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Dear Drs. Thayer & White:

During the December 2, 2015 meeting of the NTP Board of Scientific Counselors, there was discussion about the comparative sensitivity to fluoride between experimental animals (mostly rodents) and humans. Since this is a critical issue to consider when assessing the human relevance of existing and future animal research, we would like to take this opportunity to provide the following comments.

1. Rodents Require 5 to 10 Times More Fluoride Than Humans to Achieve Same Fluoride Levels in Blood

Research has firmly established that rats require significantly greater fluoride exposure than humans to achieve the same internal dose. The National Research Council (NRC) reviewed some of this research in its 2006 report. (See pages 98-99 and 442-446.) Relying on a study by Dunipace (1995), the NRC estimated that rats require about five times more fluoride in their water to achieve the same *blood* fluoride levels as humans.

Dunipace's estimate of a five-fold difference in blood fluoride levels between rodents and humans is *less* than what other laboratories have found. Pamela Den Besten's research, for example, has repeatedly found that rodents require at least *ten times* more fluoride in their water to achieve the same blood levels as humans. (Zhang et al. 2014; Smith et al. 1993). As Den Besten's team recently explained (Zhang et al. 2014):

“Serum fluoride levels of A/J mice given 50 ppm sodium fluoride (1.2 mM) in drinking water, were increased from approximately 1 μ M for control

mice (0 ppm sodium fluoride in drinking water) to 4.5 μM . Fluoride in the serum of control mice is therefore likely to be a result of the fluoride contained in mouse chow. Similar to the control mouse serum, humans drinking water containing 1 ppm fluoride have approximately 1 μM fluoride in serum. A serum fluoride concentration of 4.5 μM is likely to be found in humans ingesting about 4 ppm fluoride in drinking water. It is not known why rodents require such relatively high levels of fluoride in their drinking water to *have serum fluoride levels similar to humans who drink about ten-time less fluoride.*" (emphasis added)

Based on existing research, therefore, rodents need between 5 and 10 times more fluoride in their water to achieve the same level of fluoride in their blood.

The difference in *bone* fluoride levels between rodents and humans is even greater. As summarized by the NRC, "rats require water concentrations 10 to 20 times higher than humans to achieve comparable bone fluoride concentrations." (NRC 2006, p. 444). The NRC report also found evidence for an even higher ratio of humans to rodents of 40-fold from several studies (Table D-2, p. 445). While the difference in bone fluoride levels may not be directly relevant to neurotoxicity outcomes, it will be very relevant to bone cancer outcomes.

2. Rodents' Heightened Resistance to Fluoride Toxicity Goes Beyond Lower Blood Fluoride Levels

The differential sensitivity to fluoride between rodents and humans is likely greater than the 5-to-10 fold difference in blood fluoride levels. Indeed, it is a well-accepted toxicological principle that *toxicokinetics* (i.e., the factors that influence the concentrations of a toxicant within the body) do not fully explain the difference in reduced chemical sensitivity among rodents; *toxicodynamics* (i.e., the factors within the target tissue/organ that determine whether a toxic effect occurs) provide an additional basis for rodents' reduced sensitivity. (EFSA 2012; WHO 2005). In other words, even when rodents have the same level of a toxicant in their blood as humans, they may suffer less harm as a result.

While the differential thermodynamics for fluoride toxicity in rodents and humans has not yet been carefully examined, there are several factors that suggest a meaningful difference may exist. First, "calcium intake in rats, adjusted for body size, is an order of magnitude greater than in humans." (Turner 1992, p.586). Since calcium is known to protect against fluoride toxicity (Teotia & Teotia 1998; Massler & Schour 1952), the higher calcium intake in rodents will likely make them less susceptible to the harmful effects of fluoride. In fact, at least one study has found that calcium supplementation reduces fluoride's neurobehavioral effects in rats. (Ekambaram & Paul 2001)

Second, unlike humans, rats synthesize their own vitamin C. (Asard 2004, p.208). Vitamin C is a powerful anti-oxidant and has long been known to mitigate

against fluoride toxicity, which is now believed to occur, in large part, via oxidative stress mechanisms. (Barber 2010; Marier & Rose 1977; Pandit 1940). Research on rodents has repeatedly identified oxidative stress as one of the mechanisms underlying fluoride neurotoxicity. (Dong 2015). It can be reasonably anticipated, therefore, that an ample supply of an anti-oxidant like vitamin C may mitigate fluoride neurotoxicity – and, indeed, research has already demonstrated this to be the case. (Nabavi 2013; Basha & Madhusudhan 2010)

In short, the heightened internal reservoirs of calcium and vitamin C in rats suggest they may be less susceptible to fluoride than humans, even when exposed to the same internal dose.

