Fluoride,
Premature Birth and
Impaired Neurodevelopment

John D. MacArthur. Jr.

A global review of recent laboratory, clinical, and ecological evidence
that fluoride is a significant risk factor for premature birth
and long-term neurological disabilities in children

This report is a revised and updated version (February 2019)
of the one published in the November 2013 print edition of
the *Townsend Letter: The Examiner of Alternative Medicine.*

It's also available in the author's book
Pregnancy and Fluoride Do Not Mix
that includes his two other reports
published by the *Townsend Letter*:

"Prenatal Fluoride and Autism"

"Placental Fluorosis: Fluoride and Preeclampsia"

PregnancyAndFluorideDoNotMix.com

John Douglas MacArthur, Jr.

Contents

Fluoride, Premature Birth and Impaired Neurodevelopment

Premature or preterm birth is birth prior to 37 weeks (8.5 months) of pregnancy. According to the US Institute of Medicine:

> "Those born preterm have an appreciable risk of long-term neurological impairment and developmental delay...
>
> "Preterm infants are more likely to have lower IQs and require significantly more educational assistance than children who were born at term...
>
> "The annual societal economic burden associated with preterm birth in the United States was at least $26.2 billion in 2005, or $51,600 per infant born preterm."[1]

Preterm birth is the most common pregnancy complication that can seriously compromise the newborn brain's viability and normal development. Many studies have documented the prevalence of a broad range of neurodevelopmental disabilities and dysfunctions in people who were born preterm, including mental retardation, ADHD, and major depression.

Prenatal Brain Development

"The genesis and wiring of the human brain during fetal development is one of the most remarkable feats in all of biology." During the last trimester, the weight of the brain roughly triples from about 100 to 300 grams. The cerebrum undergoes "striking changes in white matter," and premature birth can interrupt this vital developmental process. White matter damage is the most commonly recognized pathology of prematurity.[2]

British researchers used a novel form of magnetic resonance imaging to track the growing complexity of nerve cells in the fetal brain before the normal time of birth. Maturation was most rapid in areas relating to social and emotional processing, decision making, working memory, and visual-spatial processing – functions often impaired after premature birth.

> "These findings highlight a key stage of brain development where the neurons branch out to create a complex, mature structure. We can now see that this happens in the latter stages of development that would usually take place in healthy babies when they are still in the womb... With this study we found that the earlier a baby is born, the less mature the cortex structure. The weeks a baby loses in the womb really matter." – Centre for the Developing Brain at King's College London[3,4]

US Preterm Birth Rate Unusually High

The misconception that preterm birth is a third-world problem was shattered in May 2012 by the first global report to compare preterm birthrates in 184 countries. Three years in the making, "Born Too Soon: The Global Action Report on Preterm Birth" was produced jointly by the World Health Organization, Save the Children, March of Dimes, and Partnership for Maternal, Newborn and Child Health.[5]

America lags behind 130 other nations in preterm birth rate. The United States is similar to developing countries in the percentage of mothers who give birth before their children are due. "It does worse than any Western European country and considerably worse than Japan or the Scandinavian countries," reported Donald G. McNeil, Jr. in the *New York Times*. Most European countries are in the 7% to 9% range, while the United States shares the 12% range with Kenya, Turkey, Thailand, East Timor, and Honduras – meaning that one in nine births is early.[6]

"This report offers conclusive evidence that the United States rate of preterm birth has been far too high for far too long," says March of Dimes president Dr. Jennifer Howse. "We have failed to do enough to prevent preterm births and help more mothers carry their babies full-term."[7]

"If somebody had a simple explanation of why the UK and Europe do much better, I wouldn't believe them," says preterm birth expert Dr. Gordon C. S. Smith. "The reality is, for most preterm births, we just don't understand the cause."[6]

Residence in the US a Risk Factor for Preterm Birth

A 2012 study involving 2,141 women revealed that duration of stay in the US is associated with increased risk of preterm birth for Hispanic women. Dr. Radek K. Bukowski, an expert on premature birth at the University of Texas Medical Branch in Galveston, found that the longer a woman lived in this country, the greater her chances of giving birth prematurely.

Women living in the US for less than 10 years had a 3.4% frequency of preterm birth. Those here for 10+ years had a 7.4% frequency. Women born in the US had a 10% frequency of preterm birth.[8]

The findings support the hypothesis that preterm birth is, at least in part, related to environmental, potentially preventable, factors. It remains unclear what specific environmental factors protect or predispose women to preterm birth. Even after controlling for risk factors such as age, poverty, smoking, obesity, and diabetes, Bukowski admitted: "We really don't have an explanation for what's behind it. It's something they acquire here."[6]

Best-Available Science Will Reduce Preterm Birth by Only 5%

Although preterm birth is the leading cause of death for children younger than five years in high-income countries, second leading cause worldwide, and a major contributor to the "global burden of disease," it wasn't until 2013 that the first multi-country analysis of trends in preterm birth rates was published.

