NOTE: THIS DOCUMENT WAS REVISED NOVEMBER 14, 2020.
REVISION NOTES CAN BE FOUND AT THE END OF THE DOCUMENT.

October 23, 2020

NASEM Committee to Review the Revised NTP Monograph on Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects
The National Academies of the Sciences, Engineering, and Medicine
500 Fifth St., N.W.
Washington, D.C. 20001
USA

Sent via email to bulrich@nas.edu

Re: Review of the Revised NTP Monograph on Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects

Dear Ben,

We are hereby submitting comments for the Committee's consideration regarding the review of the *Revised NTP Monograph on Systematic Review of Fluoride Exposure and Neurodevelopmental and Cognitive Effects*.

We would like to note that the NTP removed the link to our earlier submission (2016) from their website sometime before the first NASEM review. While our submission is still listed, it is not accessible. For this reason, we are unsure if the 2016 submission was available to the first NASEM review committee, hence we are attaching it to this email.

We would like to thank the Committee for the invitation to submit comments.

Introduction

In a statement released on September 24, 2020, the NASEM presidents warned of political interference in science:

> ***"Policymaking must be informed by the best available evidence without it being distorted, concealed, or otherwise deliberately miscommunicated. At this critical time in the course of the pandemic, any efforts to discredit the best science and scientists threaten the health and welfare of us all."***

We fully agree with this statement and would like to believe that this standard must also apply to public health agencies and monographs such as this one under review.

Ever since 1970, every major review done on the adverse effects of fluoride has distorted, concealed, or otherwise miscommunicated the scientific findings on fluoride effects on thyroid hormone metabolism.

For example, although over 400 studies have been published on this subject since 1980, not one was considered in the EPA's 2010 Report on Dose-Response Analysis for Non-cancer Effects.

Likewise, the EFSA 2013 Scientific Opinion on Dietary Reference Values for Fluoride did not mention the word "thyroid" even once.

A recent review by 31 authors investigating the "totality of currently available scientific evidence", mysteriously missed all human studies on the thyroid - again. Not a single one was considered *(Guth et al., 2020)*.

As the NTP listed many of the earlier reviews in its literature review from 2016, we called attention to some long-standing misrepresentations of the scientific literature in our 2016 submission *(PFPC, 2016; Appendix A)*.

All our comments about the revised NTP monograph pertain to the thyroid issue, as the vast and overwhelming amount of evidence clearly points to thyroid dysfunction being the mechanism to explain the IQ studies under review.

It is firmly established that thyroid hormone deficiency leads to loss of IQ, and many excellent reviews are available on this topic. This knowledge forms the very basis of global efforts to reduce iodine deficiency. TSH levels in infants are tested to reduce the incidence of congenital hypothyroidism, and guidelines for trimester-specific upper TSH limits have been established for pregnant women *(Stagnaro-Green et al., 2011)*. The developing embryo/fetus is at greatest risk because of the dependency on the maternal supply of thyroid hormones (TH).

It is equally established that fluoride affects thyroid hormone metabolism. The literature documenting the effects of fluoride on the thyroid spans over 150 years *(PFPC 2015)*. Out of 250 papers published in the last 20 years, 95% document adverse effects of fluoride on thyroid hormone metabolism *(PFPC, 2020)*.

Those findings are further supported by 40 studies documenting the 30-year long pharmacological use of fluoride as an anti-thyroid drug, specifically to reduce thyroid activity in iodine-induced hyperthyroidism *(PFPC, 2006)*. In addition, there are 70 studies easily available from *in vitro* investigations conducted between 1970 and 1995 documenting the application of fluoride as a TSH analogue. The TSH receptor is the only receptor known to activate all four G-protein families dose-dependently. As a TSH analogue, fluoride may influence all aspects of thyroid hormone metabolism, including iodine organification, thyroid hormone secretion, and synthesis.

We wish for the NASEM Committee to realize that in other parts of the world, such as in China, the effects of fluoride on the thyroid are firmly established and acknowledged to be the cause of abnormal development of the child - including loss of IQ, of course. This knowledge informs public health intervention programs in areas with either iodine deficiency or iodine excess.

In China, many million people are affected by fluoride poisoning as a result of industrial pollution, contaminated water supplies, and indoor coal burning.

Since the late 1980s, fluoride/thyroid issues have been discussed at major Chinese health conferences *(Qiu, 2008; Jin, 1991, 1989; Zhang, 1991)*. Hundreds of studies have been conducted investigating fluoride effects on the thyroid - in humans (adults and children), established animal fluorosis models, as well as in *in vitro* experiments *(PFPC 2014)*. Studies also include investigations on established endocrine disruptor models *(amphibian metamorphosis, Zebrafish)*.

Is is therefore quite astonishing to read the NTP's repeated claim that *"the data do not support a clear indication that thyroid effects are a mechanism by which fluoride causes these effects in humans" (Page 56)*, or that *"no specific mechanism has been determined for fluoride effects on learning and memory or other neurodevelopmental or cognitive outcomes" (Page 65).*

The opposite is true - the data do support a clear indication that thyroid effects are the mechanism by which fluoride causes adverse effects on learning and memory and other neurodevelopment and cognitive outcomes.

Not only have basic mechanisms been demonstrated, but numerous pathways have been identified, right down to a particular intracellular loop of the thyroid-stimulating hormone receptor (TSHr), and the pathways affected downstream from TSHr activation.

Unfortunately, the NASEM Committee did not address the thyroid studies, data collection and discussion in the first NTP Draft review *(NASEM, 2020).*

As a result, no changes have been made in the revised NTP monograph.

We are asking for the Committee to consider this issue with the utmost urgency.

Are the findings documented correctly?

To our disappointment, the NTP misrepresented the scientific results of the fluoride/thyroid studies.

Many instances could be cited as the majority of the thyroid studies have been misrepresented, but by far the most egregious example is the handling of the 2018 study by Dr. Arjun Khandare and colleagues.

The Khandare report is one of the most important studies that presently exist on this issue, for one simple reason - it is the only long-term thyroid/water fluoride study so far that has included an *intervention*.

Khandare et al. *[Department of Food Toxicology, National Institute of Nutrition (ICMR), Ministry of Health and Family Welfare, Gov't of India]* conducted this UNICEF-funded study on school children in India, comparing three areas with increasing amounts of fluoride in the water to a fourth where there was an initial high fluoride level, but then fluoride was removed. TSH and total thyroid hormones (T3, T4) were measured.

The areas were followed for 5 years.

The researchers found that the TSH levels increased dose-dependently with the increase in fluoride. T4 levels were increased, and T3 levels were lowered. In the intervention area the TSH and thyroid hormone (TH) levels returned to values close to the control area.

These findings were unequivocal evidence that fluoride had caused the changes in thyroid hormone metabolism. The removal of fluoride normalized TSH and TH levels.

