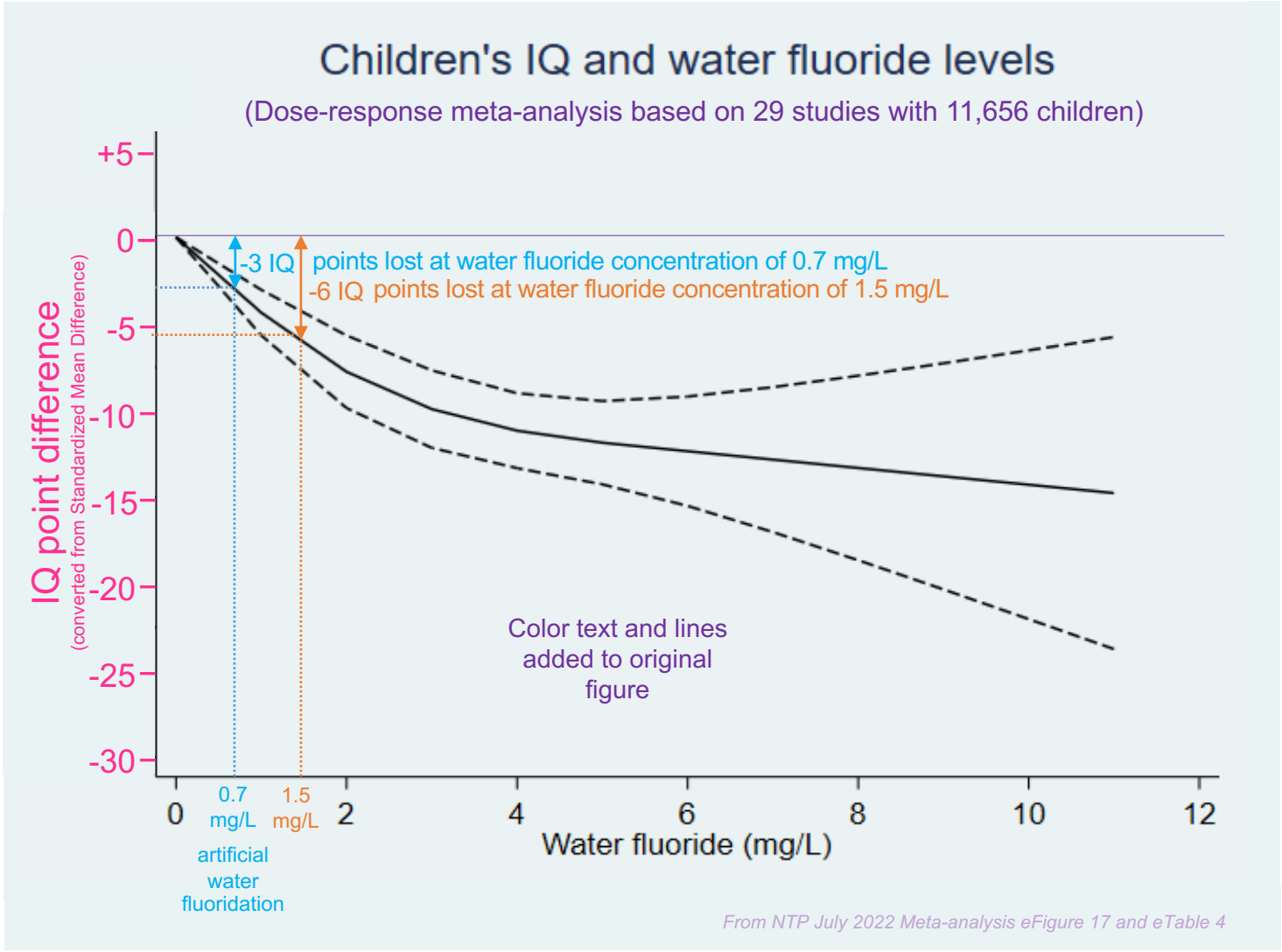
eFigure 17

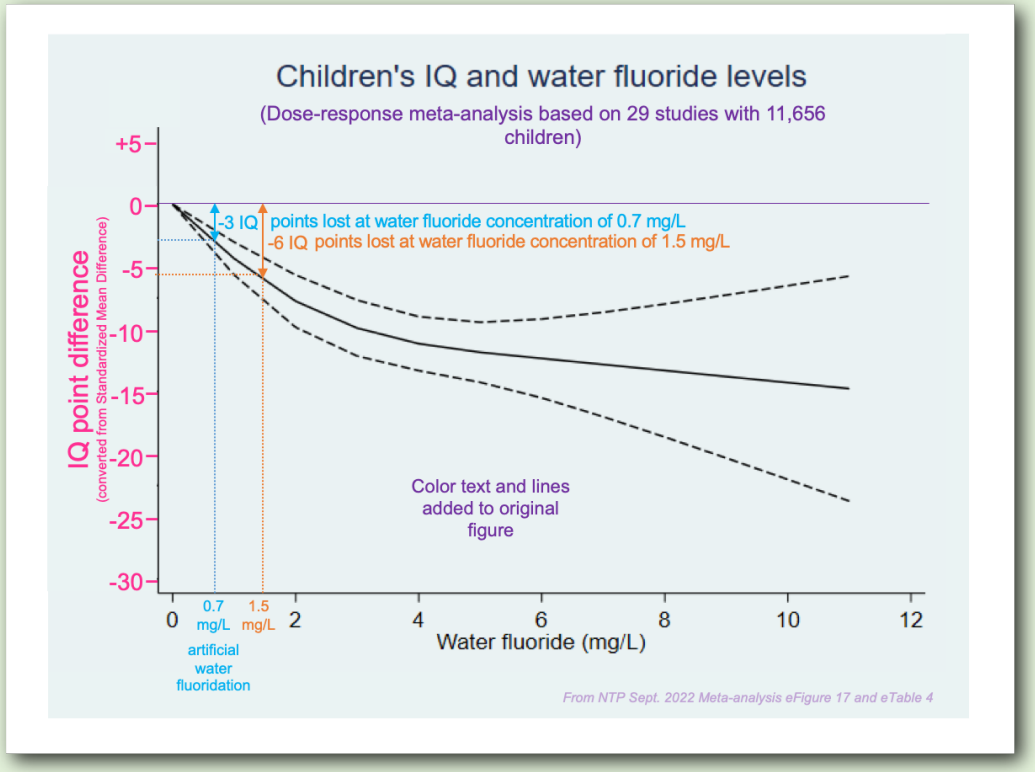


No evidence of a threshold at 1.5 mg/L