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Lori White, PhD, PMP BSC
Designated Federal Officer NIH/NIEHS NTP
Office of Liaison, Policy, and Review
P.O. Box 12233, MD
K2-03 111 TW
Alexander Drive Research Triangle Park, NC 27709

sent electronically to: whiteld@niehs.nih.gov

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

Dear Dr. White,

We welcome the opportunity to provide comments on the Proposed NTP Evaluation on Fluoride Exposure and Potential for Developmental Neurobehavioral Effects.

These comments are submitted on behalf of our organization PFPC (Parents of Fluoride-Poisoned Children).

We believe that NTP/OHAT should place the review of developmental neurotoxicity as a high priority.

All of our comments are concerning fluoride effects on thyroid function. It is established that thyroid hormones are essential for fetal and neonatal brain development, and that even slight alterations during critical periods of development can have severe consequences on the development of the child.

We will use the phrase "fluoride effects on thyroid function" as a general term to describe fluoride effects on all related aspects of thyroid physiology, including effects on hormone levels (T4, FT4, T3, FT3, rT3, TSH), deiodinase (D1, D2, D3) activity, TPO or TPOa levels, iodine uptake, as well as thyroid gland damage.

Although fluoride effects on thyroid function have been documented for more than 100 years, the issue remains largely misunderstood. Past reviews on the subject have distorted scientific findings reported by others.

1. PAST REVIEWS

Firstly, we would like to offer a few comments regarding reviews discussed in the NTP background paper, as well as in comments by others already submitted. These reviews are often cited as evidence that fluoride does not have effects on thyroid function at "realistic" levels found in "optimally fluoridated areas".

It should be understood from the outset that an "optimally fluoridated area" is not indicative of dosage – but rather of a concentration. Toxicity of fluoride is dependent on **total intake from all sources** - intake from fluoridated water being one of them (*US PHS, 1991*). Total intake and resulting serum levels, as well as duration of exposure, are of concern in assessing toxicity, regardless if one is to evaluate conditions like dental fluorosis (*e.g. DenBesten & Li, 2011; Bronckers et al., 2009*), skeletal fluorosis (*US PHS 1991*) or thyroid dysfunction (*e.g. May 1951; Zhao et al., 1998*). In industrialized countries total fluoride intake no longer reflects residence in a community with a non-fluoridated or fluoridated water supply (*Maguire et al., 2007*).

The 2011 SCHER Report

In 2011, the EU Scientific Committee on Health and Environmental Risks (SCHER) published the paper “Opinion on critical review of any new evidence on the hazard profile, health effects, and human exposure to fluoride and the fluoridating agents of drinking water” (*SCHER 2011*). Although others refer to this paper as a critical review, we would disagree. It is properly defined in the official title as an opinion.

While the particular directive given to SCHER was to “consider evidence that has become available after 2005, but also evidence produced before which was not considered by the SCCP and EFSA panels at the time”, this was not done. The literature provides over 50 studies between 2005 and 2010 that address fluoride effects on thyroid function, both on humans and animals; however, not one of them is listed. Instead, SCHER not only referred to previous reviews (*EFSA 2005; ATSDR, 2003*) - but further falsified the already questionable information given in those earlier reviews.

We list here several examples.

Example 1:

SCHER states:

Section 4.1.3, Page 17:

*“Some animal studies have suggested a potential for thyroid effects following fluoride exposure. The available information is inconsistent and **no effects on the thyroid were observed in long-term studies with fluoride in rats** [emphasis added]. Apparently, fluoride does not interfere with iodine uptake into the thyroid. However, after long-term exposure to high fluoride content in food or water, the thyroid glands of some animals have been found to contain increased fluoride levels (EFSA 2005).”*

EFSA 2005 is given as the only reference here. However, EFSA 2005 stated the opposite:

*“Rats administered 0.5 mg fluoride/kg/day via drinking water during two months **showed decreased thyroxine levels and an increased T3-resin uptake ratio** [emphasis added] (Bobek et al., 1976).”*

NOTE: Not only did the animals show a decrease in T4, they also showed a decrease in T3. There was a direct dose-response relationship. The table with the data by Bobek (1976) can be seen here:

http://poisonfluoride.com/pfpc/Bobek_19763.jpg

Example 2:

SECTION 4.1, Page 3:

“There is no strong evidence that fluoride exposure in sub-populations with endocrine disorders (diabetes, thyroid dysfunction) have an increased risk for adverse health effects.”