Table 4 Serum T3, T4, and TSH levels in the school children among all the categories

Category	Mean drinking water fluoride levels (mg/L)	T3 (ng/mL)	T4 ng/mL)	TSH (μIU/mL)
I	0.877 ± 0.108	2.17 ± 0.419	112.69 ± 21.970	1.66 ± 0.487
II	2.53 ± 0.606	1.57 ± 0.357[a]*	116.03 ± 17.321	1.85 ± 0.461
III	3.77 ± 0.197	1.34 ± 0.316[a]*[b]*	132.80 ± 21.901[a]*[b]*	2.65 ± 1.038[a]*[b]*
	The effect of fluoride-free water for 5 years on biochemical parameters			
IV	< 1.0	1.46 ± 0.376[a]*	84.40 ± 21.608[a]*[b]*[c]*	1.58 ± 0.438[c]*
Normal range		0.8 – 2.0	61–118	0.17 to 11.05

*Statistically significant ($p < 0.05$)

[a] Compared to category I

[b] Compared to category II

[c] Compared to category III

TABLE 4: Khandare et al., 2018

The NTP monograph mentions Khandare's important work only once, in passing and only to state the exact **opposite** in regards to TSH levels:

> *"Two of the nine higher risk-of-bias studies reported **decreases in TSH** levels in children with higher fluoride (Khandare et al. 2017, Khandare et al. 2018)." (Page 55)*

This is a misrepresentation of the scientific record and needs to be corrected.

The data tables also contain this incorrect information.

Coincidentally, the findings on T4 and T3 levels by Khandare et al. mirror those found by Zhao et al. *(1998)* in a long term study on mice, results of which were equally distorted into their opposite in the ATSDR Toxicological Profile on Fluoride from 2003. This was addressed in our submission to the NTP from 2016.

Another example is the study by Hosur et al., 2012.

The NTP writes about this study:

> *"One of the nine studies found no significant alterations in TSH levels in children from fluorosis-endemic areas (Hosur et al. 2012)." (Page 58)*

Hosur et al. did not evaluate children from a fluorosis-endemic area. They studied children's TSH and TH levels and compared to the occurrence and severity of dental fluorosis. The majority of the children consumed water at fluoride concentrations of 0.5 to 0.6 ppm. The authors stated:

*"…a **significant** difference was found between TSH levels of moderate and severe fluorosis groups."*

[Note: In the study by Hosur et al., the authors contradict their own findings in their conclusions. This is addressed elsewhere (PFPC 2020c).]

Again, the NTP's interpretation of the data is a misrepresentation of findings and needs to be corrected.

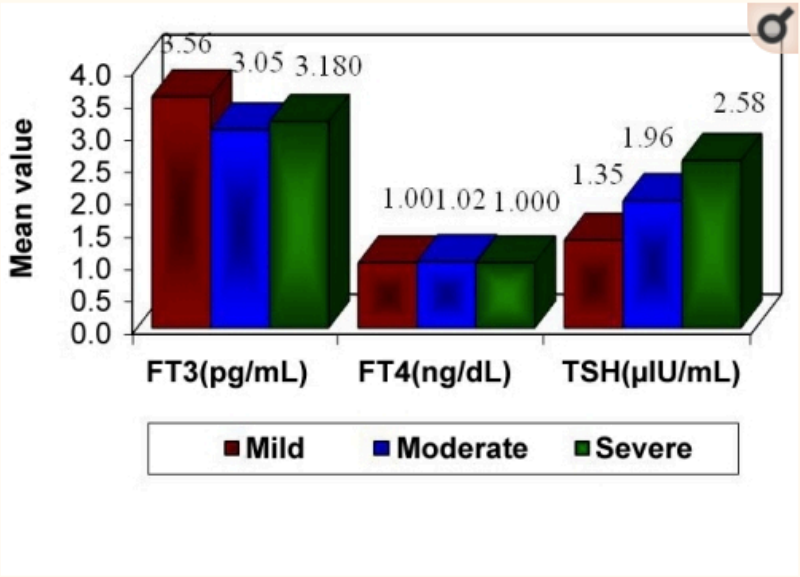


Figure 1.

Hosur et al, 2012: Figure 1 - TSH increase with degree of DF
NOTE: Mild DF = only 4 subjects, Moderate DF = 33, Severe DF = 28
42 dental fluorosis subjects (62%) consumed water with fluoride levels of 0.5–0.6 ppm.
Control area is listed at <1ppm.

Animal Studies

There are two important aspects to discuss concerning the NTP's handling of the animal studies.

1) The reason given for non-evaluation of animal thyroid studies

2) The NTP decision to use a 20 ppm fluoride/water concentration as a cut-off for ALL animal studies.

1) The reason for non-evaluation of animal thyroid studies

The NTP states that the animal studies were not evaluated further because the human studies *"have failed to identify consistent evidence to suggest that thyroid effects are a*

requisite mechanism by which fluoride causes neurodevelopmental or cognitive effects in humans." (Page 65)

The human data did not fail to identify consistent evidence.

Forgetting for a moment that the NTP chose only a very limited number (19) of human studies (there have been 100 studies since 1980) - what was the evidence in the ones they picked?

Out of 14 studies comparing fluoride intake to actual TSH levels *(not reference ranges, like Barberio et al., 2017)*, 11 show an increase in TSH, with 3 studies showing effects beginning at water/fluoride concentrations at or below 0.5 ppm = **85%**.

Out of 8 studies investigating T4 and T3 levels, all 8 show disturbed ratios = **100%**.

Out of 4 studies investigating FT3 and FT4, all 4 show disturbed FT3/FT4 ratios = **100%.**

The FT3/FT4 ratio is used as an index of conversion of T4 to T3 by peripheral deiodinase activity *(Haddow et al., 2014; Pasqualetti et al., 2018; 2020)*.

(The NTP made no effort to calculate ratios, and treated total and free fractions of the thyroid hormones as if they were the same.)

The findings of fluoride causing elevated TSH levels above 2.5 mIU/L at fluoride/water concentrations below 0.5 ppm should be reason enough to re-evaluate all fluoridation programs.

As mentioned earlier, there are trimester-specific guidelines in place for an upper TSH limit of 2.5 mU/L - specifically to protect the fetus from neurological and cognitive defects.

Table 2 The amount of T_4, T_3, and TSH hormones based on two levels of fluoride in drinking water in cases and controls, YGA (Yazd Greater Area), 2017.

From: Impact of Drinking Water Fluoride on Human Thyroid Hormones: A Case- Control Study

Variable	Case median(IR)*		P Value	Control median(IR)*		P Value
	0–0.29 mg/L	0.3–0.5 mg/L		0–0.29 mg/L	0.3–0.5 mg/L	
T_4	6.56 ± 2.2	7.6 ± 4.3	0.17	8.5 ± 1.2	8.6 ± 1.2	0.45
T_3	115.3 ± 22	117.8 ± 36.6	0.19	135 ± 18.4	138.5 ± 21.6	0.026
TSH	11.85 ± 7	20.5 ± 12.8	0.003	2.2 ± 0.95	2.8 ± 0.9	0.001

*IR, Interquartile range. The normal range for T_3 hormone is (78–180 ng/dL). The normal range for T_4 hormone is (5.5–12.5 µg/dL). The normal range for TSH hormone is (0.17–4.5 mIU/L).

