Re: National Toxicology Program Board of Scientific Counselors; Announcement of Meeting; Request for Comments (Fluoride and Developmental Neurotoxicity)

Dear Dr. Lori White,

Thank you for both being willing to receive comments from the general public as well as proposing a systematic review of the scientific research regarding fluoride and developmental neurotoxicity.

I wish to present the following points regarding research on fluoride and water fluoridation.

I. The need for further studies:

A. Brief summary of 3 comprehensive systematic reviews from 1980-2015:

- 1980 EPA Reviews Of The Environmental Effects Of Pollutants XI Fluoride
- 2006 National Research Council: Fluoride in Drinking Water
- 2015 Cochrane Review on Water Fluoridation

B. Which studies and which protocols are needed:

- The importance of selecting the appropriate various dosages when testing dose-effect and dose-response relationships.

- The importance of selecting an appropriate range of animal models.

- The importance of testing both sodium fluoride (NaF) and hexafluorosilicic acid (HFSA) – most studies are on NaF, yet the majority of water fluoridation chemicals are HFSA.

- The importance of testing the effects of fluoride at different stages of development – the fluorine ion is a known endocrine disrupter.

II. Graphical/Tabular representations of 4 areas of concern:

A. The fluoride ion is absorbed in tissue, as well as in bone, depending on age of development.

B. Raw data from the initial studies on the efficacy of NaF in water are presented: not statistically significant for 10-13 year olds.

C. Recent data on emergency department (ER) visits for dental caries in 3-5 year olds in New York State, data obtained from NYS Dept. of Health website: no clear evidence of correlation between water fluoridation and reduced ER visits for dental caries.

D. Report on study showing that fluorosis, although caused by fluoride, cannot be used as the sole indicator for other possible adverse effects such as derangements in thyroid hormones.

I. The conclusions of 3 systematic reviews from 1980 to 2015.

From the 1980 EPA XI. Fluoride: regarding needed studies and protocols (emphasis added):

1. **Accurate current data on fluoride consumption** from food, water, and beverages in different geographic areas, under various economic and cultural circumstances.
2. Studies using a systematic approach based on **a dose-response plan** should be made on basic growth effects of fluoride on cells.
3. The **effects of fluoride on cell membrane permeability** should be studied.
4. Additional research is needed regarding long-term effects of fluoride-induced bone changes and **the influence of nutrition**, especially relative to fluorides' interaction with other trace elements.
5. The role of various **physiological stresses** on the expression of fluoride-induced lesions needs further study.

The NAS 2006 report on Water Fluoridation also made the following suggestions regarding future research (emphasis added):

1. Exposure assessment – **improved assessment of exposure to fluoride from all sources is needed**, characterized for individuals rather than communities and epidemiologic studies should group individuals by exposure level rather than by source of exposure, location of residence, or fluoride concentration in drinking water.
2. Intakes or exposures should be characterized **with and without** normalization for body weight.
3. Fluoride should be included **in nationwide biomonitoring surveys** and **nutritional studies**; in particular, analysis of fluoride in blood and urine samples taken in these surveys should be available.
4. **Pharmacokinetic studies**
    a. The concentrations of fluoride in human bone as a **function of exposure concentrations**, **exposure duration**, age, sex and health status should be studied.
    b. Information is particularly needed on **fluoride plasma** and bone concentrations in **people with small-to-moderate changes** in renal function as well as in those with serious renal deficiency.
    c. Improved and readily available pharmacokinetic models should be developed.
    d. **Additional cross-species pharmacokinetic comparisons would help to validate such models**.
5. **Other health effects**
    a. Carefully conducted studies of exposure to fluoride and emerging health parameters of interest (e.g. **endocrine effects and brain function**) should be performed in populations exposed to various concentrations of fluoride. It is important that exposures be appropriately documented.