or 0.7 mg/L water F concentration.

Dose-Response Relationships

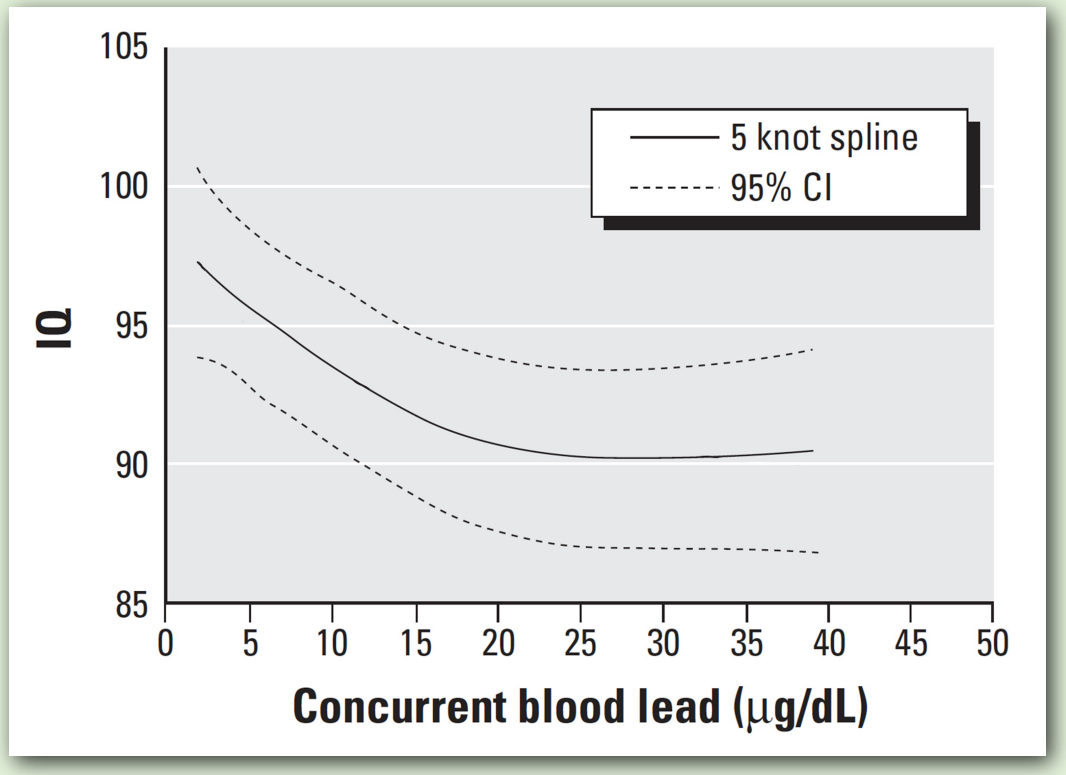
Fluoride-IQ

(NTP 2022)