Kheradishpeh et al., 2018 Table 2: In healthy control group fluoride at 0.3 to 0.5 ppm elevates TSH levels to 2.8 mIU/L - past the first trimester-specific upper limit of 2.5 mIU/L. For those with thyroid dysfunction (cases on left) the effects are greatly amplified.

2) 20 ppm fluoride/water concentration as a cut-off for ALL animal studies.

The NTP stated:

> *"…review of the mechanistic data was limited to in vivo studies with at least one concentration below 20 ppm. This is not considered a limitation for the systematic review since the mechanistic body of evidence was used to evaluate biological plausibility for the effects observed in humans; therefore, data were limited to concentrations that would be more reflective of human exposures."*

The NTP did not choose concentrations reflective of human exposure.

It is commonly accepted that chronic serum fluoride levels of 2 -12 mumol/ are required to cause dental fluorosis in humans and rodents, although it has been shown to occur at lower serum fluoride levels *(DenBesten, 2011; Bronckers et al., 2009). (Both chronic low doses and high peak doses may produce dental fluorosis.)*

If over one-half of US teens are now affected by dental fluorosis *(Wiener et al., 2018)*, it follows that they would have been exposed to fluoride intake producing serum levels of

2-12 mumol/L at critical periods of development.

To obtain such serum levels in rodents, high fluoride amounts must be given. For example, a fluoride/water concentration of 50 ppm in mice produce a serum fluoride level of 4.2 mumol/L *(Zhang et al. 2014*). Test rodents are routinely given water at fluoride concentrations of 25 to 100 ppm to produce dental fluorosis *(DenBesten, 2011; Bronckers et al., 2009)*.

The NTP based their unrealistic 20 ppm cut-off on erroneous calculations using a study by Dunipace et al., *(1995)* involving male Sprague-Dawley rats. It should be noted that no effects on the thyroid or thyroid hormones were ever investigated in that study.

In Dunipace's study, a 5 ppm fluoride/water concentration did not produce a fluoride serum level of 2 mumol/L, the lower threshold thought to cause DF in humans. The data shows that up to 50 ppm of NaF- are required to produce similar fluoride serum levels in male SD rats to those known to produce DF in humans.

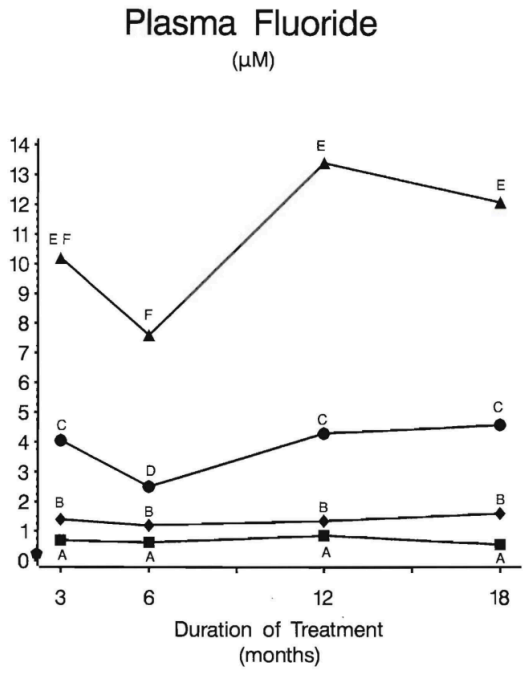


Figure 1. Plasma fluoride (μM) for the different treatment groups. F (ppm): ■■■ 0; ◆◆◆ 5; ●●● 15; ▲▲▲ 50. Baseline data are indicated on the vertical axis. Data designated with similar letters are not significantly different ($p > 0.05$) as determined by REGWQ analyses.

Dunipace et al., 1995 Figure 1: Data shows that concentrations up to 50 ppm water/fluoride concentration are required in male SD rats to produce fluoride/serum levels of 2 to 12 mumol/L - levels that produce dental fluorosis in humans *(Denbesten, 2011; Bronckers et al. 2009)*.

b) All animals are not the same.

The NTP used the 20 ppm fluoride/water concentration cut-off to exclude all animal studies done with higher concentrations - without any consideration given to actual dose, time, or species-specific differences in fluoride tolerance. In its collection of studies below 20 ppm, there are rats, mice, pigs, rabbits, buffalo calves, and Heifers. To presume that a 20 ppm fluoride/water concentration applies equally to all these animals is patently absurd.

Animals react differently to fluoride. This has been established since the 1930s and was addressed by the National Academy of Sciences as early as 1955 *(NAS, 1955)*.

We already described the difference with rodents above.

Chicks have an even higher resistance to fluoride. They require 200 to 300 ppm of fluoride in their feed to cause symptoms of fluorosis *(Weber et al., 1969; NAS, 1955)*.

If the NTP had properly understood the species-specific differences in fluoride tolerance, there would have been a large body of data available, showing fluoride effects on thyroid hormone metabolism in great detail.

In China, a poultry fluorosis model was developed in the early 2000s at Shanghai's Jiao Tong University. Extensive poultry fluorosis had become a major problem due to the use of non-defluorinated dicalcium phosphate as a mineral supplement in the rapidly expanding feed industry.

As a result of the thyroid dysfunction seen in areas with endemic fluorosis, extensive studies were conducted on the effects of fluoride on thyroid hormone metabolism in poultry, including studies on fluoride effects on iodine and thyroid hormone metabolism, thyroid peroxidase activity, structure/ultrastructure of the thyroid, deiodinase activity in liver, and more *(Liu et al., 2001, 2002a, 2002b, 2002c, 2002d, 2003, 2004; Kang et al., 2001).*

These studies should have all been consulted and translated if need be.

It is bewildering that the NTP chose to review animal studies related to oxidative stress, but not the thyroid. Thyroid hormones are the major factor in oxidative stress not only

by their stimulation of metabolism but also by their effects on antioxidant mechanisms *(PFPC 2004, 100 studies).*

In-Vitro Studies

The NTP states:

> *"Although in vitro data were collected as part of the systematic review process, NTP determined that the information on neurological effects obtained from these studies is too general, and results cannot necessarily be attributed to effects on learning and memory or other cognitive functions at this time." (Page 65)*

The NTP listed 60 in-vitro studies, only 10 of which dealt with the thyroid (out of hundreds from the last 40 years), and only a handful of which were documenting fluoride use as a TSH analogue.

In our NTP submission in 2016, we supplied a link to 70 studies documenting only the use of fluoride to substitute for TSH.

Below we present two graphs merely to provide a visual example of the similar effects of fluoride and TSH. The graphs are taken from a 1971 paper by Wolff and Jones describing the effects of TSH and fluoride on adenyl cyclase in purified bovine thyroid membranes.

