Fluoride Action Network
104 Walnut Street
Binghamton NY 13904

October 11, 2018

Re: Docket No. CDC-2018-0064
Comments on: Proposed Guidance Regarding Operational Control Range around Optimal Fluoride Concentration in Community Water Systems that Adjust Fluoride_Final

The Fluoride Action Network (FAN) submits the following comments on the "optimal fluoride concentration range in community water systems." FAN is a non-profit advocacy group dedicated to broadening awareness among citizens, scientists, and policymakers on the toxicity of fluoride compounds.

The CDC's request for guidance in achieving an "optimal fluoride concentration" of 0.7 milligrams/liter (mg/L) in community fluoridation schemes lacks an assessment of the risks to the fetus. We find it unprincipled that this request should proceed without such an assessment. As the developing embryo and fetus are undoubtedly the most susceptible of all life stages to environmental toxins, special consideration should have been given to this group when estimating fluoride exposure and relative source contribution.

As far as we know neither the U.S. EPA's Office of Water, the Department of Health and Human Services (HHS), the Food and Drug Administration, nor the Division of Oral Health at the Centers for Disease Control and Prevention has considered the effects of water fluoridation on the fetus.

On January 13, 2011, when the draft recommendation for an "optimal fluoride concentration" of 0.7 mg/L was first proposed by the HHS, the Fluoride Action Network requested that the disproportionate impact on susceptible populations, such as the fetus and for infants under 6 months of age, be assessed. However, we never received a response to our submissions and as far as we know, an assessment was never performed. You can read our comments here:

Comments on Fluoride: Exposure and Relative Source Contribution Analysis.
http://www.fluoridealert.org/wp-content/uploads/fan.exposure.revised.4-22-11.pdf

Comments on Fluoride: Dose-Response Analysis for Non-Cancer Effects
http://www.fluoridealert.org/wp-content/uploads/fan-dose-response.comments.apr_.20111.pdf

A lot has transpired since then. Most important are the recent Mother-Offspring studies that report neurocognitive effects at urinary fluoride levels that are found in communities with fluoridated drinking water.

The Mother-Offspring Studies

In September 2017, a mother-offspring study in Mexico was published in the journal *Environmental Health Perspectives*. Bashash et al. studied 299 mother-child pairs for prenatal fluoride exposure and neurodevelopment. They found that prenatal fluoride exposure as measured in the pregnant woman's urine, was significantly associated with reduced IQ in offspring at ages 4 and 6-12 years. This study found a very large effect. An increase in urine fluoride of 1 mg/L was associated with a drop in IQ of 5 to 6 points. To put this into perspective with the fluoride levels ingested by the Mexican mothers and the levels ingested in fluoridated parts of the USA, the average fluoride intake in the Mexican mothers was about the same as that in women in the USA. It was not substantially higher. The range of fluoride levels in Mexico also corresponded closely to the range found in most of the USA. The higher levels were similar to what is found in areas in the USA with fluoridated water, and the lower levels were similar to what is found in most unfluoridated parts of the USA.

Most of the Mexican women in the Bashash et al. (2017) study had urine fluoride levels between 0.5 and 1.5 mg/L. Studies have found that adults in the USA have between about 0.6 and 1.5 mg/L, almost exactly the same range. From the low end of that range to the high end is a difference of 1 mg/L which is what caused the 5 to 6 IQ point difference in the children of the study mothers. The study, funded by the U.S. National Institutes of Health (NIH) and other U.S. agencies, is titled ***Prenatal Fluoride Exposure and Cognitive Outcomes in Children at 4 and 6–12 Years of Age in Mexico*** and is online at: https://ehp.niehs.nih.gov/ehp655/

A Canadian study on fluoride urinary levels was published in October 2018 by Till et al.

