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Blood is thicker than water: Flaws in a National Toxicology Program study

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ABSTRACT

Municipal fluoridation was a mid-twentieth century innovation based on the medical hypothesis that consuming low doses of fluoride when young provided protection against cavities with only a small risk of mild dental fluorosis, a cosmetic effect. In the 21st century, more than half of American teens are afflicted by dental fluorosis with approximately one in five having moderate to severe dental fluorosis in at least two teeth. Scientific literature since the 1990s has found that even low doses of fluoride adversely affect cognitive-behavioral development and that deficits are correlated with the severity of dental fluorosis in afflicted individuals. Evidence of neurotoxic impact from low dose systemic exposure to fluoride prompted an investigation by a branch of the governmental agency that has promoted fluoridation policy since its 1940's inception. This review identifies ten significant flaws in the design of an animal experiment conducted by the U.S. National Toxicology Program as part of that investigation into the neurotoxic impact of systemic prenatal and postnatal fluoride exposure. The authors hypothesize that organizational bias can and does compromise the integrity of fluoride research.

Background

Several North American cities participated in human trials beginning in 1945 to determine the efficacy of the medical hypothesis that systemic ingestion of fluoride would reduce dental decay in children. Although designed as a 14-year experiment, government officials ended the city trials after just a few years declaring them a success. Those same officials immediately launched an aggressive campaign in 1950 to promote fluoridation even before the trial reports were published. In the 1950s, a comprehensive review of those trials by a dental researcher and statistician revealed significant study design flaws, fatal statistical flaws and conclusions that were not supported by the evidence [1].

Additional real world data and studies that emerged in the 1950s included a Public Health Service (PHS) sponsored controlled dose study of pregnant women and young children which documented a percentage of the population experienced acute adverse symptoms from even low dose consumption of fluoride [2,3]. Neurological symptoms as well as fluorosed teeth were reported in addition to gastrointestinal distress, dermatological outbreaks and debilitating fatigue syndromes [2–5]. Additionally, post hoc 1950s safety studies documented that fluoride saturates the placenta and passes into the fetal blood stream [3,6].

Over the decades, the medical hypothesis of fluoride incorporation into developing teeth as providing a dental benefit, which was a cornerstone of the original fluoridation hypothesis, has been substantially disproved [7–11] while fluoridation has continued to be justified with marketing slogans that originated circa 1950 [10].

Since 1995, the evidence of neurotoxicity from animal experiments and human studies has become particularly robust. Additionally, the 1940s promise that no more than 10% of children might experience mild fluorosis, the worst case effect of fluoridation, has been proven false. The 2011–12 surveillance data from the U.S. National Health and Nutrition Examination Survey (NHANES) reports that over half of teens have dental fluorosis on at least two teeth, an increase of 31% in the past ten years. One in five American teens have moderate to severe dental fluorosis [12,13]. Modern studies have correlated dental fluorosis with learning disabilities [14,15].

Meta-analyses in the 21st century have validated that fluoride is a developmental neurotoxicant [16–18] and that there is no evidence of any human dietary requirement for fluoride [19].

Consequently, we propose that the prematurely accepted medical hypothesis regarding the safety and effectiveness of fluoridation by political bodies is not supported by medical science despite continued political promotion of fluoridation policy that in this case compromises the integrity of scientific research. We propose that continuation of fluoridation policy in the face of both real world and scientific evidence of harm is politically sanctioned human experimentation anchored in organizational commitment to a scientifically flawed policy.

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NTP animal experiment

Dozens of human studies and hundreds of animal studies have found an adverse impact on learning from prenatal or postnatal exposure to fluoride, even when exposure is consistent with doses in communities with drinking water concentrations that are considered “optimal” by the Department of Health and Human Services (DHHS) and the Oral Health Division of the Centers for Disease Control (CDC).

At the request of scientists and dentists and at the urging of the Fluoride Action Network, the National Toxicology Program (NTP) agreed in 2015 to a multi-year investigation of the cognitive impact of prenatal and postnatal exposure to fluoride [20]. The NTP is a division of the National Institute of Environmental Health Sciences (NIEHS), which is part of the National Institute of Health (NIH). The NIH and CDC are sister agencies under DHHS.

The first part of the investigation was a review of the searchable animal literature. Many studies were excluded but 68 studies met NTP criteria [21].

That literature review of animal studies found low-to-moderate evidence of neurotoxicity according to their four level scheme. None found very low evidence. The NTP rarely offers a ‘high’ confidence level in the body of evidence. Consequently, ‘moderate evidence’ of neurotoxicity is cause for serious public health concern.

A conference call on February 16, 2016 with Dr. Kristina Thayer, NIEHS and Deputy Division Director for Analysis in the NTP Office of Health Assessment and Translation (OHAT), confirmed the seriousness of the ‘moderate’ rating and noted that the written NTP report underplayed the significance of this consistency of solid evidence of neurotoxicity [22].