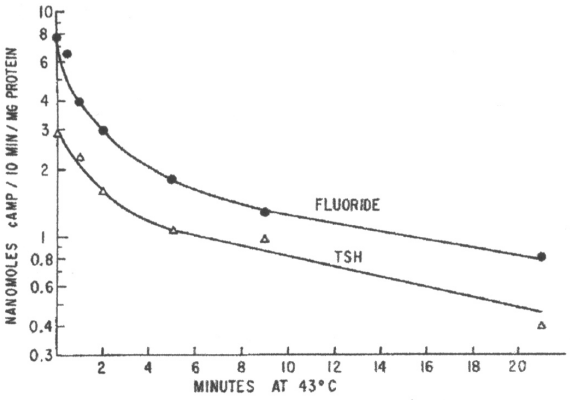
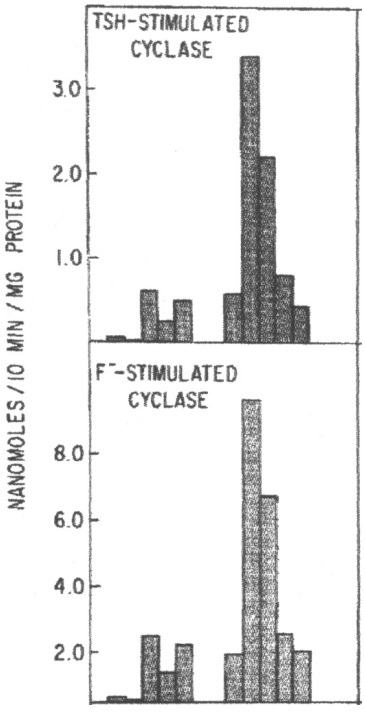


FIG. 3. Inactivation of purified thyroid membrane adenyl cyclase at 43°. Samples were incubated at 43° for the times indicated and were then cooled instantly to 0°. Subsequent assays were carried out in standard fashion with ~10 μg of protein (37% boundary) to start the reaction. TSH was 200 milliunits per ml and F^- was 10 mM.

Wolff & Jones, 1971 - Large doses of NaF and TSH inactivate adenyl cyclase *[G(i) proteins]*



Wolff & Jones, 1971, excerpt from Fig.1

The NTP stated:

> *"Four factors were considered that contribute to increased confidence: potency, dose response, consistency in terms of cellular events observed at the same or lower doses than in vivo health effects, and consistency across cellular targets on the same functional pathway." (Page 20)*

The 70 studies documenting the use of fluoride as a TSH substitute in thyroid investigations have a dose range from 0.01 mM to 15mM.

It is utterly unreasonable to consider only cellular events at the same or lower doses than *in vivo* health effects.

Much higher doses are used in *in vitro* experiments because the levels of TSH receptors are much lower than they ever are *in vivo*. The effects of TSH are dependent on TSH receptor expression and occupancy.

TSH receptor levels in the thyroid are 100-fold higher than *in vitro (Boutin et al., 2020).*

Protocol

The protocol of the NTP monograph is based on a faulty interpretation of the literature and known mechanisms of fluoride effects upon thyroid hormones, as well as misunderstanding the factors leading to loss of IQ. This has resulted in a wrong review design, as well as a flawed assessment of "risk-of-bias".

> "*Although lead and iodine sufficiency are considered potential key covariates due to their potential to be related to neurodevelopmental effects, there is no expectation that they would in general be related to fluoride exposure so should not be considered "probably high RoB" or "definitely high RoB" unless there is a reasonable expectation that these would occur with fluoride exposure and would potentially impact the results."*

Co-exposure of fluoride and iodine occurs in **all** areas. Iodine is an essential element, fluoride is not.

Water Concentration vs Total Intake (Dose)

The NTP relates fluoride effects on thyroid to water concentrations even when the researchers specifically stated that it was TOTAL fluoride amounts in urine and serum that were of significance and had to be considered, NOT just fluoride in water *(Susheela et al., 2005; Zhang et al.. 2015; Singh et al., 2014; Kumar et al., 2018; Yasmin et al., 2013).*

Or that it was serum fluoride and urine fluoride that were inversely related to IQ ($rs=-0.47$, $P<0.01$; $rs=-0.45$, $P=0.002$), not significant results were given for water fluoride ($P=0.08$) *(Zhang et al., 2015).*

Goiter

The NTP did not evaluate any fluoride/goiter studies. The reason:

> *"After review of the studies evaluating thyroid effects, studies that only evaluated goiters and other effects on thyroid size were not considered in this review. This is not considered a limitation because changes in thyroid size are not functional changes to the thyroid that could specifically indicate a mechanism for thyroid involvement in neurodevelopment."* *(Page 79)*

We did not think that one had to ever remind the NTP that an enlarged thyroid or goiter in iodine deficiency (ID) is the result of elevated TSH levels. The occurrence of goiter together with mental retardation (cretinism) is what prompted the first iodized salt programs in Switzerland 100 years ago. The primary role of iodine deficiency in goitrogenesis and the prevention of endemic goiter by iodine supplementation is firmly established *(Gaitan et al., 1991)*. Iodine deficiency is diagnosed by elevated TSH levels. Elevated TSH levels are the reason why so many authors have drawn attention to the fact that fluoride poisoning mimics the effects of iodine deficiency, including studies reviewed in this NTP monograph.

The close link of fluoride and goiter goes back over 150 years *(PFPC, 2015)*. Goiter has been associated with dental fluorosis for over 100 years *(Schuld, 2005)*.

The goiter studies should all be evaluated.

Gq/11

Our research over the last 20 years has identified pathways downstream from Gq/11 activation as the major pathways involved in fluoride toxicity. Activation of the Gq/11 family results in the stimulation of phospholipase C activity, leading to calcium mobilization and protein kinase C activation - pathways highly relevant in neurodevelopment.

Experiments with mice have shown that the Gq/11 pathway is essential for goiter formation *(Kero et al., 2007)*, and that Gq/11 is involved in the condition of dental fluorosis *(Zhang et al., 2014)*. Gq/11 have been unequivocally established to be the transducing G proteins for Ca(2+)-mobilizing receptors *(Exton, 1993)*.

In thyroid physiology, the Gq/11 pathway controls thyroid hormone synthesis and iodide organification.

2018 Study by McPherson et al.

We would like to briefly address this NTP study *(McPherson et al., 2018)*. It is discussed in detail elsewhere *(PFPC 2020b)*.

The NTP considers this study *"the highest quality experimental animal study reviewed for this monograph."* (*Page 58)*

The NTP was to evaluate the effects of an established pharmacological iodine antagonist upon thyroid hormone metabolism and to evaluate effects on learning and memory. The way this study was conducted creates reasons for concern.

