May 25, 2023

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Dear Dr. Woychik,

We are reaching out to you with utmost urgency to draw your attention to numerous critical flaws present in the NTP *Draft State of the Science Monograph* and *Draft Meta-Analysis Manuscript on Fluoride*. These issues are of such significance that we strongly advocate for the postponement of publication, allowing for the correction of errors and a thorough reevaluation of existing data.

Please note that this is our third submission in this regard.

In 2016, upon the initial release of the NTP literature review, we submitted our first concerns, highlighting longstanding misrepresentations of scientific literature in past reviews *(PFPC, 2016)*. Furthermore, we provided information on the underlying mechanism involved.

In 2020, we made a submission to the National Academy of Sciences, Engineering, and Medicine (NASEM), calling attention to numerous errors present in the draft monograph. Additionally, we provided extensive information regarding the impact of fluoride on thyroid hormone metabolism, including its historical utilization as a primary treatment for iodine-induced hyperthyroidism *(PFPC, 2020)*. Both documents are herein incorporated as references.

Unfortunately, the errors were never corrected, and they persist to this day.

While NASEM was initially tasked with assessing whether the monograph accurately reflected the scientific literature and documented the findings correctly, it later stated that it did not independently evaluate the evidence or conduct a data audit, as it deemed these tasks "beyond its scope"*(NASEM, 2020)*.

The Board of Scientific Counselors (BSC), likewise, did not offer any independent peer review but merely evaluated the adequacy of NTP responses to previous external peer reviews.

Hence, a fundamental and crucial issue has remained unnoticed and unaddressed.

The most important confounder/effect modifier has not been correctly accounted for - **iodine status** *("iodine sufficiency")*.

Protocol Revisions

In the original protocol, "iodine sufficiency" was identified as a critical confounder, but was not treated as such in the draft monograph which merely listed "*iodine deficiency or excess as a potential confounding variable"*.

In its first peer review of the monograph, NASEM had criticized the NTP for this:

> *"In the monograph, however, iodine deficiency or excess is listed as a potential confounding variable that might be considered important but not necessary; this is a major difference from the protocol, and it is unclear why it changed."*
> *(NASEM, 2020)*

According to the original protocol, failure to consider iodine sufficiency across the exposure groups would have led to studies being rated as having a "probably high risk-of-bias" or "definitely high risk-of-bias" rating.

NASEM highlighted that the protocol required studies to provide quantitative summaries of the covariate and adjust for it in the analysis in order to receive a low bias rating. However, the so-called "high-quality" studies did not adhere to this criterion.

In response to the criticism, instead of following the original protocol, the NTP decided to revise the protocol. As a result, iodine sufficiency was no longer considered a key confounder but was categorized as a "potential key covariate."

In the revised version, NTP claimed that there is no general relationship expected between iodine sufficiency and fluoride exposure. However, they also acknowledged the significance of fluoride coexposure with iodine sufficiency in areas where such coexposures are likely.

These statements are evidently illogical. It is an indisputable fact that iodine, being an element essential for thyroid hormone production, invariably co-occurs with fluoride exposure in the case of every individual.

Furthermore, fluoride effects are directly dependent on the individual's iodine/thyroid status.

The Fluoride-Iodine Antagonism

First recognized 170 years ago, the *fluoride-iodine antagonism* came to prominence in the 1910s when it was discovered that many goiterous regions deemed "iodine-deficient" were, in fact, "fluoride-excessive" *(Goldemberg, 1919; for reviews, see: DeEds, 1933; Roholm, 1937)*. This discovery prompted researchers to further explore the use of fluoride for treating **iodine-induced** hyperthyroidism, also known as Basedow Disease. The prevalence of this condition had increased due to the introduction of large-scale iodine supplementation programs.

When subsequent pharmacodynamic evaluations returned positive results, numerous fluoride compounds, both inorganic and organic, were used extensively for several decades in the treatment for this condition.

The fact that fluoride was used specifically for **iodine-induced** hyperthyroidism should have sufficed as compelling evidence of the antagonism's existence, and therefore its importance in any toxicological assessment of fluoride effects on thyroid function and neurodevelopment. More than 650 papers have been published documenting the effects of fluoride on thyroid hormone metabolism, with over 275 papers published in the last two decades alone. Fluoride effects on deiodination in peripheral tissue have long been identified as a primary mechanism, and reverse T3 (rT3) - produced almost exclusively outside the thyroid gland - is used as a biomarker in fluoride poisoning. Furthermore, the historical use of fluoride as an anti-thyroid/ anti-iodine medication has produced a wealth of evidence on pharmacodynamics.