The researchers measured the fluoride in the urine of 1,566 pregnant women living in fluoridated (water F concentrations of about 0.7 mg/L), and non-fluoridated communities. They "found that mean urinary fluoride values were almost two times higher for pregnant women living in fluoridated regions than for those in non fluoridated regions (Table 2)… Urinary fluoride levels were significantly lower among women living in non fluoridated regions, despite the so-called diffusion or halo effect..." The researchers stated that "artificially fluoridated drinking water is a major source of fluoride intake. Specifically, for every 0.5-mg/L increase in water fluoride level, we would expect to see a 74–82% increase in urinary fluoride concentration. These findings are consistent with prior studies showing that fluoride levels in drinking water are closely related to those in urine in adults (Paez and Dapas 1983), children and adults (Zipkin et al. 1956), and pregnant women (Opydo-Szymaczek and Borysewicz-Lewicka 2005)." This study was funded by the U.S. NIH and the National Institute of Environmental Health Sciences as well as Health Canada and other government agencies in Canada. The full study titled ***Community Water Fluoridation and Urinary Fluoride Concentrations in a National Sample of Pregnant Women in Canada*** is at http://fluoridealert.org/wp-content/uploads/till-2018.pdf.

While no one in the U.S. has studied urine F levels in pregnant women, this new Canadian study is the next best thing and should be fully applicable to the USA. Till et al. noted that Canada and the United States have the same optimal concentration of fluoride in drinking water set at 0.7mg/L. and that "Community water fluoridation is a major source of fluoride exposure for pregnant women living in Canada." For Americans, "Water and water-based beverages are the main sources of systemic ingestion, accounting for approximately 75% of dietary fluoride intake among adults living in communities that fluoridate their water supply in the United States."

Urine fluoride levels are one of the best ways of estimating total fluoride exposure from all sources, which is what is relevant to developmental neurotoxicity.

Attention Deficit Hyperactivity Disorder

Another recent 2018 paper found a substantial increase in ADHD symptoms in the children of women with essentially identical exposure fluoride urinary levels as were found in Canada in pregnant women drinking fluoridated water. Bashash et. al (2018) studied 213 mother-children pairs in Mexico and reported, "Higher levels of fluoride exposure during pregnancy were associated with global measures of ADHD and more symptoms of inattention." The study titled ***Prenatal fluoride exposure and attention deficit hyperactivity disorder (ADHD) symptoms in children at 6–12 years of age in Mexico City*** was funded by the NIH and other U.S. agencies as well as the Ministry of Health of Mexico. Abstract at http://fluoridealert.org/studytracker/32332/

EPA's Risk Assessments on Fluoride. In the most recent risk assessments on fluoride prepared by the Office of Water at the EPA in December 2010 (Fluoride: Dose-Response Analysis For Non-cancer Effects and Fluoride: Exposure and Relative Source Contribution Analysis) they did not take into consideration the effect of fluoride on the fetus. The latter report noted, "Some individuals may have substantially higher intakes of fluoride from their drinking water as a result of specific types of activities that increase water intake (e.g., athletes or outdoor laborers in warm climates), life stage (e.g., pregnant or lactating women), or as a result of medic conditions such as diabetes mellitus, diabetes insipidus, or renal problems (page 70)."

The Institute of Medicine (IOM), in their 1997 Dietary Reference Intakes (DRI) report for fluoride, also did not take into consideration the effect of fluoride on the fetus. However, it set an *"Adequate Intake = AI"* for pregnant woman *(see bottom of page 304, top of 305 at https://www.nap.edu/read/5776/chapter/10#304*

> ***AI Summary: Pregnancy***
> There is no evidence at this time that the AI for women during pregnancy should be increased above the level recommended for women during the nonpregnant state.
>
AI for Pregnancy	**14 through 18 years**	**3 mg/day**
AI for Pregnancy	**19 through 50 years**	**3 mg/day**

If this *Adequate Intake* level were followed it would lead to higher urinary fluoride levels in pregnant women than what was found in the pregnant women in Bashash et al's 2017 study where the offspring were found to have a 5-6 IQ points deficit.