3. When Extrapolating Rodent Studies to Human Exposures, Attention Must Be Paid to Total Fluoride Exposures (mg/kg/day), Not Just Water F Levels

When extrapolating the doses used in rodent studies to the doses that Americans are currently receiving, it is important to not just focus on the level of fluoride in water. In the U.S. and other western countries, it is well recognized that children are now receiving fluoride from many other sources besides water, such as toothpaste and tea.¹ Further, due to changes in infant feeding practices, an increasing percentage of infants are receiving high exposures to fluoride via the use of formula made with fluoridated water.

To help demonstrate the importance of considering the total daily dose (vs the water F level), we review here the daily doses used in the NTP's fluoride/cancer bioassay (NTP 1990) and compare these doses to those that have been estimated for children in western countries by the NRC (2006), Zohoori (2012), Zohoori (2013), Zohoori (2014), and Strittholt (2015).

The NTP's fluoride/cancer study included a "low dose" water fluoride level of 25 mg/L NaF, which equates to 11 mg/L of fluoride ion. In addition to reporting the water fluoride concentrations, the NTP also estimated the total daily fluoride intakes of the rodents. These estimates, from Table 22 of NTP's report, are reproduced here:

¹ While we do not address exposures from tea in this letter, it should be noted that many American children drink tea beverages, which will be a major source of fluoride exposure for some children. (Branum 2014).

TABLE 22
Estimated Total Daily Fluoride Intake from Diet and Water in the Sodium Fluoride Drinking Water Studies and in Previous NTP Studies in F344/N Rats and B6C3F₁ Mice

Dose (ppm)	0 ppm	25 ppm	100 ppm	175 ppm	Previous Studies
Male Rats	0.2 ^a	0.8	2.5	4.1	0.9
Female Rats	0.2	0.8	2.7	4.5	1.0
Male Mice	0.6	1.7	4.9	8.1	2.5
Female Mice	0.6	1.9	5.7	9.1	2.8

^a Units of mg fluoride/kg body weight per day. Fluoride (F) intake for control animals is from the diet; values for other groups represent F in the diet and water, assuming 60% of dietary F and 100% of water F is bioavailable. Values for previous studies do not include minor contribution from fluoridated tap water.

As can be seen, the rats drinking 11 mg/L (25 mg/L NaF) had intakes of 0.8 mg/kg-bodyweight/day. If we rely on Dunipace's 5-fold factor to obtain the human equivalent dose, this translates to **0.16 mg/kg/day** in humans. (If we rely on Den Besten's 10-fold factor to obtain the human equivalent dose, it would translate to **0.08 mg/kg/day**.)

To put these doses in perspective, the NRC 2006 report estimated that some infants in 1 mg/L areas ingest up to 0.14 mg/kg/day from water alone. (Table 2-2, page 29). The NRC's estimate has recently been shown to understate infant fluoride exposures. The recent study by Zohoori (2014), for example, found that infants in fluoridated areas (0.97 mg/L) in the UK ingest an *average* of **0.131 mg/kg/day** from liquids, with some infants ingesting up to **0.181 mg/kg/day**. (See Zohoori 2014, Table 2.) Zohoori's data thus shows that some infants receive more fluoride from formula alone than the human equivalent dose of experimental rats receiving 11 mg/L fluoride in their water.

Further, Zohoori (2013, Table 1) has reported that 4-year-old children swallow up to **0.113 mg/kg/day** from toothpaste alone, with the *average* amount ingested ranging from 0.037 to 0.055 mg/kg/day. In a separate study, Zohoori (2012) found that some 4-to-6 year old children ingest **0.159 mg/kg/day** fluoride from toothpaste, with 15% of children ingesting more than 0.05 mg/kg/day from this single source. (See Table 2; and p. 420).

More recently, Stritholt (2015, Table 2) found that 10% of 2-to-4 year old children ingested more than 0.384 mg of fluoride per brushing, with 5% of children ingesting more than 0.49 mg per brushing. This equates to 0.76 to 0.98 mg of fluoride for children who brush twice per day. Assuming an average weight of 14 kg (CDC 2010, Figures 9 & 10), Stritholt's data shows that over 10% of 2-to-4 year olds ingest more than 0.05 mg/kg/day from toothpaste alone, with 5% of children ingesting over 0.07 mg/kg/day from this single source.

This data on toothpaste ingestion demonstrates that, if we use Dunipace's (1995) five-fold difference in blood fluoride levels between humans and rats, some children living in fluoridated areas will have higher internal doses of fluoride

(mg/kg/day) than rats drinking water with 11 mg/L fluoride, when all sources of fluoride exposure are considered.