- Fluoride in the feed was measured but no attempt was made to measure iodine content in feed or water - a MUST for any such investigation.
- A rat chow was chosen with an iodine content that was **25 times highe**r than the amount in the standard NTP-2000 rodent chow. Excess iodine masks the effects of anti-thyroid substances.
- A rat strain was chosen - Long Evans rats - long known to have a lower iodine sensitivity *(see: Rybnikova et al., 2018; Gilbert et al., 2011; Okamura et al., 1981; Freudenberger, 1932).* The normal TSH level of Long Evans rats is nearly twice as high as that of Sprague-Dawley rats *(Rybnikova et al., 2018)*, and almost three times

as high as Wistar rats. Standard behavioural assays with Long-Evans rats do not readily detect the neurotoxicity induced by modest developmental thyroid hormone deficiency *(Gilbert et al., 2013).*

- Not surprisingly, Long-Evans rats perform better in motor tasks than other strains *(Yanai et al., 1979; Rybnikova et al., 2018),* and perform better at tasks related to learning and memory than SD or Wistar rats *(Andrews et al., 1995). [Most studies on fluoride and thyroid/IQ have used SD and Wistar rats. We only know of one other study that has ever used Long Evans rats in a fluoride/thyroid investigation, conducted in 1955.]*

- Although thyroid was to be the focus, no attempt was made to investigate thyroid tissue, while other tissue was investigated.

- No efforts were made to test at multiple time points. It is firmly established that fluoride effects are dose- and time dependent. Thyroid hormones and fluoride levels were not even measured at the same time, but at dates vastly apart.

- The thyroid data was not interpreted correctly.

- The researchers went on record, claiming falsely that a standard chow was used, and that *"there is no evidence that Long-Evans Hooded rats are differentially sensitive to fluoride exposure, at least from a toxicokinetic perspective." (Harry, 2018).*

This study should not be used to influence public health policy.

Closing Comments:

Studies on the association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology, using the Dutch Rotterdam cohort ("Generation R") have found that both excessive FT4 and TSH during early pregnancy levels are associated with grey matter in children at 10 years old. FT4 was found to have no association after adjusting for intracranial volume, suggesting that TSH might be a more specific predictor for total grey matter and grey matter development than FT4. The association was most evident at 8 weeks and seized at 14 weeks, pinpointing to a crucial timeframe in development *(Jansen et al., 2019; Korevaar et al., 2016)*.

Further, Jansen, Korevaar, and colleagues showed that maternal TSH had an inverted U-shaped association with offspring total grey matter volume and with cortical grey matter volume, and that this association differed by the duration of gestation.

A inverse U response curve is characteristic of TSH activity. It has now been termed an "IUDRC" = inverted U-shaped dose response curve *(see Boutin et al., 2020; Jang et al., 2020)*. It is a typical example of hormesis *(Calabrese, 2018)*.

It is of further interest that the “Generation R” studies also found that there was an inverse association between cord blood and early childhood TSH concentrations with the dental development of the child *(Vucic et al., 2017).*

A recent study investigating thyroid function, intelligence, and low-moderate fluoride exposure among Chinese school-aged children found significant modification effect by TSH on the association between urinary fluoride and IQ scores. TSH level was identified as an independent risk factor for IQ loss *(Wang et al., 2020)*.

The thyroid data from three studies provide evidence that even in areas with water fluoride concentrations of <0.5 ppm, TSH levels can be elevated beyond the upper limit of 2.5 mIU/L set for pregnant women for the first trimester *(Kheradpisheh, 2018; Hosur et al., 2012; Lin et al., 1991).*

In a perfect world, this should prompt health warnings to all fluoridated areas and areas with high fluoride/water concentrations. Considering that some of the documented effects of thyroid deficiency already occur within the first month of pregnancy, a pre-conception screening program in such areas should be considered.

- The available mechanistic data provide strong support for biological plausibility of the relationship between exposure and the health effects, hence the hazard identification conclusion should be upgraded from “presumed” to “known”, beginning at exposure levels from fluoride in water at concentrations of 0.3 ppm (mg/L).

We hope that our comments will be helpful for the Committee’s review of the revised NTP monograph.

Andreas Schuld, Wendy Small

PFPC Canada
The Fluoride Education Project
https://poisonfluoride.com/

REFERENCES

Andrews JS, Jansen JH, Linders S, Princen A, Broekkamp CL - "Performance of four different rat strains in the autoshaping, two-object discrimination, and swim maze tests of learning and memory" Physiol Behav 57(4):785-90 (1995)
https://pubmed.ncbi.nlm.nih.gov/7777618/

ATSDR – Toxicological Profile for Fluorides, Hydrogen Fluoride, and Fluorine (September 2003)
http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=212&tid=38
https://truthdecay.net/wp-content/uploads/2020/06/EFSA-2013.pdf

Bronckers AL, Lyaruu DM, DenBesten PK - "The impact of fluoride on ameloblasts and the mechanisms of enamel fluorosis" J Dent Res 88(10):877-93 (2009)
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3318083

Boutin A, Neumann S, Gershengorn MC - "Multiple Transduction Pathways Mediate Thyrotropin Receptor Signaling in Preosteoblast-Like Cells" Endocrinology 157(5):2173-81 (2016)
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7024874/

Boutin A, Krieger CC, Marcus-Samuels B, Klubo-Gwiezdzinska J, Neumann S, Gershengorn MC - "TSH Receptor Homodimerization in Regulation of cAMP Production in Human Thyrocytes in vitro" Front Endocrinol (Lausanne) 11:276 (2020)
https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/32425890/

Boutin A, Neumann S, Gershengorn MC - "TSH Elicits Cell-Autonomous, Biphasic Responses: A Mechanism Inhibiting Hyperstimulation" Endocrinology 1;161(8):bqaa103 (2020)

Calabrese EJ - "Hormesis: Path and Progression to Significance" Int J Mol Sci 19(10):2871 (2018)
https://pubmed.ncbi.nlm.nih.gov/30248927/

DenBesten P, Li W - “Chronic fluoride toxicity: dental fluorosis” Monogr Oral Sci 22:81-96 (2011)

EPA (Environmental Protection Agency) – “Fluoride: Dose-Response Analysis for Noncancer Effects” EPA-820-R-10-019. Office of Water, U.S. Environmental Protection Agency (2010)

Exton JH - "Role of G proteins in activation of phosphoinositide phospholipase C" Adv Second Messenger Phosphoprotein Res 28:65-72 (1993)
https://pubmed.ncbi.nlm.nih.gov/8398419/

Freudenberger CB - "A comparison of the Wistar albino and the Long-Evans hybrid strain of the Norway rat" Am J Anat 50:293-349 (1932)

Gaitan E, Nelson NC, Poole GV - "Endemic goiter and endemic thyroid disorders" World J Surg 15(2):205-15 (1991)
https://pubmed.ncbi.nlm.nih.gov/2031356/