Other Mother-Offspring Studies:

• **Mother-Offspring study by Valdez Jiménez et al. (2017):** 65 mother-baby pairs from an endemic hydrofluorosis area in Mexico were enrolled in the study. The authors concluded, "Our data suggests that cognitive alterations in children born from exposed mothers to F could start in early prenatal stages of life." The abstract of the study, titled ***In utero exposure to fluoride and cognitive development delay in infants****, is* here http://fluoridealert.org/studytracker/27898/

• **Mother-Offspring study by Thomas et al. (2018):** 401 mother-infant pairs were enrolled in this study. The authors concluded, "Our findings add to our team's recently published report on prenatal fluoride

and cognition at ages 4 and 6–12 years by suggesting that higher *in utero* exposure to F has an adverse impact on offspring cognitive development that can be detected earlier, in the first three years of life." This study, *titled* ***Prenatal fluoride exposure and neurobehavior among children 1–3 years of age in Mexico,*** was funded in part by the NIH and other U.S. agencies as well as the Ministry of Health of Mexico. The abstract is at http://fluoridealert.org/studytracker/30717/

• **Chronic low-level fluoride exposure on thyroid function.**
Malin et al. (2018) published the "first population-based study to examine the impact of chronic low-level fluoride exposure on thyroid function, while considering iodine status. The objective of this study was to determine whether urinary iodine status modifies the effect of fluoride exposure on thyroid stimulating hormone (TSH) levels." The authors concluded, "Adults living in Canada who have moderate-to-severe iodine deficiencies and higher levels of urinary fluoride may be at an increased risk for underactive thyroid gland activity." The study was funded by the Canadian Institutes of Health Research and other Canadian institutions and titled, ***Fluoride exposure and thyroid function among adults living in Canada: Effect modification by iodine status*** – available at http://fluoridealert.org/wp-content/uploads/malin-2018.pdf

This recent scientific evidence strongly suggests that to protect against loss of IQ and increases in ADHD there should be no purposeful addition of fluoride into drinking water supplies.

We urge that a moratorium be placed on drinking water fluoridation schemes forthwith.

We urge that pregnant women be informed of these studies and that fluoride-free water be made accessible to everyone living in a community with fluoridated drinking water.

Respectfully submitted by

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See the next page for an Addendum on Animal Offspring Studies

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Many of the effects in the Mother-Offspring studies have been found in Animal Offspring studies. The following are some, but not all, of these studies;

Maternal fluoride exposure during gestation and lactation decreased learning and memory ability, and glutamate receptor mRNA expressions of mouse pups
Sun et al., 2018, Human and Experimental Toxicology.

maternal mice were exposed to F (25, 50, or 100 mg/L sodium fluoride (NaF) in drinking water) during gestation and lactation… findings suggested that F can pass through the cord blood and breast milk and may have deleterious impact on learning and memory of the mouse pups, which was mediated by reduced mRNA expression of glutamate receptor subunits.

Alterations in the memory of rat offspring exposed to low levels of fluoride during gestation and lactation: Involvement of the a7 nicotinic receptor and oxidative stress.
Bartos et al., 2018, Reproductive Toxicology

we investigated the effects of oral exposure to low levels of F during the gestational and lactation periods, on the memory of adult female rat offspring. We also considered a possible underlying neurotoxic mechanism. Our results showed that this exposure reduced step-down latency in the inhibitory avoidance task, and decreased both mRNA expression of the *α*7 nicotinic receptor (nAChR) and catalase activity in hippocampus. Our data indicates that low F concentrations administrated during gestation and lactation decrease the memory of 90-day-old female offspring. This suggests that the mechanism might be connected with an *α*7 nAChR deficit in the hippocampus, induced by oxidative stress.