It has been well documented that fluoride effects are more severe under conditions of iodine deficiency, or other thyroid dysfunction, as has been documented in humans (e.g. Lin et al., 1992,1991,1988; McGlashan et al., 2014; Wang et al., 1996; Ren et al., 1989a, 1989b, 1989c) as well as in animals (e.g. Guan, 1988; Ge et al., 2013; 2005, 2003; Zhao et al., 1998, 1992, 1988; Hong et al., 2005). This occurs even at fluoride water levels in the so-called “optimal” range in humans (Lin et al., 1991) and, in rodents, at levels much below the minimum dose required to produce dental fluorosis (e.g. Guan et al., 1988, Zhao et al., 1998, 1992). In addition, it is also established that fluoride augments serious health effects reported in areas with excessive intake of iodine (e.g. Wang et al, 2001; Yang et al, 1994).

Example 3:

SUMMARY, Page 39

“Human studies do not suggest adverse thyroid effects at realistic human exposures to fluoride.”

Again, we argue that the opposite is true. See above.

Section 4.1.3, Page 18:

“The absence of thyroid effects in rodents after long-term fluoride administration and the much higher sensitivity of rodents to changes in thyroid related endocrinology as compared with humans do not support a role for fluoride induced thyroid perturbations in humans. The limited animal data can also not support the link between fluoride exposure and neurotoxicity at relevant non-toxic doses. SCHER agrees that there is not enough evidence to conclude that fluoride in drinking water at concentrations permitted in the EU may impair the IQ of children. SCHER also agrees that a biological plausibility for the link between fluoridated water and IQ has not been established.”

As already addressed above, the rodent study results were falsified. There are hundreds of additional studies on humans and animals, and biological plausibility has been firmly established, and mechanisms identified (e.g. Lin et al., 1992, 1991; Cai et al., 2009; Chen et al., 2010; Hing et al., 2005; Jin et al., 2002; Li 2011; Li et al., 2012; Liu et al., 2003; Liu X, 1998; Lu et al., 1996; Qiu et al., 2010; Qiu, 2008; Shen et al., 2004a, 2004b; Wangzhang Ting, 2010; Xu et al., 2003; Xu, 2002; Yao et al., 1996; Zhan et al., 2002; Zhang et al., 2008; Zhao et al., 2009; Sarcar & Pal, 2014, 2015; Selim et al., 2012; Basha et al., 2011)

ATSDR 2003

In 2003, the CDC's Agency for Toxic Substances and Disease Registry (ATSDR) published its updated Toxicological Profile for fluorine, hydrogen fluoride, and fluorides (*ATSDR 2003*). The 1998 study by Zhao et al., investigating thyroid hormones in mice exposed to various iodine/fluoride combinations, was also reviewed by the ATSDR, but the agency chose to falsify the findings and state the exact opposite as to what was actually reported by the authors in the original paper.

The ATSDR wrote:

“Fluoride has been shown to affect the endocrine system in rats given 0.5 mg fluoride/kg/day as sodium fluoride in drinking water every day for 2 months (Bobek et al. 1976). These animals showed decreased thyroxine levels and an increased T3-resin uptake ratio. In contrast, Zhao et al. (1998) did not find any alterations in serum T3 or T4 levels in mice exposed to 3.2 mg fluoride/kg/day as sodium fluoride in drinking water for 100 or 150 days.” [emphasis added]

The findings by Zhao et al. document the opposite. Comparing numerous fluoride/iodine intake scenarios for periods of 100 and 150 days they found that even at 0.06 mg/kg/day fluoride had significant effects on thyroid hormones after 100 days, in both iodine-deficient (ID) and iodine-normal (IN) mice. At 3.0 mg/kg/day (not 3.2 mg/kg/day - as claimed by the ATSDR) **significant alterations in T3 and T4 levels were observed**. The Zhao study is quite important as the “excess” fluoride water levels used here are comparable to those required as a minimum amount to produce dental fluorosis in rodents (*Bronkers et al., 2009*).