The 2015 Cochrane Review writes in the Author's Conclusions (emphasis added):

    a. There is very little contemporary evidence … that has **evaluated the effectiveness** of water fluoridation for the prevention of caries.
    b. There is **insufficient evidence** to determine whether water fluoridation results in a change in **disparities in caries levels across SES** (Social Economic Status).

c. (They) did not identify any evidence ... to determine the effectiveness of water fluoridation for preventing caries in **adults**.
d. There is insufficient information to determine the effect of stopping water fluoridation programmes on the prevalence of caries.
e. There is a significant association between dental fluorosis (of aesthetic concern or all levels of dental fluorosis) and fluoride level. The evidence is limited due to high risk of bias within the studies and substantial between-study variation.

Estimated Lethal Dose: Human vs Animal (as reported by NIH ToxNet: accessed 1/7/2016)

The oral lethal dose (50%) (LD50) of Sodium Fluoride is estimated to be 4 to 5 on the toxicity scale. This translates to a range from 5mg/kg to 5,000mg/kg for humans: which is between 7 drops of NaF and 1 oz of NaF for a 70kg adult. Gosselin, R.E., R.P. Smith, H.C. Hodge. (1984)

For non-humans the LD50 value can be higher:

The LD50 for the **rat** for oral dose is 430 mg/kg (CDC/NIOSH; The Registry for Toxic Effects of Chemical Substances- Silicate (2-), hexafluoro-, dihydrogen (16961-83-4).

The LD50 of the **guinea pig** oral is 200 mg/kg (1.39 mmol/kg) [LCI Ltd. Material Safety Data Sheet for Fluosilicic Acid (16961-83-4).

Given that the rat model may have a higher oral lethal dose than that of humans, it is suggested that other animal models, such as the New Zealand white rabbit, should also be considered for use in the experimental part of this proposal. See Mapara M, Thomas BS, Bhat KM. (2012) for use of the rabbit in bone studies.

Effects on cells is dose-dependent but most likely not linear:

The following is an excerpt from a published report on another chemical considered for toxicity by Melzer, D. et al., (2010):

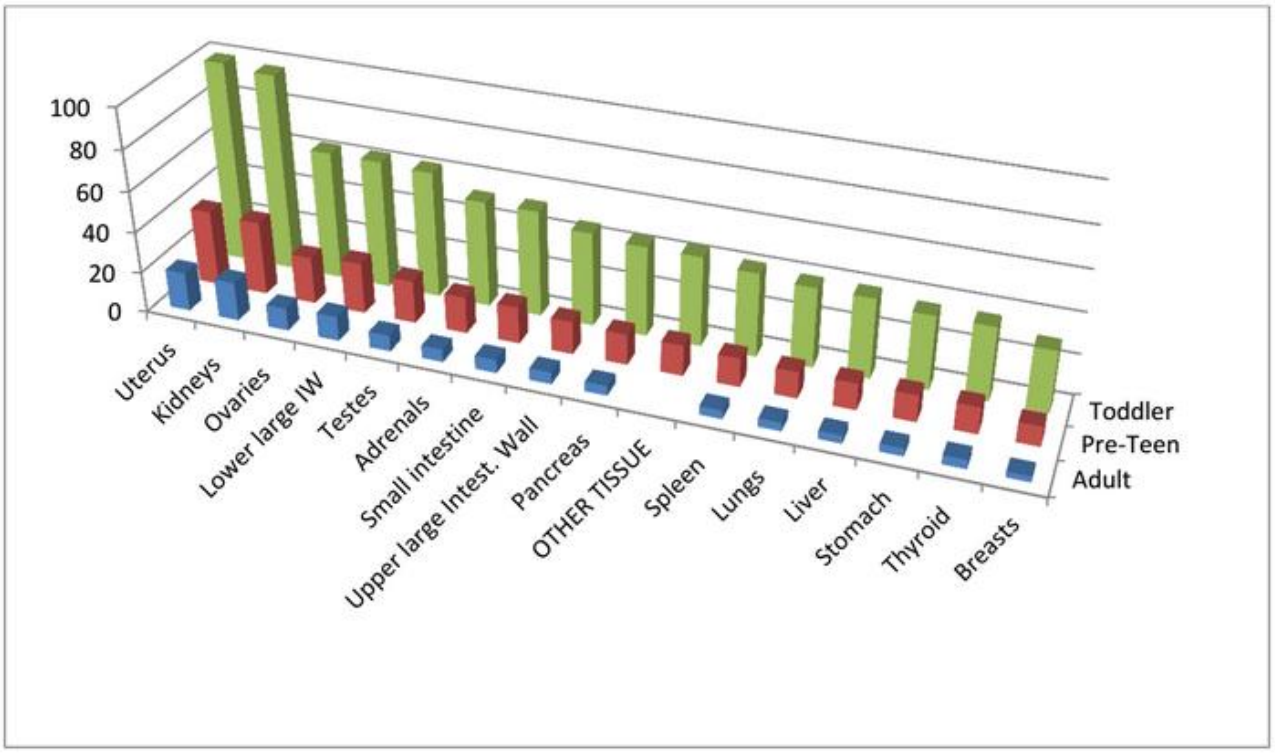
> Nonlinearity of response is not uncommon for receptor-mediated systems such as endocrine-signaling pathways that act to amplify the original signal. Large changes in cell function can occur in response to extremely low concentrations, but which may become saturated and hence unresponsive at higher concentrations (vom Saal and Hughes 2005; Welshons et al. 2003).