Gilbert ME, McLanahan ED, Hedge J, Crofton KM, Fisher JW, Valentín-Blasini L, Blount BC - "Marginal iodide deficiency and thyroid function: dose-response analysis for quantitative pharmacokinetic modeling" Toxicology 283(1):41-8 (2011)

Guth S, Hüser S, Roth A, Degen G, Diel P, Edlund K, Eisenbrand G, Engel KH, Epe B, Grune T, Heinz V, Henle T, Humpf HU, Jäger H, Joost HG, Kulling SE, Lampen A, Mally A, Marchan R, Marko D, Mühle E, Nitsche MA, Röhrdanz E, Stadler R, van Thriel C, Vieths S, Vogel RF, Wascher E, Watzl C, Nöthlings U, Hengstler JG - "Toxicity of fluoride: critical evaluation of evidence for human developmental neurotoxicity in epidemiological studies, animal experiments and in vitro analyses" Arch Toxicol 94(5):1375-1415 (2020)
https://pubmed.ncbi.nlm.nih.gov/32382957/

Haddow JE, Craig WY, Neveux LM, Haddow HR, Palomaki GE, Lambert-Messerlian G, Malone FD, D'Alton ME; First and Second Trimester Risk of Aneuploidy (FaSTER) Research Consortium - “Implications of High Free Thyroxine (FT4) concentrations in euthyroid pregnancies: the FaSTER trial” J Clin Endocrinol Metab 99(6):2038-44 (2014)

Hosur MB, Puranik RS, Vanaki S, Puranik SR - "Study of thyroid hormones free triiodothyronine (FT3), free thyroxine (FT4) and thyroid stimulating hormone (TSH) in subjects with dental fluorosis" Eur J Dent 6 (2):184-90 (2012)
https://www.ncbi.nlm.nih.gov/pubmed/22509122

Jang D, Morgan SJ, Klubo-Gwiezdzinska J, Banga JP, Neumann S, Gershengorn MC - "Thyrotropin, but Not Thyroid-Stimulating Antibodies, Induces Biphasic Regulation of Gene Expression in Human Thyrocytes" Thyroid 30(2):270-276 (2020)
https://www.liebertpub.com/doi/full/10.1089/thy.2019.0418

Jedeon K, Houari S, Loiodice S, Thuy TT, Le Normand M, Berdal A, Babajko S - "Chronic Exposure to Bisphenol A Exacerbates Dental Fluorosis in Growing Rats" J Bone Miner Res 31(11):1955-1966 (2016)
https://asbmr.onlinelibrary.wiley.com/doi/full/10.1002/jbmr.2879

Harry J - Letter to the editor (Dr Kostrzewa) of Neurotoxicity Research, July 5, 2018
https://americanfluoridationsociety.org/1363-2/

Ho B - "Excessive fluoride in feed and poultry poisoning" Agricultural Science and Technology and Information, Issue #10 (2004)

Jansen TA, Korevaar TIM, Mulder TA, White T, Muetzel RL, Peeters RP, Tiemeier H - "Maternal thyroid function during pregnancy and child brain morphology: a time window-specific analysis of a prospective cohort" Lancet Diabetes Endocrinol 7(8):629-637 (2019)
https://pubmed.ncbi.nlm.nih.gov/31262704/

Jedeon K, De la Dure-Molla M, Brookes SJ, Loiodice S, Marciano C, Kirkham J, Canivenc-Lavier MC, Boudalia S, Bergès R, Harada H, Berdal A, Babajko S - "Enamel defects reflect perinatal exposure to bisphenol A" Am J Pathol 183(1):108-18 (2013)
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3703547/

Jin ZS - "Iodine and fluoride in water and endemic cretinism" [A] Fourth National Iodine Deficiency Disorders Conference Papers, Harbin: Chinese Journal of Medicine editorial department (247) (1991)

Kang SL Liu GY, Chai CY - "Effects of fluoride on the metabolism of iodine in thyroid in chicken" Progress In Veterinary Medicine (3) (2001)
http://poisonfluoride.com/phpBB3/viewtopic.php?p=671

Kero J, Ahmed K, Wettschureck N, Tunaru S, Wintermantel T, Greiner E, Schütz G, Offermanns S - "Thyrocyte-specific Gq/G11 deficiency impairs thyroid function and prevents goiter development" J Clin Invest 117(9):2399-407 (2007) doi: 10.1172/JCI30380. PMID: 17694176; PMCID: PMC1937498.
https://pubmed.ncbi.nlm.nih.gov/17694176/

Khandare AL, Validandi V, Gourineni SR, Gopalan V, Nagalla B - "Dose-dependent effect of fluoride on clinical and subclinical indices of fluorosis in school going children and its mitigation by supply of safe drinking water for 5 years: An Indian study" Environ Monit Assess. 190(3):110 (2018)
https://link.springer.com/article/10.1007%2Fs10661-018-6501-1

Koulouri O, Moran C, Halsall D, Chatterjee K, Gurnell M - "Pitfalls in the measurement and interpretation of thyroid function tests" Best Pract Res Clin Endocrinol Metab 27(6):745-62 (2013)

Kumar V, Chahar P, Kajjari S, Rahman F, Bansal DK, Kapadia JM - "Fluoride, Thyroid Hormone Derangements and its Correlation with Tooth Eruption Pattern Among the Pediatric Population from Endemic and Non-endemic Fluorosis Areas" J Contemp Dent Pract 19(12):1512-1516 (2018) PubMed PMID: 30713182
https://pubmed.ncbi.nlm.nih.gov/30713182/

Laugwitz KL, Allgeier A, Offermanns S, Spicher K, Van Sande J, Dumont JE, Schultz G - "The human thyrotropin receptor: a heptahelical receptor capable of stimulating members of all four G protein families" Proc Natl Acad Sci U S A 93(1):116-20 (1996)
http://www.pnas.org/cgi/pmidlookup?view=long&pmid=8552586

Liu G, Kang SH - "Effects of fluoride on the structure of chicken thyroid" Chin J Endemiology 20(2):90-93 (2001)
http://poisonfluoride.com/phpBB3/viewtopic.php?t=460

Liu G, Kang SH, Chai CY - "Effects of fluoride on the ultrastructure of thyroid in chicks" Chinese Journal of Veterinary Science 22(5) (2002a)
http://poisonfluoride.com/phpBB3/viewtopic.php?p=1293

Liu G, Kang SH, Chai CY - "Effects of fluoride on thyroid hormone metabolism in chickens" Chinese Journal of Veterinary Science 22 (1) (2002b)
http://poisonfluoride.com/phpBB3/viewtopic.php?p=1232

Liu G, Kang SH, Chai CY - "Effects of fluoride on thyroid peroxidase activity of chicken" Chinese Journal of Veterinary Science and Technology (5)(2002c)
http://poisonfluoride.com/phpBB3/viewtopic.php?p=649

Liu G, Kang SH, Chai CY - "Effects of fluoride on the structure of thyroid parafollicular cell in chicks" Animal Husbandry & Veterinary Medicine 34(9) (2002d)
http://poisonfluoride.com/phpBB3/viewtopic.php?p=623