The complete study by Zhao et al. et al. can be seen here:

<http://www.sav.sk/journals/endo/full/er0298a.pdf>

A table showing the study data can be seen here:

http://poisonfluoride.com/Science/NRC_Review/NRC_Comments/NRC_Zhao/Zhao_Table/zhao_table.html

The data shows that even at 0.06 mg/kg/day fluoride may have effects on deiodination and deiodinase activity.

MRC 2002

In 2002, the UK Medical Research Council published the report “Water Fluoridation and Health“, based on findings of the York Review.

Regarding fluoride effects on the thyroid, the MRC wrote:

5.3.7 Thyroid (goitre)

“The York Review listed three studies in which goitre was the outcome of interest. Two of these studies (Gedalia & Brand, 1963; Jooste et al., 1999) found no significant association with water fluoride level. The third (Lin et al., 1991) found a significant positive association between combined high fluoride/low iodine levels and goitre. However, because this study looked at combined fluoride/iodine uptakes, and has not been published in a peer reviewed journal, the findings should be treated cautiously. Further work on this aspect is of low priority.”

Goitre was not the “outcome of interest” in the study by Lin et al., *subclinical endemic cretinism* was.

The “high” fluoride level in the water was 0.88 ppm – within the range of what was considered an “optimally” fluoridated area at the time (0.7 – 1.2 ppm).

The data by Lin Fa Fu et al. had been published in the Endemic Diseases Bulletin (*now called the Bulletin of Disease Control and Prevention*), the official award-winning and peer-reviewed journal of the Xinjiang Center for Disease Control and Prevention (comparable to the CDC in the US). The 3-year study had been sponsored by UNICEF. A translation of this study was published in the official newsletter of the International Council for Control of Iodine Deficiency Disorders (ICCDCC), and was submitted by the PFPC to the York Review (CRD) in 1999.

WHO - Demole 1970 & Bürgi 1984

Besides a short review that appeared in the journal Fluoride in 1976 (*McLaren, 1976*), there have only been two major reviews in the Western literature on the effects of fluoride on thyroid function in the last 50 years. One was authored by Victor Demole (*WHO 1970*), the other by Hans Bürgi et al. in 1984.

Both, Victor Demole and Hans Bürgi, were long-time executive members of the Swiss *Fluoride Commission* (known since 1977 as the Fluoride/Iodine Commission). Founded in 1950, this organization was responsible for the implementation of all Swiss programs concerning the fluoridation of water, salt and milk, as well as tablet programs.

In addition to both reviews omitting the majority of studies showing the adverse effects of fluoride on thyroid function, both also falsified study results.

We here list just a few examples to illustrate the scope of scientific misconduct.

Bürgi et al., 1984

Bürgi writes:

*“In a very detailed study, rats receiving 0.75 mg fluoride/day for 2 months had an **unchanged content of total thyroidal iodine, as well as of iodine in iodotyrosines and thyroid hormones** [emphasis added], even though in this latter study the incorporation of ¹³¹I into hormones was slowed down [56].”*

[Reference #56 is: Stolc V, Podoba J – “Effect of fluoride on the biogenesis of thyroid hormones” Nature 188:855–856 (1960)]

The actual evidence is to the contrary. In the words of authors Stolc & Podoba:

*“Fluorised rats showed a **significantly decreased amount of thyroxine [T4] (P<0.01) and of 3: 5: 3’ triiodothyronine [T3] (P<0.05) as against the control [emphasis added]...At the daily dose-rate of 0.2 ugm of iodine, the protein-bound iodine-level in fluorised animals (n = 12) was lower than in the controls (n = 7), receiving the same diet... This finding is considered as confirmation of the fact that a special enzymatic system which it is possible to inhibit by means of fluoride, is responsible for the synthesis of thyroxine and 3: 5: 3'-triiodothyronine.” [emphasis added]***

NOTE: This was one of the first scientific studies, as published in the journal Nature in 1960, showing that fluoride can influence the deiodinases (as the enzyme system is now known) and thus influence thyroid hormone metabolism.