Therefore, it is extremely important to have an appropriate gradient of dosage during the experimental part of the proposal. Furthermore, it is also possible that, as fluoride is a known endocrine disruptor, it may have more than one phase of response, i.e. is biphasic (see Lau BW, Lee YP. (1982) re fluoride and biphasic reaction in E. coli experiments).

II. Graphical/Tabular representations of several areas of concern:

A. Estimated Absorbed Radiation Doses after IV Administration of the fluoride ion using F-18 as a tracer in imaging studies.

- The fluoride ion is not only absorbed by bone, but is also absorbed by other tissues.
- The fluoride ion is not absorbed evenly from one stage of development to another.
- The fluoride ion in absorbed at different levels in different tissues, depending on stage of development.



Data from Nuclear Regulatory Commission Report, Radiation dose estimates for Radiopharmaceuticals, NUREG/CR-6345, page 10, 1996 and from ICRP publication 53, Radiation Doses to Patients from Radiopharmaceuticals, Ann ICRP, Volume 18, pages 15 and 74, 198, measured in uGy/MBq. See full table in Appendix A.

B. The original Grand Rapids study shows no significant statistical benefit in 10-13 year olds:

There are no statistically significant differences between tooth decay in 10-13 year olds from 1944/1945 to 1950.

There are no statistically significant differences between tooth decay in 10-13 year olds between non-fluoridated city (Muskegon) and fluoridated city (Grand Rapids).

6 out of the 10 age groups studied had reduction in tooth decay (DMFT) in the non-fluoridated city over the span of the study time period.

Study did not control (or publish data) regarding sex, SES, race, health/nutrition status, blood fluoride concentration, fluoride sensitivity or thyroid function (NaF was known to be used to treat hyper-thyroid at the time of the study).

Table 3. Dental caries findings, deciduous teeth, in Grand Rapids and Muskegon, Mich., school children, 4–13 years of age, according to year of examination