Lead-IQ

(Lanphear et al 2005)



Research | Children's Health

Low-Level Environmental Lead Exposure and Children's Intellectual Function: An International Pooled Analysis

Bruce P. Lanphear,[1,2] Richard Hornung,[1,2,3] Jane Khoury,[1,2] Kimberly Yolton,[1] Peter Baghurst,[4] David C. Bellinger,[5] Richard L. Canfield,[6] Kim N. Dietrich,[7,2] Robert Bornschein,[2] Tom Greene,[7] Stephen J. Rothenberg,[8,9] Herbert L. Needleman,[10] Lourdes Schnaas,[11] Gail Wasserman,[12] Joseph Graziano,[13] and Russell Roberts[14]

The NTP's response to an HHS agency comment about exposures from drinking water in the United States:

The comment implies that our conclusions are based solely on "studies [that] were conducted on populations with higher exposures from water than are routinely found in the United States." This implication is not accurate. …

… the confidence assessment also includes findings from studies with fluoride exposures that are similar to, or lower than, those associated with optimally fluoridated water supplies in the United States. …

As demonstrated in Green et al. (2019), who used repeated individual urinary measurements, drinking water measures likely capture only a portion of a person's total exposure to fluoride as personal preferences and habits may increase total exposures to unknown levels. Therefore, this document, as well as any associated communication, focuses on total fluoride exposures from all sources, not just drinking water.

[BSC WG report page 26]

Summary of NTP findings

- "moderate confidence" of developmental neurotoxicity
- large and very consistent body of evidence supports "presumed hazard" conclusion
- no safe threshold observed
- "moderate confidence" conclusion applies to water fluoride of 0.7 mg/L

No wonder the divisions of HHS that promote fluoridation have tried to alter, delay, and suppress the NTP evaluation!

From documents obtained through Freedom of Information Act (FOIA) the political pressure has come from fluoridation promoting divisions of **HHS** including **NIDCR**, **CDC Oral Health**, and the **PHS Surgeon General's office**, together with dental lobby groups like the **American Dental Association**.

These government and dental agencies have been vigorously promoting fluoridation for over 70 years.

They are using the same science manipulation tactics the lead, tobacco, and chemical industries have used to defend their toxic products.

Request to BSC members:

Uphold the scientific integrity of the NTP and its dedicated staff

FREE the NTP report

Additional Slides

Dose-Response

Did NTP find a safe threshold?

Dose-Response

Did NTP find a safe threshold?

NTP also did dose-response meta-analysis of studies with individual-level continuous exposure measures.

These included the highest quality longitudinal cohort studies.

Dose-Response

Did NTP find a safe threshold?

The BSC workgroup recommended NTP display results of these dose-response analyses graphically and we concur.

Nevertheless, the consistency of these studies finding adverse effects on IQ with various regression models at several ranges of exposures can be assessed from eTable 4.

Dose-Response

Did NTP find a safe threshold?

NTP fit linear, quadratic, and spline models, and restricted included studies by several cut-off exposure levels.

Evidence for or against a safe threshold can be derived from comparing model results at the different cut-off exposure levels.

eTable 4. Dose-Response Meta-analysis Using Mean Effects—Model Selection[a]