Since this 1984 Bürgi review, much research has shown (in humans and animals) that fluoride influences deiodination as is observed in the increase of rT3 levels, altered T4/T3 ratios, and elevated TSH levels (e.g. Shashi et al., 2003a, 2003b; Lin et al., 1991, 1992; Liu et al., 2003a, 2003b). Lin has proposed using rT3 levels as a bio marker in endemic fluorosis (Lin, 1992). rT3 levels and D3 activity are of great importance in fetal and neonatal development (Bianco & Kim, 2006).

WHO 1970 – Victor Demole

The WHO 1970 Demole review on the “toxic effects of fluoride on the thyroid” is still one of the most cited reviews in the dental literature as evidence that fluoride does not affect the thyroid (ADA 2005).

For anyone familiar with the history and scientific evidence available, it is astounding how Demole ever got away with this review. For example, Demole denies that any fluoride-iodine antagonism exists, and that fluoride medications used in the treatment of hyperthyroidism (Basedow) were ineffective. Meanwhile, fluorides were used for over 30 years as effective anti-thyroid medications in the treatment of iodine-induced hyperthyroidism, not just in Germany (May 1951, 1950, 1937, 1935, 1932; Litzka 1937a, 1937b; May R, 1950; Casterra, 1947), but other countries as well, including Japan (Inouye et al., 1939, 1938; Hosoi & Okura, 1938), Argentina (e.g. Goldemberg 1926, 1930) and Austria (Gorlitzer von Mundy, 1932,1963). May treated over 10,000 patients in his clinic alone (May R, 1950). Even at levels of 0.9mg – 4.5 mg/F- per day fluoride was effective (Galetti et al., 1958, 1957), a figure well within the intake levels documented in humans in fluoridated areas (US PHS, 1991).

2. OF MICE AND MEN - INTAKE LEVELS RODENTS VS HUMANS

Ever since it was discovered that fluoride was the cause of "mottled teeth" (dental fluorosis), it has been known that rats require at least 10 times more fluoride than humans to produce similar serum levels and dental defects (Smith & Leverton, 1934; Schour & Smith, 1935; ADA 1937; Martínez-Mier et al., 2003; Denbesten & Li, 2011; Bronkers et al., 2009). For this reason, fluoride water concentrations of 25 to 100 ppm are routinely used in rodent model examinations. Dental researchers state that the reason for this is not known (Zhang Y et al., 2014; Denbesten & Li, 2011; Bronkers et al., 2009).

An explanation for this can be easily found: rats have a much higher T4 secretion rate than humans. T4 production rate (rate/kg/bw) is 10 times higher in the rat. TSH levels in rodents are also much higher (6 to 60 times) (EPA, 1998; Choksi, 2003).

It is not understandable how reviews on fluoride toxicology fail to account for this, and apply results from rodent studies to humans as if there were no difference.

NOTE: While dental researchers claim that no toxic effects in rodents can be observed at these fluoride water levels (25 to 100 ppm) (*Bronckers et al., 2009*), the literature lists hundreds of studies (e.g. *Guan, 1988, 1989; Zhao et al., 1998, 1992, 1988; Lu et al., 1998; Li et al., 2012; Cai & Hong, 2010; Zhuan et al., 1994; Liu et al., 2013*).

3. FLUORIDE - THE TSH ANALOGUE

It was noticed that the NTP meeting on December 2, 2015 was held at the Rodbell Auditorium. Martin Rodbell was the brilliant molecular endocrinologist who, together with Alfred Gilman, received the 1994 Nobel Prize in Medicine for their discovery of G proteins. Incidentally, both Rodbell and Gilman used fluoride in their research, which helped define the activity of G proteins, explaining how hormones such as TSH exert their activity. For decades fluoride was used extensively as the “universal G protein activator”, meaning it was able to activate all G protein families.