Age last birthday	Number of def [1] deciduous teeth per child							
	Basic examinations 1944–45	1945	1946	1947	1948	1949	1950	1951
	Grand Rapids, Mich.							
4	4.186	5.398	3.427	3.190	3.022	2.747	2.462	2.131
5	5.369	6.151	5.083	3.893	4.027	3.273	2.501	2.273
6	6.431	6.979	5.725	5.379	4.784	4.590	3.730	2.977
7	6.293	7.658	6.110	5.841	5.200	4.833	4.715	4.031
8	5.782	8.000	5.097	5.074	4.877	4.748	4.908	4.123
9	4.591	.....	4.446	4.110	4.428	4.410	4.229	3.856
10	2.837	.....	2.835	3.157	3.063	2.856	2.359	2.426
11	1.345	.....	2.118	2.778	1.773	1.193	1.162	1.351
12	.473	.276	.129	.105	.250	.354	.245	.295
13	.176	.130	.139	.136	.170	.103	.147	.117
	Muskegon, Mich.							
4	5.050	[2]	3.442	4.667	4.385	4.412	5.317	4.460
5	6.820	.....	5.860	5.052	5.552	5.556	5.649	5.248
6	7.167	.....	6.239	6.179	6.056	5.992	6.019	5.667
7	6.663	.....	6.833	5.952	6.917	6.333	5.825	5.771
8	6.061	.....	4.833	3.846	4.800	6.083	5.063	5.320
9	4.885	.....	4.315	4.344	4.714	4.482	4.088	4.173
10	3.084	.....	3.145	3.667	2.788	2.769	3.490	2.855
11	1.328	.....	1.667	2.900	.643	1.212	1.085	1.460
12	.422	.....	.143	.368	.636	.679	.605	.312
13	.234	.....	.289	.174	.106	.112	.127	.147

[1] Decayed, extraction indicated, or filled deciduous teeth. A decayed and filled tooth is counted only as a filled tooth.

[2] The 1944–45 basic examinations in Muskegon were not done until late spring of 1945; therefore, no repeat examinations were made in the fall of 1945.

Arnold FA Jr, Dean HT, Jay P, Knutson JW. Effect of fluoridated public water supplies on dental caries prevalence.Seventh year of Grand Rapids-Muskegon study. Bull World Health Organ. 2006 Sep;84(9):761-4. Effect of fluoridated public water supplies on dental caries prevalence. *Public Health Rep.* 1953 Feb;68(2):141–148.

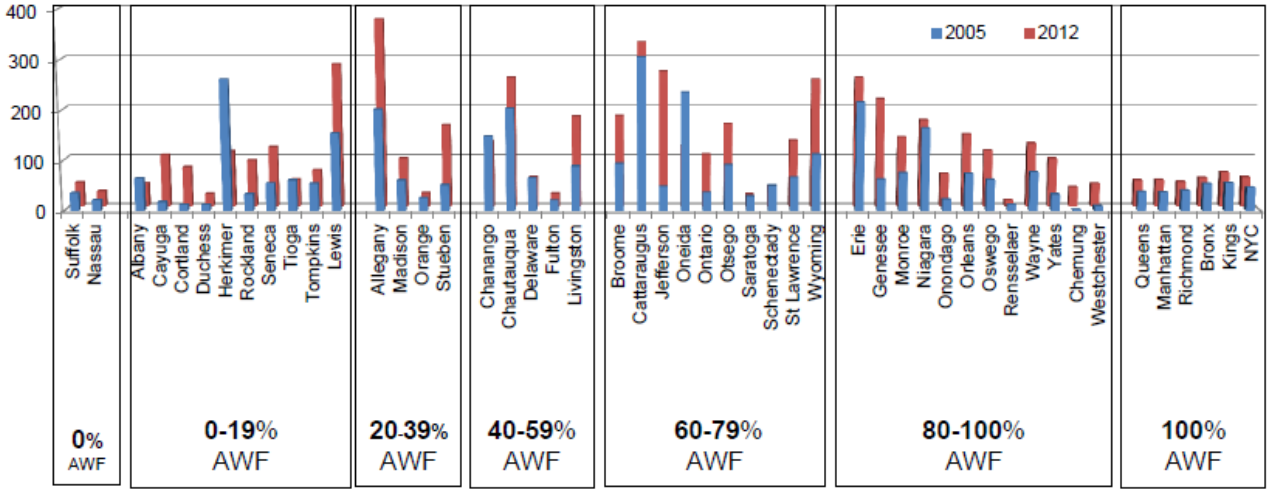
C. Latest data on dental caries per NYS by county do not show any correlation between reduction in caries and water fluoridation systems:

One of the main purposes of water fluoridation systems is to reduce caries across all SES.