The international team of researchers concluded, "The current potential for preterm birth prevention is shockingly small." If five proven interventions were implemented, it would lower the preterm rate from an average 9.6% of live births to 9.1%. The most effective of these evidence-based interventions is decreasing non-medically indicated caesarean deliveries and induced labor. Dr. Joy Lawn of Save the Children, who coordinated the research, says, "The best-available science will allow just 5 percent relative reduction in high-income countries' preterm birth rates by 2015." Note: of the 39 countries with a "very high human development index," the US has the third highest preterm birth rate (after Cyprus and Bahrain).[9,10]

Because the triggers for premature labor are not fully understood, the poor performance by the US is partly a mystery, said Dr. Alan E. Guttmacher, Director of the National Institute of Child Health and Human Development. "This underscores the need for more research," especially because, as the March of Dimes points out, in up to 40% of cases, the cause of preterm birth is unknown.

It also underscores the need to acknowledge existing research: laboratory, clinical, and ecological evidence that fluoride consumption is a significant risk factor for preterm birth – as this report documents. Unfortunately, health agencies and organizations in the United States typically ignore such research.

Fluoride: Ancient Enemy of Biological Systems

Many Americans think there's nothing wrong with fluoride, a chemical added to nearly three-fourths of their public water supplies and now permeates the nation's processed food and beverage chain. Even Ronald R. Breaker, PhD, a National Academy of Sciences award-winning molecular biologist with a doctorate in biochemistry "did not know that biology cared much about this ion."[11]

Breaker and his team of experts in microbiology and bioinformatics at Yale University's Howard Hughes Medical Institute study a type of noncoding RNA called a *riboswitch* that helps turn genes on and off. In 2011, they discovered a new riboswitch but could not figure out its function, until a chemistry graduate student "overcame any biases" and quickly demonstrated that pure fluoride indeed triggers riboswitch function that helps cells fight fluoride's "antimicrobial properties."[11-13]

"Despite this evidence, we were still unwilling to accept that fluoride was the natural target," admits Breaker. "It is very likely no one would have solved the mystery of fluoride riboswitches for several more decades, if we had not been lucky enough to receive a contaminated chemical sample spiked with fluoride."[11]

Genes associated with fluoride-sensitive riboswitches are very widespread in biology. Breaker said this new riboswitch is "one of the only non-coding RNAs we've ever found that's present in both bacteria and archaea," a recently identified major domain of life. This suggests an ancient biological system that cells have evolved to deal with fluoride's toxicity.[13,14]

Molecular Mechanisms of Fluoride Toxicity

The authors of a comprehensive 2010 scientific review note that until the 1990s, the toxicity of fluoride was largely ignored due to its "good reputation" for preventing dental caries via topical application in toothpastes. In the last decade, however, interest in its undesirable effects has resurfaced due to the awareness that "this element interacts with cellular systems even at low doses."[15]

> "Even though some studies report no clear evidence on the potential negative effects of fluoride exposure at permissible concentrations (e.g., studies that support water fluoridation), others have shown evidence of fluoride's effects on cellular processes at biologically relevant concentrations. When discussing these controversial results, it is important to highlight that fluoride must be actively considered as a potent toxic compound in the field of toxicology...
>
> "Fluoride can interact with a wide range of cellular processes such as gene expression, cell cycle, proliferation and migration, respiration, metabolism, ion transport, secretion, endocytosis, apoptosis/necrosis, and oxidative stress, and that these mechanisms are involved in a wide variety of signaling pathways."[15]

Fluoride Inhibits the Enzyme Enolase

"Although the toxicity of fluoride is well known, it has been ignored for a long time... As a result, the consumption of fluoride by humans became uncontrolled and unpredictable, often exceeding its therapeutic window," say the authors of the 2012 scientific review, "Molecular Mechanisms of Cytotoxicity and Apoptosis Induced by Inorganic Fluoride." The Russian researchers detail the many ways fluoride harms life. One mechanism: "Fluoride is a well-known inhibitor of enzymes of the glycolytic pathway, first of all enolase."[16]

"Inhibition of glycolysis by fluoride is central to the concept that the anti-microbial effect of fluoride has a role in caries prevention," reported Canada's leading dental journal, *Oral Health*. The bacterium that inhabits the human mouth, *Streptococcus mutans*, causes dental caries by converting dietary sugars into enamel-corroding lactic acid. Fluoride interferes with the complete breakdown of glucose by inhibiting enolase, an intermediary enzyme in the pathway. This results in a reduction in the synthesis of lactic acid and in a significant reduction in the metabolic activity of the cariogenic bacteria.[17]