For many years, fluoride was used in countless investigations, specifically as a TSH analogue, as it was able to produce the exact same effects as TSH.
[see <http://poisonfluoride.com/Science/TSH/tsh.html>]

Fluoride was used extensively in thyroid cancer investigations to help explain why even slightly elevated TSH levels promoted thyroid cancer growth, or how aberrant TSH signalling caused auto-immune thyroid disease (e.g. *Clark & Gehrend, 1995; Orgiazzi et al, 1976; Saltiel et al 1981; Toccafondi et al., 1979; Walinder et al., 1979; Carajon et al., 1978; Macchia et al; Kalderon & Sheth, 1978, Mizukami et al, 1982; Bech and Madsen, 1978*).

Pro-fluoridation groups are quick to dismiss these studies (*ADA 2005*), stating that the amounts of fluoride used in these experiments were hundreds of times higher than would ever be observed in the human organism. They fail to realize that these studies were done in isolated cell environments, and that the TSH levels were also up to 200 times higher. It is now established that, when other regulatory nucleotides are present, mere micromolar amounts (0.01mM) are able to activate G proteins (Gs, G_{q/11}), while higher amounts will inhibit, exactly like TSH in thyroid physiology (e.g. *Jenq et al, 1993*). Fluoride effects are bi-phasic. (NOTE: These levels are lower than those thought to produce dental fluorosis in humans (*Bronckers et al. 2009*). When fluoride is complexed with aluminum or beryllium, effects can be seen in the nanomolar range (e.g. *Misra et al, 2000*).

Fluoride is thus an endocrine disruptor in the true sense of the word - it mimicks TSH activity. All conditions for the Bradford-Hill criteria for causation can be fulfilled.

The TSH receptor (TSHr) is the only known receptor to be able to activate all G protein families (*Laugwitz et al, 1996*). All thyroid hormone activity, iodine uptake, deiodination, etc. is under external TSH control. The TSHr receptor is not only expressed in the thyroid, but has also been identified in liver, retroorbital muscle and fibroblasts, orbital tissue and dermal fibroblasts (*Paschke et al, 1994*), peripheral lymphocytes, fat, cardiac muscle (*Drvota et al, 1995*), gastrointestinal tract (*Duntas et al, 1998*), thymus, peripheral blood mononuclear cells, brain (where it is over-expressed in patients with Down Syndrome or Alzheimer's Disease, *Labudova et al, 1999*), osteoblasts and osteosarcoma cells (*Inoue et al, 1998*).

By understanding TSH and the tissue-specific effects of thyroid hormones, the many observed toxic effects ascribed to fluoride poisoning can be explained - be it in bone, thyroid, teeth, brain, or elsewhere.

4. DENTAL FLUOROSIS & THYROID DYSFUNCTION - BRIEF DISCUSSION

Dental researchers to this date state that the exact mechanisms that lead to the condition of “dental fluorosis” are not yet known (*e.g. Lei et al, 2015; Sierant & Bartlett, 2012; Wright et al, 1996*); yet they declare this defect to be one of “cosmetic concern” only. Considering what is now known about the mechanisms involved in dental fluorosis, it is simply impossible for this to be a “cosmetic defect” only. We have proposed previously that this condition should be seen as a sign that thyroid hormone metabolism has been disturbed at a crucial time of development (*Schuld, 2005*).

Research from China on aborted fetuses in women with fluorosis has provided evidence that dental fluorosis already starts in-utero (*Du et al, 1992; Zhan et al, 1995*) and that there is fetal thyroid damage and brain damage occurring at the same time (*Zhao et al, 2009; Yu Y, 2000; 1999*). Animal experiments have confirmed these findings (*Chang et al, 2002, 1998; 1997; 1991*).

Already in the late 1930s, Prof. DeEds from the University of Stanford was able to cause dental fluorosis in rats by administering either desiccated thyroid (*Wilson & DeEds, 1940*) or TSH (*DeEds, 1940; 1941*).

"Fluorine toxicity is not an isolated problem, but must be considered in relation to the functional state of the thyroid gland." (DeEds, 1941)

In case the NTP is interested, we have a large database with the studies from China. From there, full papers can be accessed. We started it in 2007 to help practitioners in China. It is located at: <http://poisonfluoride.com/phpBB3/viewtopic.php?f=12&t=986>

We will be glad to assist in any way possible.

Sincerely,

Andreas Schuld, Jirong Huang, Vishal Sandhu, Wendy Small
Parents of Fluoride-Poisoned Children (PFPC)

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