There is no correlation between emergency department (ER) visits for tooth decay and percentage of water fluoridation systems per county.

The most recent review on dental caries prevalence in 3rd Graders in NYS does not present data per zip code or county. See: [Public Health Reports 3rd Graders Caries Prevalence]

ER Outpatient Visits per 10,000 for Tooth Decay per County: Aged 3-5 years, In Order of Fluoridated Water Supplies, 0 to 100%, in 2009 and 2012, Showing No Correlation with Artificial Water Fluoridation (AWF).



No correlation between increased levels of fluoridated water supplies and decrease in ER visits for tooth decay.

In nearly every county caries rate **increased** from 2005 to 2012, fluoridated or non-fluoridated.
In all NYC counties caries rates increased from 2005 to 2012 despite 100% access to fluoridated water

*This data is not controlled for social economic status, or blood- and/or urine-fluoride content.

Chart Data Compiled using **Schuyler Center's water fluoridation by county at http://www.scaany.org/policy-areas/health/oral-health/ and NYS DOH http://www.health.ny.gov/statistics/chac/ed/e1.htm Accessed 10/9/2015.

D. Derangement of TSH (Thyroid Stimulating Hormone) with high and low water fluoridation, and levels of fluorosis.

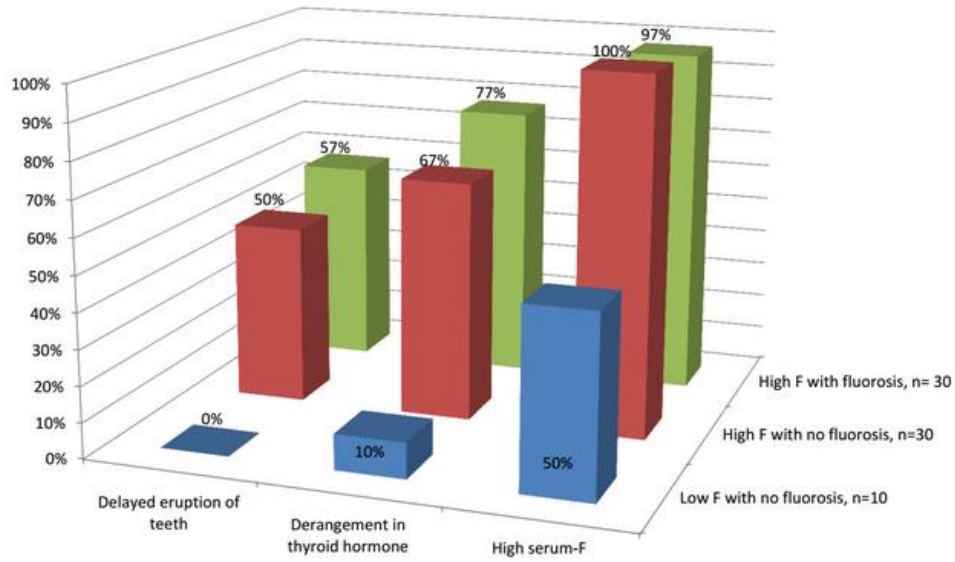
Although dental fluorosis is indicative of overexposure of fluoride, this study illustrates the fact that there can be an adverse effect on other systems with and without the presence of dental fluorosis.

High levels of serum-fluoride, according to this study, increased the disruption or *derangement* in thyroid hormones, with and without presence of fluorosis.

Furthermore, higher levels of fluoridation, according to this study, will delay eruption of teeth, thereby delaying onset of tooth decay.

Derangement in Thyroid Hormone (FT3, FT4, TSH) Levels and Serum-Fluoride levels in children, high and low fluoride levels, with and without fluorosis.