The situation is even more striking if we use Den Besten's 10-fold difference in blood fluoride levels. (Zhang et al. 2014; Smith et al 1993) Under Den Besten's estimate, highly exposed children in fluoridated areas will have higher internal doses of fluoride than rats exposed to 22 mg/L of fluoride in water.

4. Adjustment Factors Must Be Applied to Account for Both Inter-species and Intra-species Variation in Sensitivity

Finally, in considering which doses from rodent studies are relevant for assessing the risk of current human exposures in the United States, it is critical to keep in mind the realities of interspecies and intraspecies variation. Animal studies involve very small numbers of test animals when compared to the human population, and involve groups of animals with much more homogeneous genetic and health characteristics as compared to a human population as large and heterogeneous as the United States. Because of this, it has become standard regulatory and toxicological practice to apply "uncertainty" or "safety" factors to animal findings in order to account for both interspecies (animal-to-human) and intraspecies (human-to-human) variations in sensitivity. (Martin 2013; EFSA 2012; WHO 2005). These differences in sensitivity reflect differences in *both* *toxicokinetics* (i.e., the concentrations of the toxicant within the various parts of the body) and *toxicodynamics* (i.e., the concentration of the toxicant that is able to cause harm).

4a) Interspecies Variation

In the absence of "chemical-specific adjustment factors" (CSAFs), a "default" uncertainty factor of 10 is used to account for expected variations in interspecies sensitivity. (WHO 2005; Martin 2013). This default factor of 10 is based on a factor of 4 to account for differences in toxicokinetics, and a factor of 2.5 to account for differences in toxicodynamics. (WHO 2005, Figure S-1)

As discussed earlier, there is some chemical-specific information available for fluoride with respect to interspecies variation; this data, however, is almost entirely limited to toxicokinetics (i.e., the reduced concentrations of fluoride in blood and bone in rodents compared to humans receiving the same external dose). As already discussed, available toxicokinetics data shows that rats have between 5-to-10 times less fluoride in their blood than humans when exposed to the same level of fluoride in water. (Zhang 2014; Dunipace 1995; Smith 1993.) Based on this data, a CSAF of between 5 and 10 would be appropriate to use for toxicokinetics.

Since there appears to be little, if any, available data to quantitatively define species differences in fluoride *toxicodynamics*, a CSAF is not yet possible for this

sub-component of interspecies variation. Accordingly, the NTP should apply the default sub-factor of 2.5 to account for expected differences in fluoride thermodynamics between rats and humans. When combined with the 5-to-10 factor for thermokinetics, the total adjustment factor for interspecies variation would be in the range of 12.5 to 25.

4b) Intraspecies Variation

In addition to applying an adjustment factor to account for interspecies variation, it is standard regulatory and toxicological practice to apply an adjustment factor for intraspecies variation (Martin 2013). In the absence of sufficient chemical-specific information, a default factor of 10 is applied, which is comprised of a factor of 3.16 for toxicokinetics, and a factor of 3.16 for toxicodynamics. (WHO 2005, Figure S-1)

It is well established that the toxicokinetics of fluoride are significantly influenced by certain diseases, particularly kidney disease. In their review of the literature, Marier & Rose (1977) estimated that the level of fluoride in blood and bone is approximately four times higher among individuals with renal insufficiency. Few studies, however, have reported blood fluoride levels among *children* with kidney disease. The findings of Warady (1989) indicate that children with kidney disease may have markedly elevated blood fluoride concentrations. According to Warady, infants receiving long-term peritoneal dialysis had between 0.10 and 0.18 ppm fluoride in their blood, which was 2 to 4 times higher than the levels found in age-matched controls, and 5 to 9 times greater than the average blood fluoride levels (1 $\mu\text{mol/L}$ = ~ 0.019 ppm) in healthy adults living in fluoridated areas. (NRC 2006, p. 442). The default factor of 3.2 would thus appear to be too low to account for intraspecies toxicokinetic variations seen in human populations. A CSAF of between 4 to 9 would appear more appropriate to account for age and kidney-related variations in the population.

Current data also demonstrates the existence of significant intraspecies variation in fluoride toxicodynamics. It is well established that genetic polymorphisms can profoundly influence an individual's susceptibility to the neurotoxicity of a chemical. In the case of methylmercury, for example, it has been estimated that some genetic variants amongst humans cause them to be "at least 25-fold more susceptible" than others (Julvez & Grandjean 2013).