The second phase of the NTP investigation was conducting its own animal neurotoxicity study. That study was published as an animal experiment [23].

In seeming disagreement with the findings of its own literature review, the 2018 NTP animal experiment by McPherson et al. [23] did not find evidence of neurotoxic harm. This was not a complete surprise to those who had been following the progress of the NTP project since the animal model chosen and study design were inconsistent with previously published animal experiments showing fluoride’s effects on behavior.

The following are major flaws in the 2018 NTP animal experiment:

1. The NTP study used Long-Evans Hooded rats. Not only is this strain known to have different embryonic susceptibilities to teratogens than other strains [24], Long-Evans Hooded rats were identified in the NTP literature review as an animal strain that possessed a particularly high tolerance to fluoride exposures, which is undoubtedly the reason these animals are not commonly used in fluoride studies. In 1967, Elliott reported no effects were observed in Long-Evans Hooded rats treated for 4 months with 4.24 or 42.4 ppm F- in an elevated multiple T-maze [25]. Long-Evans Hooded rats are a fundamentally inappropriate animal model system to study the effects of fluoride on behavior.
2. The NTP study only used male rat pups. This is an odd decision because their own NTP review identified a lack of evidence in comparing responses between genders as a knowledge gap. In humans, females respond differently to fluoride toxicity. This approach calls into question the applicability of the NTP findings to the real world.
3. Although the study was supposed to approximate the cognitive-behavioral effect when exposed to fluoride throughout pregnancy and/or through bottle-feeding with formula made with fluoridated water, the dams were not exposed to fluoride during the first trimester of pregnancy (until day G6).
   The ability of fluoride to cross the placental barrier in humans has been consistently confirmed since the start of fluoridation [3,6,26–29]. In recent decades, it has been established that dose and timing of exposure to neurotoxins such as fluoride is critical to central nervous system development in both animal experiments and real world human experience [30–34].
4. There was no valid effort made to expose newborn rats to fluoridated water during their nursing period that in any way approximated the real world experience of bottle-fed babies living in fluoridated communities. Although the maternal strain continued to consume fluoridated water post day G6, both rat and human milk fluoride concentrations can be quite low even when maternal consumption is much higher than that used in the NTP animal experiment. Milk concentration also varies by species and strain [35,36].
   The 2018 NTP study by McPherson et al. did not measure the fluoride in maternal milk as has been done in other studies. Luke simulated the human bottle-fed experience with gerbils and measured fluoride concentrations in both milk and plasma in 1997. Luke found significant changes in brains and other tissue [37].
   McPherson et al. reported that fluoridated water was made available to the pups, but blind rat pups do not drink water from the water dispenser until weaned. The NTP pups were weaned on postnatal day 21 and thereafter drank fluoridated solutions. Consequently, this study design did not deliver a reliable dosage of fluoride throughout the most vulnerable periods of brain development and wholly excluded exposure comparable to that received by infants fed formula prepared with fluoridated tap water.
5. The NTP animal experiment used purified sodium fluoride (NaF) rather than any of the three fluoridation chemical products used in community fluoridation schemes. Although scientists prefer eliminating other contaminants that could confound the results of their study, if the NTP purpose is to determine whether fluoridation chemicals are having a neurotoxic impact on consumers, the rational approach would be to study all three fluoridation chemicals in its animal experiment rather than only use a purified proxy.
   We suggest that two 21st century studies that considered lead poisoning in relation to use of fluoridation chemicals were both more rational and more scientifically disciplined. Macek et al. found an interesting pattern of higher blood lead concentrations in children relevant to type of fluoridation chemical used and age of home [38]. An animal experiment by Sawan et al. subsequently found that any fluoride in water increases mammalian uptake of lead into tissue [39].
6. One of the ways to verify sufficient fluoride exposure in developing rats is to monitor and quantify dental fluorosis. The authors claimed that dental fluorosis was evident, but the fluorosis identified in the supplementary material was barely detectable and should be quantified as questionable. This data further validates that Long-Evans Hooded rats are not a good model system as this strain was not even vulnerable to the most visible symptom of fluoride poisoning as is clearly evident by comparing the images provided in the NTP report supplementary material with those from fluoride studies using Wistar rats [23,38,39].
   It is well established that dental fluorosis in humans increases in fluoridated communities to about double that of non-fluoridated communities [35]. Hispanic and African American communities also have been documented to have significantly higher rates of dental fluorosis and worse severity within fluoridated communities as compared to their neighbors suggesting a genetic susceptibility mirrored in animal strains [38,39]. Any model attempting to claim lack of neurologic harm from water fluoridation in man must at the very least use an exposure that is comparable to that occurring in humans which is reflected by the incidence of dental fluorosis in all segments of the population [12,13,40–44].
7. In a conference call on Feb. 16, 2016, DHHS Associate Director Dr. John Bucher conceded that the NTP did not have the capacity to recreate all of the tests of animal behavior that had been used in