Liu GY, Chai CY, Kang SL - "Effects of fluoride on the activity of deiodinase in the liver of chickens" Chin J Vet Med 39:14-5 (2003)
http://poisonfluoride.com/phpBB3/viewtopic.php?t=567

McPherson CA, Zhang G, Gilliam R, Brar SS, Wilson R, Brix A, Picut C, Harry GJ - "An Evaluation of Neurotoxicity Following Fluoride Exposure from Gestational Through Adult Ages in Long-Evans Hooded Rats" Neurotox Res 34(4):781-798 (2018)
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6077107/

Moog NK, Entringer S, Heim C, Wadhwa PD, Kathmann N, Buss C - “Influence of maternal thyroid hormones during gestation on fetal brain development” Neuroscience 342:68-100 (2017)
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4819012/

National Academies of Sciences - "The Fluorosis Problem in Livestock Production: Chapter: Safe levels of fluorine in livestock rations" (1955)
https://www.nap.edu/read/21251/chapter/7

NASEM - "NAS and NAM Presidents Alarmed By Political Interference in Science Amid Pandemic" Statement, September 24, 2020
https://www.nationalacademies.org/news/2020/09/nas-and-nam-presidents-alarmed-by-political-interference-in-science-amid-pandemic

NAS - "On Being a Scientist: A Guide to Responsible Conduct in Research" 3rd ed. Committee on Science, Engineering, and Public Policy, National Academy of Science, National Academy of Engineering, and Institute of Medicine of the National Academies, Washington (DC): National Academies Press (US) (2009)
https://www.ncbi.nlm.nih.gov/books/NBK214564/

NASEM - "NAS and NAM Presidents Alarmed By Political Interference in Science Amid Pandemic" Statement, September 24, 2020
https://www.nationalacademies.org/news/2020/09/nas-and-nam-presidents-alarmed-by-political-interference-in-scince-amid-pandemic

National Academies of Sciences, Engineering, and Medicine; Division on Earth and Life Studies; Board on Environmental Studies and Toxicology; Exposure and Neurodevelopmental and Cognitive Health Effects; Committee to Review the NTP Monograph on the Systematic Review of Fluoride - “Review of the Draft NTP Monograph: Systematic Review of Fluoride Exposure and Neurodevelopmental and

Cognitive Health Effects" Washington (DC): National Academies Press (US); 2020 Mar 5. (2020)
https://pubmed.ncbi.nlm.nih.gov/32200598/

National Research Council (US) Committee on Applications of Toxicogenomic Technologies to Predictive Toxicology. Washington (DC): National Academies Press (US) (2007)

Neustaeter B - "Scientists call for independent probe of Canadian professor's research linking fluoride to lower IQ" CTV News, October 8, 2020

Okamura K, Taurog A, Krulich L - "Strain differences among rats in response to Remington iodine-deficient diets" Endocrinology 109(2):458-63 (1981)
https://pubmed.ncbi.nlm.nih.gov/7250050/

Pasqualetti G, Schirripa M, Dochy E, Fassan M, Ziranu P, Puzzoni M, Scartozzi M, Alberti G, Lonardi S, Zagonel V, Monzani F, Loupakis F - "Thyroid hormones ratio is a major prognostic marker in advanced metastatic colorectal cancer: Results from the phase III randomised CORRECT trial" Eur J Cancer 133:66-73 (2020)

Pasqualetti G, Calsolaro V, Bernardini S, Linsalata G, Bigazzi R, Caraccio N, Monzani F - "Degree of Peripheral Thyroxin Deiodination, Frailty, and Long-Term Survival in Hospitalized Older Patients." J Clin Endocrinol Metab 103(5):1867-1876 (2018)
https://pubmed.ncbi.nlm.nih.gov/29546287/

Peckham S, Lowery D, Spencer S - "Are fluoride levels in drinking water associated with hypothyroidism prevalence in England? A large observational study of GP practice data and fluoride levels in drinking water" J Epidemiol Community Health 69(7):619 (2015)
http://jech.bmj.com/content/early/2015/02/09/jech-2014-204971.short

PFPC - The Thyroid & Oxidative Stress - 100 Studies (2004)
https://poisonfluoride.com/Oxidative_Stress/Oxidative_Stress___TH/oxidative_stress___th.html

PFPC - "History of the Fluoride - Iodine Antagonism" (2015)
https://poisonfluoride.com/History/history_0.html

PFPC - NTP Submission (2016)
https://poisonfluoride.com/NTP-Jan-8-2016-PFPC-4.pdf

PFPC - Fluoride=TSH [70 studies] (2003)
https://poisonfluoride.com/Science/TSH/tsh.html

PFPC - "Fluoride use as anti-thyroid medication" (2006)
https://poisonfluoride.com/phpBB3/viewtopic.php?f=7&t=2800

PFPC - Recent Research - Fluoride/Thyroid - 250 Papers (2020)
https://poisonfluoride.com/phpBB3/viewtopic.php?f=7&t=1345

PFPC - Comments on the study by McPherson et al. (2020b)
https://poisonfluoride.com/phpBB3/viewtopic.php?f=7&t=2099

PFPC - Comments on the study by Hosur et al., 2012 (2020c)
https://poisonfluoride.com/phpBB3/viewtopic.php?f=7&t=2389

PFPC - A Survey of the Chinese Literature: Fluoride & Thyroid [200+ studies] (2014)
https://poisonfluoride.com/phpBB3/viewtopic.php?f=12&t=218

PFPC - TSH within "Normal" Range: Adverse Effects (2020d)
https://poisonfluoride.com/phpBB3/viewtopic.php?f=7&t=2300

Qiu Yanhong et al. - "Effects of fluoride on rat thyroid function and cognitive abilities" Proceedings, First International Integrative Medicine Conference and Academic Endocrine and Metabolic Diseases Diabetes Forum (2008)
http://poisonfluoride.com/phpBB3/viewtopic.php?p=1268

Rybnikova EA, Vetrovoi OV, Zenko M Yu - "Comparative Characterization of Rat Strains (Wistar, Wistar–Kyoto, Sprague Dawley, Long Evans, LT, SHR, BD-IX) by Their Behavior, Hormonal Level and Antioxidant Status" Journal of Evolutionary Biochemistry and Physiology 54:374–382 (2018)

Schuld A - "Is dental fluorosis caused by thyroid hormone disturbances?"
Fluoride 38(2):91-94 (2005)
http://www.fluorideresearch.org/382/files/38291-94.pdf

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 3:7 (2014)
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3890436/

Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R, Nixon A, Pearce EN, Soldin OP, Sullivan S, Wiersinga W; American Thyroid Association Taskforce on Thyroid Disease During Pregnancy and Postpartum. - "Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum" Thyroid 21(10):1081-125 (2011)
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3472679/