Fluoride-induced alterations of synapse-related proteins in the cerebral cortex of ICR offspring mouse brain.
Ge et al., 2018, Chemosphere

In this study, an animal model of fluoride exposure was created by providing ICR mice were treated with vehicle F at a dose of 0 (control group), 50 (low-fluoride group) or 100 mg/L (high-fluoride group) in water for one month. After the mice mated, parents and offspring were treated and maintained under these conditions. The cognitive abilities of the mice were examined using a Morris water maze test. Results indicated that fluoride exposure significantly prolonged the escape latency period and decreased the number of crossings in a particular zone. Histopathologic analysis revealed the shrinkage and fragmentation of glial cells in the fluoride-treated groups. Pyramidal cells in the cerebral cortices of fluoride-treated groups were fewer than those of the control group. The expression of microtubule-associated protein 2 (MAP2) and synaptic proteins of the cerebral cortex in mouse offspring was assayed using RT-PCR and Western blot. Fluoride exposure possibly induced a significantly decreased expression of MAP2, synaptophysin (SYP) and developmentally regulated brain protein (Dbn) at protein and mRNA levels. Glutamate receptor (N-methyl-d-aspartate receptor, NMDAR) was also expressed, and this finding was consistent with the reduced MAP2, SYP and Dbn expression. Therefore, fluoride-mediated reduction in cognitive dysfunction is likely caused by the disruption of the expression of these synapse-associated proteins, resulting in attenuated neuronal function

Effects of perinatal fluoride exposure on the expressions of miR-124 and miR-132 in hippocampus of mouse pups.
Wang et al., 2018, Chemosphere

To investigate the effects of perinatal fluoride exposure on learning and memory ability of mouse offspring, ICR female mice were received different doses of sodium fluoride (0, 25, 50, 100 mg/L NaF) from pregnant day 7 to lactational day 21.
Open field test showed that compared to the control group, perinatal fluoride exposure significantly decreased the number of entries into the center zone in 100 mg/L NaF group. In the eight-arm maze test, the number of working memory errors, reference memory errors, and the total arm entries were significantly increased in fluoride treatment groups, compared to the control group…cAMP-response element binding protein (CREB) mRNA level was significantly decreased in all fluoride groups. These findings suggested that the impairment of learning and memory in mouse offspring induced by perinatal fluoride exposure may partly result from the enhanced miR-124 and miR-132 and the alterations of their target genes… he numbers of Nissl bodies in neurons in the hippocampus and cortex of brains from both adult rats and their pups with fluorosis were lowered. Such reduction in Nissl bodies, showing large granular bodies consisting of rough endoplasmic reticulum with rosettes of free ribosomes carrying out protein synthesis, indicates injury of neurons.

Changed expressions of N-methyl-D-aspartate receptors in the brains of rats and primary neurons exposed to high level of fluoride
Wei et al., 2018, Journal of Trace Elements in Medicine and Biology

Expressions of N-methyl-d-aspartic acid receptors (NMDARs) in the brains of rats and primary neurons exposed to high fluoride were investigated. Sprague-Dawley rats were divided randomly into a fluorosis group (50 ppm fluoride in the drinking water for 6 months) and controls (<0.5ppm fluoride) and the offspring from these rats sacrificed on postnatal days 1, 7, 14, 21 and 28.

ERK1/2-mediated disruption of BDNF–TrkB signaling causes synaptic impairment contributing to fluoride–induced developmental neurotoxicity
Chen et al., 2017, Toxicology

Using Sprague-Dawley rats developmentally exposed to sodium fluoride (NaF) from pregnancy until 6 months of delivery as in vivo model, we showed that fluoride impaired the cognitive abilities of offspring rats, decreased the density of dendritic spines and the expression of synapse proteins synaptophysin (SYN) and postsynaptic density protein-95 (PSD-95) in hippocampus, suggesting fluoride-induced cognitive deficit asxsociates with synaptic impairment. Consistently, NaF treatment reduced dendritic outgrowth and expression of SYN and PSD-95 in human neuroblastoma SH-SY5Y cells. Collectively, these data suggest that the developmental neurotoxicity of fluoride is associated with the impairment of synaptogenesis…

Effects of fluoride exposure on thyroid hormone level and intelligence in rats.
Cui et al., 2017, Chinese Journal of Industrial Hygiene and Occupational Diseases

The offspring rats in the medium-and high-fluoride exposure groups had significantly lower serum TSH and FT(4) levels than those in the control group (P<0.05)…

Conclusion: High fluoride exposure can reduce the secretion of thyroid hormone and the abnormality of mitochondrial dynamics in peripheral lymphocytes may provide a clue to identifying the biomarkers of intellectual impairment induced by fluoride exposure.