Exposure Analysis	Parameters	Fluoride Exposure: All data	<4 mg/L	<2 mg/L	<1.5 mg/L
Water Fluoride – All Studies					
No. Studies/No. Observations Number of Children		29/39 11,656	21/27 8,723	7/9 2,971	7/7 2,832
Linear Model[b]	Beta (95% CI) p-value AIC	−0.15 (−0.20, −0.11) p < 0.001 AIC = 53.8	−0.22 (−0.27, −0.17) p < 0.001 AIC = 16.1	−0.15 (−0.41, 0.12) p = 0.274 AIC = 11.8	0.05 (−0.36, 0.45) p = 0.816 AIC = 8.2
Quadratic Model[c]	Beta (95% CI); p-value Beta (95% CI); p-value AIC p-value*	−0.27 (−0.34, −0.21); p < 0.001 0.02 (0.01, 0.03); p < 0.001 AIC = 48.8 p* < 0.001	−0.12 (−0.35, 0.11); p = 0.318 −0.04 (−0.10, 0.03); p = 0.280 AIC = 21.2 p* = 0.012	0.79 (−0.01, 1.58); p = 0.052 −0.56 (−0.97, −0.16); p = 0.006 AIC = 12.5 p* = 0.007	0.30 (−0.53, 1.14); p = 0.477 −0.23 (−1.01, 0.55); p = 0.561 AIC = 11.3 p* = 0.04
Restricted Cubic Splines Model[d]	Beta (95% CI); p-value Beta (95% CI); p-value AIC p-value*	−0.29 (−0.39, −0.20); p < 0.001 0.48 (0.18, 0.78); p = 0.002 AIC = 42.3 p* < 0.001	−0.14 (−0.34, 0.06), p = 0.162 −0.23 (−0.66, 0.20), p = 0.295 AIC = 16.9 p* = 0.009	1.15 (0.07, 2.22) p = 0.037 −1.20 (−2.03, −0.36) p = 0.005 AIC = 10.5 p* = 0.010	0.49 (−0.50, 1.47) p = 0.334 −0.69 (−2.40, 1.02) p = 0.428 AIC = 10.2 p* = 0.05
Water Fluoride – Low Risk-of-bias Studies					
No. Studies/No. Observations Number of Children		6/11 4,355	6/9 4,251	3/4 921	3/3 879
Linear model	Beta (95% CI) p-value AIC	−0.19 (−0.34, −0.05) p = 0.009 AIC = 10.3	−0.22 (−0.36, −0.07) p = 0.003 AIC = 3.9	−0.34 (−0.72, 0.03) p = 0.070 AIC = 4.5	−0.32 (−0.91, 0.26) p = 0.276 AIC = 4.1

Exposure Analysis	Parameters	Fluoride Exposure: All data	<4 mg/L	<2 mg/L	<1.5 mg/L
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Notes:
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Pink highlighting on Beta coefficient indicates negative association between F and IQ.

[BSC WG report pages 697-699]

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A majority of models have negative associations (IQ reduced as F increases), including a majority of models restricted to those studies with <1.5 mg/L

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Restricted Cubic Splines Model[d]	Beta (95% CI); p-value Beta (95% CI); p-value AIC p-value*	−0.29 (−0.39, −0.20); p < 0.001 0.48 (0.18, 0.78); p = 0.002 AIC = 42.3 p* < 0.001	−0.14 (−0.34, 0.06), p = 0.162 −0.23 (−0.66, 0.20), p = 0.295 AIC = 16.9 p* = 0.009	1.15 (0.07, 2.22) p = 0.037 −1.20 (−2.03, −0.36) p = 0.005 AIC = 10.5 p* = 0.010	0.49 (−0.50, 1.47) p = 0.334 −0.69 (−2.40, 1.02) p = 0.428 AIC = 10.2 p* = 0.05
Water Fluoride – Low Risk-of-bias Studies					
No. Studies/No. Observations Number of Children		6/11 4,355	6/9 4,251	3/4 921	3/3 879
Linear model	Beta (95% CI) p-value AIC	−0.19 (−0.34, −0.05) p = 0.009 AIC = 10.3	−0.22 (−0.36, −0.07) p = 0.003 AIC = 3.9	−0.34 (−0.72, 0.03) p = 0.070 AIC = 4.5	−0.32 (−0.91, 0.26) p = 0.276 AIC = 4.1