Fluoride's inhibition of enolase, however, is not limited just to the mouth. Exposure of red blood cells (erythrocytes) to fluoride produces a variety of metabolic alterations.[18]

Via its effect on enolase in human red blood cells, fluoride inhibits active sodium transport, aerobic glucose utilization, and lactate formation.[19,20]

Working with red blood cells of rats, researchers found that sodium fluoride leads to impairment of the cellular antioxidant system; severe energy depletion; and triggers rapid progression of cell death in a dose- and time-dependent manner. Long-term intoxication of the rats with fluoride triggers premature death of their erythrocytes due to intrinsic death-associated biochemical defects and development of anemia.[21-23]

Fluoride, Anemia, and Preterm Birth: A.K. Susheela's Research

Anemia is a condition marked by a deficiency of red blood cells or of hemoglobin, the red protein in blood cells responsible for transporting oxygen in the blood. Anemia is common in pregnancy, because a woman needs to have enough red blood cells to carry oxygen around her body and to her baby.

The leading expert on the connection between fluoride, anemia, and preterm birth is A.K. Susheela, PhD, who has spent more than 25 years researching fluoride toxicity and has over 80 scientific publications in Western and Indian journals**.** She is executive director of the Fluorosis Research and Rural Development Foundation in India, winner of the 2013 Spirit of Humanity Award in Women's Health presented by AmeriCares India.

"There is now ample scientific evidence to support the fact that ingestion of fluoride prevents biosynthesis of hemoglobin, leading to anemia in human beings," says Susheela.[24] "Fluoride decreases production of erythrocytes (red blood cells) by the bone marrow and other hemopoietic tissues and increases erythrocyte abnormalities resulting in premature death of red blood cells."[25]

In 2010, Susheela conducted a clinical program that emphasized a greatly reduced intake of fluoride and the inclusion of essential nutrients in the daily diet during pregnancy. "Effective Interventional Approach to Control Anemia in Pregnant Women" was the first report dealing with fluoride, pregnancy, anemia, low birthweight babies and the linkages to act upon for the benefit of maternal and reproductive child health programs.[26]

The 205 pregnant women in the study were all anemic. Their hemoglobin levels were less than 9 g/dl, and their urinary fluoride levels were more than 1 mg/l. Ninety pregnant women formed the sample group, and 115 formed the control group. "The major focus of the investigation of the sample group was to eliminate ingestion of fluoride as much as possible," says Susheela. "The sample group was counseled to avoid consumption of fluoride-containing food, water, and other substances." They even changed their toothpaste to a low-fluoride paste. The women were also counseled to ensure an adequate intake of essential nutrients: calcium, vitamins, and antioxidants from dairy products, fruits, and vegetables. The women in the control group were not counseled, but both groups received the standard iron and folic acid tablets.[25,26]

By the time of delivery, improvements in the women's body-mass index were considerably better in the sample group than in the control group, suggesting that the sample group was absorbing nutrients more efficiently. Also, hemoglobin increased by an average of 78% in the sample group compared to 57% in the controls.

> "A striking impact of these interventions for improving the gestation period was also noted." In the sample group, 32% of the women delivered before 37 weeks – compared to 50% in the control group.[25,26]

At the Global Maternal Health Conference convened in New Delhi in 2010, Susheela presented results of a similar but larger study of 481 pregnant women, further confirming:

> "Maternal and child under-nutrition and anemia is not necessarily due to insufficient food intake, but because of the derangement of nutrient absorption due to damage caused to GI mucosa by ingestion of an undesirable chemical substance, namely fluoride through food, water and other sources."[26,27]

Prenatal Fluoride Linked to Low Birthweight

In Susheela's clinical study, the number of low birthweight babies was reduced to 22% in the sample groups of mothers who avoided fluoride, as opposed to 52% in the control groups.[26]

A 2011 study with 108 pregnant women (17-36 years old) concluded: "With increased serum fluoride in the mother, there is an inclination towards preterm delivery, low birthweight, and poor APGAR count."[28] APGAR evaluates a newborn's appearance, pulse, grimace, activity, and respiration.

A 2012 case-control study found a significant association between fluoride levels in the drinking water consumed, dental fluorosis in mothers, and low birthweight of newborns.[29]

Low Birthweight, Cognitive Problems, Autism, and Obesity
Links between low birthweight and a range of motor and cognitive problems have been well known for some time. The 2007 National Summit on America's Children presented an analysis of 35 years of data on more than 12,000 individuals – the first to link birthweight with adult health and socioeconomic success, using a full nationally representative sample of the US population. Some findings:

> "Compared to their normal birth weight siblings, low birthweight children are 30 percent less likely to be in excellent or very good health in childhood. They also score significantly lower on reading, passage comprehension, and math achievement tests... Low birthweight children are nearly twice as likely as their normal birth weight siblings to be in problematic health by ages 37-52."[30]

