June 12, 2020

Excerpts from Dr. Kathleen Thiessen's statement for the TSCA Trial

Paul Connett has inserted his commentary in blue italics.

SUMMARY OF OPINIONS

1. Under EPA's *Guidelines for Neurotoxicity Risk Assessment*, there is sufficient evidence to conclude that neurotoxicity is a hazard of fluoride exposure.

2. 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.

3. 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.

In this document Thiessen explains the steps required by the US EPA for completing a risk assessment to determine a safe reference dose for fluoride (RfD) to protect children from harm to the brain starting from LOAELs (lowest observable adverse effect levels) or NOAELS (no observable adverse effect levels) observed in appropriate animal studies.

She explains the 5 required steps:

1. Hazard Characterization

2. Quantitative Dose Response Analysis

3. Exposure Assessment

4. Risk Characterization

5. Risk Determination

1) Hazard Characterization: Pursuant to the (EPA) *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.

2) Quantitative Dose Response Analysis:

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 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.

Thiessen summarizes the steps for her RfD calculations in Table 5 Thiessen explained that she did not use just one POD (point of Departure) (i.e a LOAEL or NOAEL) she used five (based on five different animal studies, see Column A below) to arrive at a range of 5 RfD values (see Column G below). Her five RfDs were:

0.0007 ***mg of fluoride*** *per* ***kg bodyweight of the child*** *per* ***day*** *(most proetective)*

0.003 mg/kg/day

0.006 mg/kg/day

0.01 mg/kg/day

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	B	C	D	E	F	G
Observation	Intake rate	POD_{HED}	NOAEL	$UF_H = 10$	$UF_A = 3$	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).

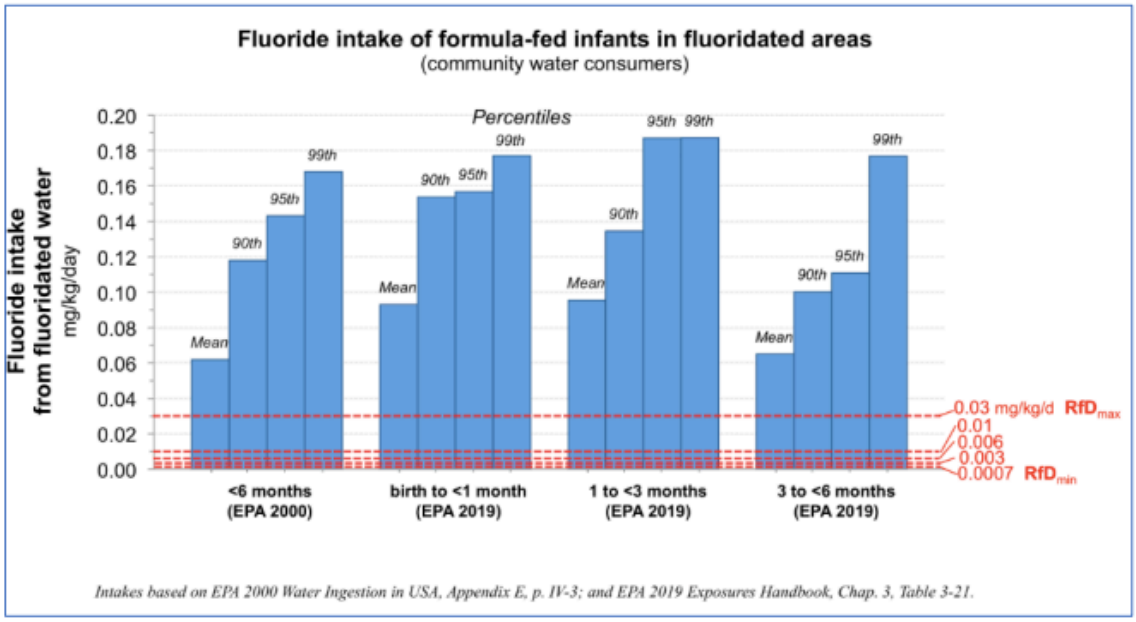
Column F: The estimated NOAEL after application of an additional uncertainty factor for interspecies variability (UF_A), where $UF_A = 10$. The adjusted NOAEL from Column E is divided by UF_A (i.e., NOAEL / 3).

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.

3) Exposure Assessment:

I conducted an Exposure Assessment that focused solely on the condition of use at issue in this case: fluoridation of drinking water… 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.

4) Risk Characterization: Consistent with the *Guidelines*, I integrated the information on hazards and exposures in a risk characterization …



What Theissen has shown in this figure above is that whichever of the five RfD values she has derived(using standard EPA risk assessment assumptions applied to animal data), the whole population of children will exceed each of her RfD values.

5. Risk Determination: For the risk determination, I considered the risk-related factors that EPA has identified as relevant for risk determinations under TSCA…

UNREASONABLE RISK.

Thiessen's discusses the reasons why "the risk of neurotoxicity posed by fluoridation chemicals constitutes a clear and unreasonable risk."

A. Effects of Fluoridation Chemicals Under the Condition of Use

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 (my emphasis, PC).** 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.

Under the Guidelines, prospective cohort data permit "direct estimates of risks attributed to a particular exposure**." 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 (my emphasis, PC).**

B. Number of Peopled Exposed to Fluoridation Chemicals

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**."

…**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 (my emphasis, PC).**, 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 (my emphasis, PC).. 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.

To put these numbers in perspective, EPA has found unreasonable risks for conditions of use involving as few as 1,046307 and 1,900 occupationally.

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

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. (my emphasis, PC).**

D. The Severity of the Hazard (Cognitive Deficits/IQ Loss)

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 (my emphasis, PC).**

To put this in perspective, EPA has recognized that a loss of a single IQ point is associated with a loss in lifetime earnings 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 (my emphasis, PC).**

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 context(my emphasis, PC).**

E. Uncertainties

Uncertainties are a pervasive aspect of risk assessment (my emphasis, PC).; 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 (my emphasis, PC).

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 (my emphasis, PC).

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 (my emphasis, PC).

Another factor weighing in favor of an unreasonable risk finding is that the exposure estimates are more straightforward (my emphasis, PC).—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, 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.

Estimating exposure to fluoridation chemicals involves much less uncertainty (my emphasis, PC)., 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."

Thiessen concludes

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 (my emphasis, PC).