As mentioned above, we have called attention to this matter in our previous submissions, but to no avail.

As iodine is the essential component of thyroid hormone, and thyroid hormone, in turn, is essential for neurodevelopment *(Bernal, 2022)*, the *fluoride-iodine antagonism* should have been the main relationship considered, and the protocol should have never been changed.

How does the fluoride-iodine antagonism manifest?

1. In situations of elevated iodine intake, a greater quantity of fluoride is necessary to counteract the effects of excessive iodine exposure on thyroid function. If fluoride intake is greatly exceeded, some effects of excessive iodine intake might be augmented by fluoride. This explains why certain studies demonstrate a threshold in IQ assessment based on urinary fluoride levels *(Yu et al., 2018, 2021; Bashash et al., 2017)*. It is also likely the reason behind the reported "beneficial" impact of low fluoride on IQ in scenarios where iodine intake is high *(An et al., 2018; Du et al., 2019; Ibarluzea et al., 2021; Thomas, 2014)*.

2. When fluoride exposure is low, and iodine exposure *more-than-adequate* or *excessive*, it is iodine toxicity that is predominant *(e.g., MIREC data)*.

3. When iodine intake is low, very low amounts of fluoride may greatly exacerbate the adverse effects of iodine deficiency *(e.g., Lin et al., 1991)*. Fluoride toxicity will be predominant.

4. When iodine intake is sufficient, even low amounts of fluoride may affect thyroid function. These effects will often be bi-phasic *(nonlinear U/reverse U-shape)* - stimulatory /inhibitory - and may vary based on dose, duration, race, age and sex.

The continued failure by the NTP to consider the fluoride-iodine relationship appropriately has now led to the following situation:

Fluoride is implicated as the cause of IQ loss in specific regions despite abundant evidence indicating that excessive iodine intake is the primary factor responsible.

It is well-established that both iodine deficiency and iodine excess may produce thyroid dysfunction such as subclinical hypothyroidism and auto-immune thyroid disease, resulting in thyroid hormone deficiency. Likewise, iodine deficiency/excess may cause hyperthyroidism, resulting in thyroid hormone excess. Iodine effects on thyroid dysfunction are observed in a U-shape with the "optimal" iodine intake residing within a rather narrow window *(e.g., Laurberg et al., 2009, 2010; Wang et al., 2019; Zhang et al., 2022; Fan et al., 2018)*.

Pregnant women, fetuses, and neonates are highly sensitive to the inhibitory effects of excess iodine *(Kalarani & Veerabathiran, 2022)*.

While the NTP went to great lengths to determine potential exposures to arsenic when studies themselves did not disclose this information, even consulting groundwater maps, it undertook no such efforts when it came to determining iodine exposure - certainly a much more important and pressing concern for any fluoride toxicity investigation.

Had these efforts been made, it would have been realized that the vast majority of the "high quality" fluoride/IQ studies from the last 10 years and included in the NTP report were done under conditions of *more-than-adequate* and *excessive* iodine intake, in both mothers and children.

This includes the 12 studies conducted in Tianjin *(China)*, the MIREC studies *(Canada)*, as well as the ELEMENT studies *(Mexico)*.

Tianjin Studies

It appears that the NTP was satisfied that "iodine was considered" when the authors merely stated that the areas under investigation were not "iodine-deficient". That **excessive** iodine might have been a factor to account for was never truly considered by the NTP, even when authors did supply iodine status data and reported the association - as is the case in a few of the Tianjin studies (*e.g., Cui et al., 2020)*.

> *The proportion of people with low average and lower intelligence in UIC ≥ 300 μg/L group was significantly higher than that in control group."* *(Cui et al., 2020)*

If the high iodine group is identical to the high fluoride group - as is the case in Cui et al. *(2020, 2018)*, and other Tianjin studies - how did the NTP determine that it was fluoride responsible for any loss of IQ, and not iodine? Did the NTP come up with some kind of fluoride-iodine ratio calculation that helped it make such a conclusion? Why did the NTP assess data presuming

fluoride was the cause, even when authors concluded that it was excess iodine that was the likely principal factor *(e.g., Hong et al., 2001)*?

As the core authors of all 12 Tianjin studies are **identical** they should have been questioned why info on iodine status was omitted in the remaining studies, especially in light of the fact that the **same** authors had previously conducted research specifically on excess iodine intake, thyroid effects and IQ - in the **same** areas.