Exposure Analysis	Parameters	Fluoride Exposure: All data	<4 mg/L	<2 mg/L	<1.5 mg/L
Urinary Fluoride – All Studies					
No. Studies/No. Observations Number of Children		18/32 8,502	13/26 6,885	7/11 4,654	5/8 3,992
Linear Model[b]	Beta (95% CI) p-value AIC	−0.16 (−0.24, −0.08) p < 0.001 AIC = 73.8	−0.17 (−0.30, −0.05) p = 0.005 AIC = 68.0	−0.06 (−0.14, 0.01) p = 0.094 AIC = 1.2	−0.09 (−0.16, −0.01) p = 0.026 AIC= 2.8
Quadratic Model[c]	Beta (95% CI); p-value Beta (95% CI); p-value AIC p-value*	−0.10 (−0.31, 0.11); p = 0.360 −0.01 (−0.05, 0.02); p = 0.496 AIC = 84.3 p* = 0.14	0.07 (−0.23, 0.38); p = 0.645 −0.07 (−0.16, 0.01); p = 0.071 AIC = 75.8 p* = 0.08	−0.22 (−0.65, 0.20); p = 0.303 0.08 (−0.13, 0.30); p = 0.456 AIC = 9.2 p* = 0.42	0.65 (−1.46, 2.76); p = 0.548 −0.66 (−2.11, 0.80); p = 0.379 AIC = 8.3 p* = 0.10
Restricted Cubic Splines Model[d]	Beta (95% CI); p-value Beta (95% CI); p-value AIC p-value*	−0.12 (−0.28, 0.04); p = 0.150 −0.10 (−0.43, 0.23); p = 0.545 AIC = 79.6 p* = 0.13	−0.03 (−0.22, 0.16); p = 0.741 −0.24 (−0.47, −0.002); p = 0.048 AIC = 73.3 p* = 0.07	−0.14 (−0.32, 0.04); p = 0.130 0.13 (−0.17, 0.43); p = 0.395 AIC = 8.5 p* = 0.37	−0.52 (−1.65, 0.62); p = 0.371 0.63 (−1.32, 2.59); p = 0.524 AIC = 6.7 p* = 0.07
Urinary Fluoride – Sensitivity analysis including Ibarluzea et al. (2021)[87] Bayley MDI scores					
No. Studies/No. Observations Number of Children		19/33 8,815	14/27 7,445	8/12 4,967	6/9 4,305
Linear model	Beta (95% CI) p-value AIC	−0.15 (−0.23, −0.07) p < 0.001 AIC = 75.0	−0.15 (−0.28, −0.03) p = 0.015 AIC = 69.0	−0.04 (−0.14, 0.05) p = 0.371 AIC = 1.7	−0.08 (−0.15, −0.003) p = 0.043 AIC = 3.6
Urinary Fluoride – Sensitivity analysis including Ibarluzea et al. (2021)[87] McCarthy GCI scores					
No. Studies/No. Observations Number of Children		19/33 8,749	14/27 7,445	8/12 4,901	6/9 4,239

Exposure Analysis	Parameters	Fluoride Exposure: All data	<4 mg/L	<2 mg/L	<1.5 mg/L
Linear model	Beta (95% CI) p-value AIC	−0.15 (−0.23, −0.07) p < 0.001 AIC = 74.5	−0.16 (−0.28, −0.04) p = 0.011 AIC = 68.6	−0.05 (−0.14, 0.04) p = 0.259 AIC = 1.3	−0.08 (−0.16, −0.01) p = 0.036 AIC = 3.0
Urinary Fluoride – Low Risk-of-bias Studies					
No. Studies/No. Observations Number of Children		9/15 5,713	9/15 5,713	5/8 4,141	4/7 3,952
Linear model	Beta (95% CI) p-value AIC	−0.10 (−0.21, 0.01) p = 0.082 AIC = 5.9	−0.10 (−0.21, −0.01) p = 0.082 AIC = 5.9	−0.05 (−0.17, 0.08) p = 0.472 AIC = 2.8	−0.08 (−0.16, −0.01) p = 0.028 AIC = 2.5

Notes:
AIC = Akaike information criterion; SMD = standardized mean difference; p = p-value for effect estimate; p* = p-value for likelihood ratio tests; MDI = Mental Development Index; GCI = General Cognitive Index
[a]Parameter estimates are changes in SMDs (beta [95% CI]) based on the restricted maximum likelihood models; model fit is represented by the maximum likelihood AIC.
[b]The estimates represent change in SMD for the linear model and AIC, respectively.
[c]The estimates represent change in SMD for the linear term, change in SMD for quadratic term, AIC, and p-values for likelihood ratio test versus linear model, respectively. Potential departure from a linear trend was assessed by testing the coefficient of the quadratic term equal to zero.
[d]The estimates represent change in SMD for the first spline term, change in SMD for the second spline term, AIC, and p-value for likelihood ratio test vs linear model, respectively. Potential departure from a linear trend was assessed by testing the coefficient of the second spline equal to zero.

Pink highlighting on Beta coefficient indicates negative association between F and IQ.

[BSC WG report pages 697-699]

Latest NTP 2022 meta-analysis

- **44 of 56 dose-response meta-analysis regression models found lower IQ as F increases**
- **23 of 24 linear dose-response meta-analysis regression models found lower IQ as F increases**
- **9 of 14 dose-response meta-analysis regression models restricted to studies with <1.5 mg/L F found lower IQ as F increases**
- **5 of 6 linear dose-response meta-analysis regression models restricted to studies with <1.5 mg/L F found lower IQ as F increases**

A majority of models have negative associations (IQ reduced as F increases), including a majority of models restricted to those studies with <1.5 mg/L

Thus, no threshold is suggested