From: Whitford, Gary [mailto:GWHITFOR@augusta.edu]
Sent: Monday, August 15, 2016 4:15 PM
To: Thayer, Kristina (NIH/NIEHS) [E]
Subject: Comments on 2016 NTP Fluoride Literature Review

TO: Kristina Thayer, Ph.D.
Deputy Director for Analysis, Division of the NTP
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SUBJECT: Comments on 2016 NTP Fluoride Literature Review

Dear Dr. Thayer:

The following are my comments about the 2016 NTP Systematic Literature Review on the Effects of Fluoride on Learning and Memory in Animal Studies. The Review is thorough and useful. It summarizes a large number of reports that meet the NTP's criteria for adequately conducted and presented studies on the effects of fluoride on learning and memory in laboratory animals.

According to the Review, NTP is currently conducting rodent studies to fill data gaps in the available literature that were identified during the review process. One such gap is the lack of information about the effect of fluoride exposure on learning and memory at water levels closer to 0.7 ppm (mg/L), which is the concentration recommended for fluoridated drinking water. I agree that this is a gap that should be filled.

Of equal or more importance, however, will be data from studies with water fluoride concentrations that result in rat plasma concentrations comparable to those in persons who drink optimally fluoridated water.

We reported (Caries Res 16:334-339, 1982; Caries Res 18:25-32, 1984) and Dunipace et al confirmed (J Dent Res 74:358-368, 1995) that, in order to achieve similar plasma fluoride concentrations, the concentration in water provided to rats should be 4-5 times higher than the concentration in water consumed by humans. The NTP investigators should be encouraged to include that level of fluoride exposure in their current and future studies.

Also related to this issue is an important error regarding the relation between the concentrations of fluoride in drinking water and human plasma (see Discussion in the Review, bottom of page 56 and top of page 57). It is said that there is an equivalence between the fluoride concentrations in water when expressed as mg/L and in plasma when expressed as µg/L There is, in fact, a "numerical equivalence" but not an "actual equivalence", i.e. 1.0 mg F/L in drinking water results in 1.0 µmole/L in plasma. So, the units for the actual relation of the equivalence are mg/L in water and µmoles/L in plasma. Since the molecular weight of fluoride is 19, there are 19 µg/µmole. Thus there is an error factor of 19 in their statement. NTP investigators should be made aware of the error.

The NTP Review also suggested (see Discussion, page 55, 2nd paragraph) that there may have been only an apparent negative effect of fluoride on learning or memory tasks that was actually due to physical limitations associated with skeletal fluorosis. For example, performance in studies that require pressing a bar or swimming could be negatively affected by such limitations. Our study, however, with chronic exposure (8 months) to various water fluoride concentrations (up to 155 mg/L) did not produce any evidence of difficulty with movement, mobility or pressing a bar to receive a reward. In fact the rats in the fluoride groups performed as well or better than those in the control group despite having bone, plasma and brain fluoride concentrations that were up to 99, 305 and 221 times higher than those in the control group. (See Appetitive-based learning in rats: Lack of effect of chronic exposure to fluoride. Neurotoxicology and Teratology 31: 210-215, 2009). Future studies that include chronic exposure to high levels of fluoride should include some assessment of movement and mobility.

Please let me know if you have questions or comments. Best regards, Gary Whitford