MIREC *(Maternal-Infant Research on Environmental Chemicals - Canada)*

Regarding the MIREC studies, it has recently come to light that almost 90% of the women in the study had taken iodine supplements resulting in *more-than-adequate* and *excessive* iodine intake *(Hall et al., 2023; Krzeczkowski et al., 2023)*, according to global guidelines from the WHO. The mean daily iodine intake for the entire cohort was 80% higher than the recommended amount.

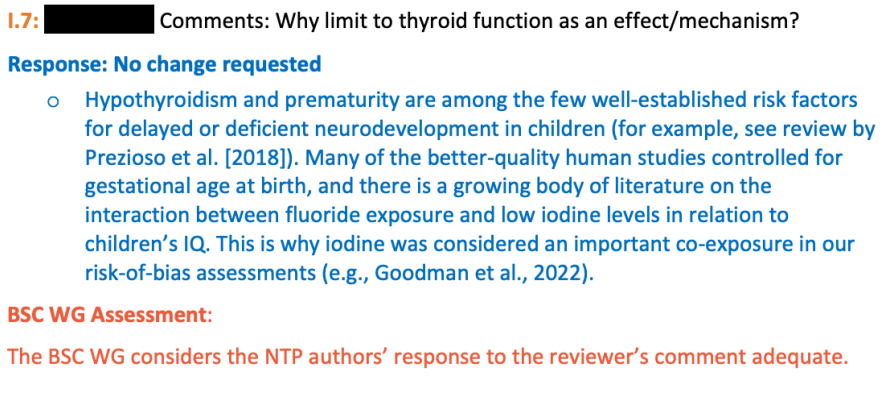
For many MIREC women, the observed urinary iodine levels were much higher than those now commonly associated with subclinical hypothyroidism and auto-immune thyroid disease (>250 µg/L) - both conditions prevalent in MIREC women - and both long associated with loss of IQ in the offspring, as well as ADHD *(Kampouri etc al., 2021; Wasserman et al., 2012; Pop et al, 1995)*. The use of iodine supplements during pregnancy has been implicated as a contributory factor in numerous large international studies *(e.g., Zhou et al., 2019)*.

In addition, the majority of Canadian children between the ages of 3 and 5 consume too much iodine, with close to 40% of the children having **excessive** iodine intake (UIC >300 µg/L) *(Canadian Health Measures Survey, 2009-2011)*. This high intake - by itself - has been associated with loss of IQ in many international studies *(e.g., Carvalho et al., 2022)* - including the Tianjin ones *(e.g., Cui et al., 2020)*. Iodine/thyroid status of the children themselves was never considered by the York/MIREC researchers.

York researchers, unfortunately, have continued to misinterpret the MIREC data in spite of having been informed of this vital issue since 2021 *(e.g., Goodman et al., 2022; Hall et al., 2023; Krzeczkowski et al., 2023)*.

MIREC: Goodman Study

Special mention is made here of the MIREC study by Goodman et al. *(2022)*. The NTP, in one of their responses to a reviewer, claimed that it had considered iodine as an important co-exposure in their risk-of-bias assessments and cited the Goodman paper as an example:



I.7: [redacted] Comments: Why limit to thyroid function as an effect/mechanism?

Response: No change requested

- Hypothyroidism and prematurity are among the few well-established risk factors for delayed or deficient neurodevelopment in children (for example, see review by Prezioso et al. [2018]). Many of the better-quality human studies controlled for gestational age at birth, and there is a growing body of literature on the interaction between fluoride exposure and low iodine levels in relation to children's IQ. This is why iodine was considered an important co-exposure in our risk-of-bias assessments (e.g., Goodman et al., 2022).

BSC WG Assessment:

The BSC WG considers the NTP authors' response to the reviewer's comment adequate.

However, the Goodman paper, published in 2022, is nowhere to be found in either the monograph or the meta-analysis. Why was it used as an example? The fact remains that the NTP did **not** evaluate iodine co-exposure, as can be easily verified by checking the Tianjin examples already given above. If the NTP had been aware of this issue, it would have recognized that the Goodman data showed *more-than-adequate* iodine intake (as a result of iodine supplements consumed) that was wrongly categorized, leading to faulty model construction and data evaluation.

ELEMENT *(Early Life Exposure to ENvironmental Toxicants - Mexico)*

A situation similar to MIREC must be presumed for the mothers and children in the ELEMENT (Mexico City) study. Although iodine/thyroid status has yet to be investigated in that cohort, the data that is available in the recent literature on iodine/thyroid status of Mexican adults and children clearly indicate similar conditions of high iodine intake *(Galván et al., 2020; Flores-Rebollar et al., 2014, 2015; Gonzalez-Nunez et al., 2021)*.