Fluoride and arsenic exposure affects spatial memory and activates the ERK/CREB signaling pathway in offspring rats
Zhu et al., 2017., Neurotoxicology

This study explored the effects of fluoride and arsenic exposure in drinking water on spatial learning, memory and key protein expression in the ERK/CREB signaling pathway in hippocampal and cerebral cortex tissue in rat offspring… Compared with controls, ERK and p-ERK levels decreased in the hippocampus and cerebral cortex in pups exposed to combined fluoride and arsenic. CREB protein expression in the hippocampus and cerebral cortex decreased in pups exposed to fluoride, arsenic, and the fluoride and arsenic combination. p-CREB protein expression in both the hippocampus and cerebral cortex was decreased in PND42 pups, and p-CREB expression in the cerebral cortex was decreased in PND21 pups exposed to fluoride and arsenic in combination compared to the control group... These data indicate that exposure to fluoride and arsenic in early life stage decreases ERK, p-ERK, CREB and p-CREB protein expression in the hippocampus and cerebral cortex of rat offspring at PND21 and PND 42, which may contribute to impaired neurodevelopment following exposure.

Neurobehavioural effects of exposure to fluoride in the earliest stages of rat development
Bartos et al., 2015, Physiology & Behavior

- Exposure to low levels of Fluoride during pregnancy and lactation was studied.
- Fluoride produces a delay in eye opening development in all offspring.
- Adult offspring exposed to low Fluoride concentrations showed hypoactivity.
- Exposure to F reduced anxiety levels in young female and in all adult offspring.
- Low F concentrations produce dysfunction in the central nervous system.

Fluoride toxicity and status of serum thyroid hormones, brain histopathology, and learning memory in rats: a multigenerational assessment.
Basha et al., 2011, Biological Trace Element Research

Significant decrease in the serum-free thyroxine (FT4) and free triiodothyronine (FT3) levels and decrease in acetylcholine esterase activity in fluoride-treated group were observed. Presence of eosinophilic Purkinje cells, degenerating neurons, decreased granular cells, and vacuolations were noted in discrete brain regions of the fluoride-treated group. In the T-maze experiments, the fluoride-treated group showed poor acquisition and retention and higher latency when compared with the control. The alterations were more profound in the third generation when compared with the first- and second-generation fluoride-treated group. Changes in the thyroid hormone levels in the present study might have imbalanced the oxidant/antioxidant system, which further led to a reduction in learning memory ability. Hence, presence of generational or cumulative effects of fluoride on the development of the offspring when it is ingested continuously through multiple generations is evident from the present study.

Investigation on the role of Spirulina platensis in ameliorating behavioural changes, thyroid dysfunction and oxidative stress in offspring of pregnant rats exposed to fluoride.

Banji et al., 2013, Food Chemistry

- Sodium fluoride exposure from pregnancy to lactation induces thyroid toxicity.
- This can affect neurodevelopment and induce behavioural changes.
- *Spirulina platensis* role in reversing fluoride-induced toxicity was ascertained.
- Significant protection was exerted by *Spirulina*

Effects of high fluoride and low iodine on thyroid function in offspring rats
Ge et al., 2013, Journal of Integrative Agriculture