Singh N, Verma KG, Verma P, Sidhu GK, Sachdeva S. A comparative study of fluoride ingestion levels, serum thyroid hormone & TSH level derangements, dental fluorosis status among school children from endemic and non-endemic fluorosis areas. *SpringerPlus*. 2014;3:7.



Facts regarding fluoride about which the consumer of fluoridated public water should be informed:

1. Fluoride is no longer considered a nutrient.

2. The “fluoride” used in water fluoridation systems is most often hexafluorosilicic acid, not calcium fluoride, and is not “naturally occurring”.

3. The fluoride ion is a known endocrine disruptor and developmental neurotoxin. What is not known is the safe level of fluoride concentration for all consumers of water, irrespective of their sex, stage of development, physical and mental health and nutritional status. This can only be known through individual monitoring by a health care professional.

As concluded by the National Academies of Science, 2006 and The Cochrane Review 2015, and contrary to popular belief, the proper studies have not been done on the chemicals we use for “fluoridation”. I am very hopeful that the NTP studies will fill in the many gaps in our scientific knowledge about these substances.

Thank you again for this important work.

Yours sincerely,
Robin Warwick, Au.D., B.S.
Resident of New York City, New York.
[Redacted]

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APPENDIX A

Center for Drug Evaluation and Research: Labeling: Application Number 022494Orig1s000

Table 1: Estimated Absorbed Radiation Doses after Intravenous Administration of Sodium Fluoride F 18 Injection						
Organ		Estimated Radiation Dose mGy/MBq				
		Adult 70 kg [1]	15 year 56.8 kg [2]	10 year 33.2 kg [2]	5 year 19.8 kg [2]	1 year 9.7 kg [2]
Adrenals		0.0062	0.012	0.018	0.028	0.052
Brain		0.0056	N/A	N/A	N/A	N/A
Bone surfaces		0.060	0.050	0.079	0.13	0.30
Breasts		0.0028	0.0061	0.0097	0.015	0.030
GI	Gallbladder wall	0.0044	N/A	N/A	N/A	N/A
	Stomach wall	0.0038	0.008	0.013	0.019	0.036
	Small intestine	0.0066	0.012	0.018	0.028	0.052
	Upper large intestine wall	0.0058	0.010	0.016	0.026	0.046
	Lower large intestine wall	0.012	0.016	0.025	0.037	0.063
Heart wall		0.0039	N/A	N/A	N/A	N/A
Kidneys		0.019	0.025	0.036	0.053	0.097
Liver		0.0040	0.0084	0.013	0.021	0.039
Lungs		0.0041	0.0084	0.013	0.020	0.039
Muscle		0.0060	N/A	N/A	N/A	N/A
Ovaries		0.011	0.016	0.023	0.036	0.063
Pancreas		0.0048	0.0096	0.015	0.023	0.044
Red marrow		0.028	0.053	0.088	0.18	0.38
Skin		0.0040	N/A	N/A	N/A	N/A
Spleen		0.0042	0.0088	0.014	0.021	0.041
Testes		0.0078	0.013	0.021	0.033	0.062
Thymus		0.0035	N/A	N/A	N/A	N/A
Thyroid		0.0044	0.0084	0.013	0.020	0.036
Urinary bladder wall		0.25	0.27	0.4	0.61	1.1
Uterus		0.019	0.023	0.037	0.057	0.099
Other tissue		N/A	0.010	0.015	0.024	0.044
Effective Dose Equivalent mSv/MBq		**0.027**	**0.034**	**0.052**	**0.086**	**0.17**

[1] Data from Nuclear Regulatory Commission Report, *Radiation Dose Estimates for Radiopharmaceuticals,* NUREG/CR-6345, page 10, 1996.

[2] Data from ICRP publication 53, *Radiation Dose to Patients from Radiopharmaceuticals* , Ann ICRP, Volume 18, pages 15 and 74, 1987