Meta-Analysis

Failure to properly account for the fluoride-iodine antagonism has resulted in a meta-analysis that is highly flawed if not entirely unusable.

The NTP claims to have *"excluded studies for which there was evidence that co-exposures to iodine might be differential"* but the evidence shows that this is not the case. Excluded were merely a few studies where the word "iodine" appeared in the abstract. These included studies evaluating effects of low fluoride levels in the context of iodine deficiency *(Lin et al., 1991, Ren et al., 1989)*. **No real investigation on iodine status was ever conducted.**

Out of the 10 studies used for the mean-effects dose-response meta-analysis, it can be shown that at least 8 of the *low risk-of-bias* studies were done under conditions of *more-than-adequate/ excessive* iodine intake - 3 were Tianjin studies. Out of the 9 *low risk-of-bias* studies used for the regression slopes meta-analysis, all were done under conditions of *more-than-adequate/excessive* iodine intake - 4 were Tianjin studies.

OTHER ISSUES

Overlapping Studies

In addition to the serious issues discussed in this and our previous submissions, other concerns have arisen, such as overlapping studies in the monograph. Although the NTP reassured reviewers that no overlapping publications would be used in the same meta-analysis, this has evidently not been honoured. Again, numerous examples can be given *(Hong 2001b, Wang, 2001; Guo et al., 2021, Cui et al., 2018, 2020, Zhao et al., 2018)*.

Waugh Review

It has been noticed that a new footnote has been added by the NTP on page 2 of the draft monograph:

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[1]The current review has evaluated the fluoride literature with an eye toward potential thyroid effects because a large literature base has accumulated examining the interaction of fluoride with iodine uptake by the thyroid gland and consequential effects on synthesis of thyroid hormones, which are recognized to play significant roles in neurodevelopment in utero and during early childhood. This literature, along with a detailed proposed mechanism of action, was recently reviewed by Waugh (2019).

Please be informed of the following:

As discussed previously, the impacts of fluoride as an anti-iodine agent have been well-documented to occur in peripheral tissue since the 1930s. While fluoride may certainly affect thyroid morphology and function, the primary mechanisms at work here have little to do with any effect on the actual thyroid gland itself but are related to effects on deiodination, a subject not covered at all in the Waugh review. This is most obvious in the elevated rT3 levels seen in fluoride poisoning. The thyroid gland only secretes very little of rT3 (0.9%). rT3 is produced in peripheral tissue by the deiodinase D3. D3 is highly active in placenta, pregnant uterus as well as in various fetal tissues. It is of crucial importance during development as it protects the fetus from excessive thyroid hormone *(Peeters & Visser, 2017)*.

We strongly encourage the NTP to reconsider the assessment of IQ studies by incorporating the fluoride/iodine data specific to the investigated areas and adhering to the protocol.

Furthermore, we call for the proper evaluation of the toxicity of fluoride on neurodevelopment based on the extensive body of evidence that addresses the impact on iodine and thyroid hormone metabolism.

A proper meta-analysis would certainly show that there is **no safe level** of fluoride for anyone who is iodine-deficient or iodine-sufficient. Based on the evidence from high iodine/high fluoride areas, combined with the pharmacodynamic data available from the medicinal application of fluoride, potential benefits may be observable in those who suffer adverse effects from iodine-induced thyroid dysfunction.

As fluoride toxicity is directly related to iodine status - and iodine toxicity to fluoride status - , both mass-supplementation programs require urgent reassessment on a global scale.

Should you require more information on any of the studies or issues mentioned, please do not hesitate to contact us.

Andreas Schuld, Jirong Huang, Wendy Small

Parents of Fluoride-Poisoned Children (PFPC)
The Fluoride Education Project

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

"Through iodine deficiency an excess of fluoride is produced."
(May, 1951)

"The influence of excessive fluoride is related to the iodine nutrition status of the body: in normal iodine nutrition conditions excess fluoride can seriously damage thyroid cells; under iodine excess nutrition, the damage caused by high iodine is the main one."
(Guo et al., 2006)

"Iodide cytotoxicity is dominant with a low fluoride concentration, while the fluoride cytotoxicity is dominant with a high fluoride concentration."
(Liu et al., 2015)

"Iodine and fluorine do have mutually interacting effects on both goiter and fluorosis."
(Zhao et al., 1998)

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