Thirty-two Wistar rats were divided randomly into four groups of eight with six females and two males in each group. The rats were exposed to high fluoride drinking water (45 mg F- L-1 from 100 mg NaF L-1), low dietary iodine (0.0855 mg kg-1), or both together in order to assess the effects of these three regimens on the thyroid function of the offspring rats. After the animal model was established, the offspring rats were bred and 10-, 20-, 30-, 60-, and 90-d-old rats were used for the experiment… In comparison with control rats, the relative thyroid glands were changed by three regimens, but the mean values of thyroid weight in the experimental groups saw no marked difference. Serum TT3 levels were increased in all stages in the low iodine (LI) group. In the high fluoride (HiF) group, increase in TT3 levels was observed except in 20-d-old rats. Decrease in TT3 at 20- and 90-d and increase in TT3 at 30- and 60-d were found in HiF+LI group. Serum TT4 levels first saw an increase, and then dropped in the LI and HiF+LI group. However, an increase in TT4 was found in the HiF group. The levels of TSH in serum rocketed at d 20, and then dropped in the next stages in experimental groups. The results suggested that thyroid disorder could be induced by high flroride in drinking water, low iodine diet, or both of them. Exposure time to fluoride or low iodine diet was one of the important factors that fluoride can induce the development of thyroid dysfunction.

Fluoride increases lead concentrations in whole blood and in calcified tissues from lead-exposed rats.
Sawan et al., 2010, Toxicology

we examined whether fluoride co-administered with lead increases BPb and lead concentrations in calcified tissues in Wistar rats exposed to this metal from the beginning of gestation. We exposed female rats and their offspring to control water (Control Group), 100mg/L of fluoride (F Group), 30mg/L of lead (Pb Group), or 100mg/L of fluoride and 30mg/L of lead (F+Pb Group) from 1 week prior to mating until offspring was 81 days old… findings show that fluoride consistently increases BPb and calcified tissues Pb concentrations in animals exposed to low levels of lead and suggest that a biological effect not yet recognized may underlie the epidemiological association between increased BPb lead levels in children living in water-fluoridated communities.

Decreased learning ability and low hippocampus glutamate in offspring rats exposed to fluoride and lead.
Niu et al., 2009, Environmental Toxicology and Pharmacology

Results showed that the learning abilities and hippocampus glutamate levels were significantly decreased by F and Pb individually and the combined interaction of F and Pb. The activities of AST and ALT in treatment groups were significantly inhibited, while the activities of GAD were increased, especially in rats exposed to both F and Pb together. These findings suggested that alteration of hippocampus glutamate by F and/or Pb may in part reduce learning ability in rats.

Neurofunctional effects of developmental sodium fluoride exposure in rats.
Bera et al., 2007, European Review for Medical and Pharmacological Sciences

NaF solution was administered to pregnant rats by intragastric gavage at a daily dose of 2.5 and 5.0 mg/kg from gestational day 0 to day 9 after parturition. Developmental NaF exposure caused sex and dose specific behavioural deficits which affected males more than females in the majority of the evaluated end-points. In particular, the perinatal exposure to NaF 5.0 mg/kg, significantly affected learning, memory, motor coordination and blood pressure only in male rats. Conversely, a lack of habituation upon the second presentation of the objects and failure in the ability to discriminate between the novel and the familiar object were observed only in NaF 5.0 mg/kg female rats. Finally, a significant impairment of sexual behaviour was observed in male rats at both NaF dose levels. The present data indicate that perinatal rat exposure to NaF results in long lasting functional sex-specific alterations which occur at fluoride levels approaching those experienced by offspring of mothers.

Effects of high fluoride and low iodine on oxidative stress and antioxidant defense of the brain in offspring rats.
Wang et al., 2004, Fluoride

Superoxide dismutase (SOD) activity and the malondialdehyde (MDA) content in the brain of the combined high fluoride and low iodine group were significantly higher during and at the end of the 90-day period than in the control group, but the SOD/MDA ratio in this high fluoride and low iodine group was consistently lower than in the control group. These results suggest that brain stress from high fluoride and low iodine is one of the causes of reduction in learning and memory in offspring rats.