The one study to examine the influence of genetic polymorphisms on fluoride neurotoxicity found that they may exert a major influence. (Zhang 2015). In the population studied by Zhang (2015), each 1 mg/L increase in urine fluoride concentration was associated with a non-significant decrease of 1.85 IQ points among those with variant genotypes. When limited to only those children with the COMT polymorphism, however, each 1 mg/L increase in urine fluoride was

associated with a significant decrease of 9.67 IQ points—an approximately 5-fold difference in effect size.²

In addition to genetics, iodine deficiency is another factor that has been identified as significantly exacerbating fluoride's effect on the brain. Human studies have repeatedly found that fluoride can exacerbate the neurotoxic effects of iodine deficiency, as reflected by reduced IQ scores (Hong 2001; Xu 1994; Lin 1991; Ren (1989). Animal studies have confirmed the interactive neurotoxic effects³ of suboptimal iodine intake and fluoride exposure. (Ge 2011; Ge 2005; Shen 2004; Wang 2004).

While there are very likely other factors that enhance the neurotoxicity of fluoride in humans, the evidence on genetic polymorphisms and iodine deficiency underscores the need to account for intraspecies toxicodynamic variations. If the default factor of 3.16 is used to account for this, then the uncertainty factor for intraspecies variation would be approximately 12.6 to 28.5 (i.e., 4 to 9 for toxicokinetics and 3.16 for toxicodynamics). When combined with the aforementioned factor of 12.5 to 25 for interspecies variation, the total adjustment factor would be at least 150, and as high as 700.⁴

These relatively high adjustment factors mean that animal studies which use what might be considered high doses of fluoride are relevant to human exposures in fluoridated communities *among highly susceptible individuals*.

4c) Broadbent Study Does Not Justify a Reduced Uncertainty Factor

Extensive human epidemiological data can justify using a reduced uncertainty factor when extrapolating animal findings to humans. Despite the suggestions made by some at the recent NTP Board of Scientific Counselors meeting, the recent study by Broadbent (2015) does not support using a reduced uncertainty factor.

Broadbent examined the impact of fluoridated water (1 mg/L) on IQ in New Zealand. In contrast to most of the studies from China, India, Iran, and Mexico, Broadbent did not detect an effect of waterborne fluoride exposure on IQ. The study, however, had very low power to detect small effects, as there was minimal difference in total fluoride exposure between the fluoridated and non-fluoridated areas due to the widespread utilization of fluoride supplements and fluoride

² An ongoing NIH-funded study by Den Besten, et al., is specifically exploring the role of genetics in fluoride neurotoxicity in mice, and could thus help provide important insights into genetic variations in sensitivity. See: <http://tinyurl.com/pt788by>

³ Animal studies have also found interactive neurotoxic effects between fluoride and lead, thus suggesting that individuals exposed to elevated levels of lead may be more vulnerable to fluoride's neurotoxicity, and vice versa. (Niu 2015, Niu 2009).

⁴ The low end of this range is based on the following calculation: 12.5 (interspecies) X 12.6 (intraspecies) = 157.5. The high end of the range is reached by the following: 25 (interspecies) X 28.5 (intraspecies) = 712.5.

toothpaste in the non-fluoridated communities. The average difference in total fluoride intake in the study has been estimated to be a mere 0.2 mg/day, with non-fluoridated children ingesting 0.5 mg/day and fluoridated children ingesting 0.7 mg/day (Osmunson, in press). Further, the study had no capacity to isolate and assess the impact on susceptible individuals, such as those with genetic variations or suboptimal iodine deficiency. Accordingly, the Broadbent study does not provide a basis for concluding that exposures in fluoridated communities are neurologically safe for the full range of sensitivities in large, heterogeneous human populations.

5. Conclusion

Rodent studies using higher fluoride concentrations than are used in water fluoridation programs can be directly applicable to humans living in fluoridated communities. First, from a toxicokinetic perspective, rodents require 5 to 10 times higher levels of fluoride in their water to achieve the same level of fluoride in their blood and soft tissues. Second, from a toxicodynamic perspective, rats have several features (e.g., higher calcium intake, and biosynthesis of vitamin C) that evidence suggests render them less susceptible to fluoride toxicity, even when exposed to the same concentrations of fluoride in the blood. Third, due to the advent of non-water sources of fluoride such as toothpaste, any extrapolation of rodent studies to human populations needs to consider the respective total daily doses, not just the respective water fluoride levels. Finally, it is standard toxicological and regulatory practice to utilize adjustment (“uncertainty”) factors when extrapolating animal studies to humans in order to account for the expected intraspecies and interspecies variations in toxicokinetics and toxicodynamics. Applying these adjustment factors to the rodent studies on fluoride neurotoxicity suggests that adverse effects found in rodents at water concentrations *over 150 times greater* than humans ingest may be directly applicable to highly susceptible individuals.

If we can provide any further information regarding the issues raised above, please do not hesitate to let us know.

Sincerely,

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