Susheela AK, Bhatnagar M, Vig K, Mondal AK - "Excess fluoride ingestion and thyroid hormone derangements in children living in Delhi, India" Fluoride 38(2):151-161 (2005)
http://www.fluorideresearch.org/382/files/38298-108.pdf

Villanueva I, Alva-Sánchez C, Pacheco-Rosado J - "The role of thyroid hormones as inductors of oxidative stress and neurodegeneration" Oxid Med Cell Longev 2013:218145 (2013)
https://www.hindawi.com/journals/omcl/2013/218145/

Vucic S, Korevaar TIM, Dhamo B, Jaddoe VWV, Peeters RP, Wolvius EB, Ongkosuwito EM - "Thyroid Function during Early Life and Dental Development" J Dent Res. 96(9):1020-1026 (2017)

Wang M, Liu L, Li H, Li Y, Liu H, Hou C, Zeng Q, Li P, Zhao Q, Dong L, Zhou G, Yu X, Liu L, Guan Q, Zhang S, Wang A - "Thyroid function, intelligence, and low-moderate fluoride exposure among Chinese school-age children" Environ Int 134:105229 (2020)
https://pubmed.ncbi.nlm.nih.gov/31698198/

Weber CW, Doberenz AR, Reid BL - "Fluoride toxicity in the chick" Poult Sci 48(1):230-5 (1969)

Wiener RC, Shen C, Findley P, Tan X, Sambamoorthi U - "Dental fluorosis over time: a comparison of National Health and Nutrition Examination Survey data from 2001–2002 and 2011–2012" J Dent Hyg 92(1):23–9 (2018)
https://pubmed.ncbi.nlm.nih.gov/29500282/

Yanai J - "Strain and sex differences in the rat brain" Acta Anat (Basel) 103(2):150-8 (1979)

Yasmin S, Ranjan S, Hilaluddin, D'Souza D - "Effect of excess fluoride ingestion on human thyroid function in Gaya region, Bihar, India" Toxicological & Environmental Chemistry 95(7): 1235-1243 (2013)
https://www.tandfonline.com/doi/abs/10.1080/02772248.2013.847619

Yildirim Simsir I, Cetinkalp S, Kabalak T - "Review of Factors Contributing to Nodular Goiter and Thyroid Carcinoma" Med Princ Pract 29(1):1-5 (2020)
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7024874/

Zhang Y, Kim JY, Horst O, Nakano Y, Zhu L, Radlanski RJ, Ho S, Den Besten PK - "Fluorosed mouse ameloblasts have increased SATB1 retention and Gαq activity" PLoS One 9(8):e103994 (2014)
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4121220/

Zhang S, Zhang X, Liu H, Qu W, Guan Z, Zeng Q, Jiang C, Gao H, Zhang C, Lei R, Xia T, Wang Z, Yang L, Chen Y, Wu X, Cui Y, Yu L, Wang A - "Modifying effect of COMT gene polymorphism and a predictive role for proteomics analysis in children's intelligence in endemic fluorosis area in Tianjin, China" Toxicol Sci 144(2):238-45 (2015)
https://academic.oup.com/toxsci/article/144/2/238/1716015

Zhao W, Zhu H, Yu Z, Aoki K, Misumi J, Zhang X - "Long-term Effects of Various Iodine and Fluorine Doses on the Thyroid and Fluorosis in Mice" Endocr Regul 32 (2):63-70 (1998)
https://www.sav.sk/journals/endo/full/er0298a.pdf

Zimmermann MB - "Research on iodine deficiency and goiter in the 19th and early 20th centuries" J Nutr 138(11):2060-3 (2008)

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November 4, 2020:

REVISIONS made to original document since Oct. 26, 2020

1) The following sentence (Pg. 3):

"This knowledge informs public health intervention programs in areas with either iodine deficiency and or iodine excess."

was changed to:

"This knowledge informs public health intervention programs in areas with either iodine deficiency or iodine excess."

2) The following sentence (Pg. 17):

The available mechanistic data provide strong support for biological plausibility of the relationship between exposure and the health effects, hence the hazard identification conclusion should be upgraded from "presumed" to "known", at exposure levels of <0.5 ppm.

was changed to:

The available mechanistic data provide strong support for biological plausibility of the relationship between exposure and the health effects, hence the hazard identification conclusion should be upgraded from "presumed" to "known", beginning at exposure levels from fluoride in water at concentrations of 0.3 ppm (mg/L).

November 14, 2020

Further REVISIONS made to original document sent Oct. 26, 2020

3) The following sentence (Pg. 17):

"The thyroid data from three studies provide evidence that even in areas with water fluoride concentrations <5 ppm, TSH levels can be elevated beyond the upper limit of 2.5 mIU/L set for pregnant women for the first trimester *(Kheradpisheh, 2018; Hosur et al., 2012; Lin et al., 1991)*."

was changed to:

"The thyroid data from three studies provide evidence that even in areas with water fluoride concentrations of <0.5 ppm, TSH levels can be elevated beyond the upper limit of 2.5 mIU/L set for pregnant women for the first trimester *(Kheradpisheh, 2018; Hosur et al., 2012; Lin et al., 1991)".*

4) The following sentence (Pg. 14):

"The NTP relates fluoride effects on thyroid in relation to water concentrations even when the researchers specifically stated that it was TOTAL fluoride amounts in urine and serum that were of significance and had to be considered, NOT just fluoride in water (*Susheela et al., 2005; Zhang et al.. 2015; Singh et al., 2014; Kumar et al., 2018; Yasmin et al., 2013)*."

was changed to:

"The NTP relates fluoride effects on thyroid to water concentrations even when the researchers specifically stated that it was TOTAL fluoride amounts in urine and serum that were of significance and had to be considered, NOT just fluoride in water *(Susheela et al., 2005; Zhang et al.. 2015; Singh et al., 2014; Kumar et al., 2018; Yasmin et al., 2013).”*

5) The following sentence (Pg. 8):

“Out of 14 studies investigating comparing fluoride to actual TSH levels (not reference ranges, like Barberio et al., 2017), 11 show an increase in TSH, with 3 studies showing effects beginning at water/fluoride concentrations at or below 0.5 ppm = **85%**.”

was changed to:

*“*Out of 14 studies comparing fluoride intake to actual TSH levels *(not reference ranges, like Barberio et al., 2017)*, 11 show an increase in TSH, with 3 studies showing effects beginning at water/fluoride concentrations at or below 0.5 ppm = **85%**.”

6) The following sentence (Pg. 14):

“Co-exposure of fluoride and iodine exposure occurs in **all** areas. Iodine is essential.”

was changed to:

“Co-exposure of fluoride and iodine occurs in **all** areas. Iodine is an essential element, fluoride is not.”

7) The following sentence (Pg. 13):

"TSH receptor levels in the thyroid are 100-fold higher (*Boutin et al., 2020)*."

was changed to:

“TSH receptor levels in the thyroid are 100-fold higher than *in vitro (Boutin et al., 2020).”*