In 2011, researchers at the University of Pennsylvania found that the rate of autism spectrum disorders is highly elevated in children and adults who were born at low birthweight. For 21 years, they followed a regional birth cohort of 1,105 children who weighed less than 2,000 grams (4 pounds, 6 ounces) at birth – finding that 5% of the low birthweight children were diagnosed with autism, compared to 1% of the general population.[31]

Low-birthweight infants also have an increased risk for developing adult obesity.[32] Obesity increases the risk of preterm delivery. A 2013 study of 1.5 million deliveries in Sweden found that women with the highest Body Mass Index also had the highest statistical risk of giving preterm birth. Researchers at Karolinska Institutet say that maternal overweight and obesity have replaced smoking as the most important preventable risk factor for adverse pregnancy outcomes in many countries. In the US, where preterm delivery rates are twice as high as in Sweden, 53% of pregnant women are either overweight or obese compared to 34% of pregnant women in Sweden.[33] (Sweden has prohibited water fluoridation since 1971.)

Iron-Deficiency Anemia
Iron is the main constituent of the hemoglobin molecule, hence a deficiency in iron is a major cause of anemia. About half of all pregnant women don't have enough iron in their body. Pregnant women need about twice as much iron as usual, therefore they have a higher risk of iron-deficiency anemia, which can increase the risk of preterm delivery and low birthweight.

As with most mineral nutrients, iron from digested food is absorbed in the intestinal lining by epithelial cells whose microvilli provide the huge surface area needed to efficiently absorb nutrients. "Fluoride not only decreases production of red blood cells by the bone marrow but also destroys microvilli – the microscopic protrusions lining the intestine," notes Dr. Susheela.[34] "Fluoride diminishes beneficial microbial growth in the gut... resulting in poor absorption of nutrients critical for the biosynthesis of hemoglobin."[25]

In June 2013, Susheela and her team submitted to the Indian Council of Medical Research results of a three-year study to correct anemia in more than 2,500 adolescent school children, ages 10 to 17. When fluoride was withdrawn and nutritious food promoted, the children's anemia was corrected. In contrast, anemia continued in the control group that consumed fluoride, even though they ate a nutritious diet.

Microflora in the GI Tract
The human gut is the natural habitat for a large and dynamic bacterial community. Major functions of the gut microflora include metabolic activities that result in salvage of energy and absorbable nutrients. Colonic microorganisms also play a part in vitamin synthesis and in absorption of calcium, magnesium, and iron.[35]

Lactobacillus acidophilus belongs to a group of bacteria that live in the human small intestine. These beneficial microorganisms aid digestion, help maintain a healthy intestinal tract, and prevent harmful bacteria from congregating there. *L. acidophilus* has been shown to increase iron bioavailability in studies with animals.[36]

When children were fed an iron-fortified probiotic milk beverage supplemented with *L. acidophilus*, they "exhibited higher red blood cell status and a positive correlation between iron intake and hemoglobin" – evidence to support the use of *L. acidophilus* to prevent anemias in children.[37]

When fluoride comes in contact with *L. acidophilus*, it inhibits this beneficial bacterium that aids in the absorption of iron. Fluoride-containing resin-based dental sealants have proved "capable of contact inhibition of *L. acidophilus* and *S. mutans* growth."[38] A statistically significant 49% reduction in *L. acidophilus* counts was obtained 24 hours following mouth rinsing by Egyptian children with 0.05% sodium fluoride solution.[39]

In a 2013 interview, Dr. Susheela explained why India's Iron and Folic Acid Supplementation Program has failed to prevent anemia. As long as fluoride consumption is high, she said:

> "No amount of tablets is going to solve anything. Withdrawal of fluoride on the other hand permits the regeneration of microvilli in the gut which improves the absorption of nutrients from the diet and hemoglobin levels improve.
>
> "The evidence is there for the scientific community, bureaucrats, and policymakers, but no one has reproduced it nationally or globally. They're simply not willing to accept the truth."[34]

Thyroid Disorders and Preterm Birth

Subclinical hypothyroidism is associated with an increasing number of adverse effects including infertility, miscarriage, and preterm birth.[40] In a 2005 study of 25,756 women, preterm birth was almost two-fold higher in women with subclinical hypothyroidism compared to women with normal thyroid-stimulating hormone levels.[41]

Each year in the US, at least 80,000 pregnant women have thyroid diseases. A 2013 analysis of 223,512 pregnancies in the United States (2002-2008) found that women with thyroid disorders face greater risk of preterm birth and other complications that have short- and long-term consequences for the health of mother and child, including preeclampsia.[42]

Anemia is often the first sign of hypothyroidism,[43] perhaps in part because thyroid hormones modulate the glycolytic enzyme enolase.[44]

Because of its antagonism to iodine, fluoride has long been known to interfere with the function of the thyroid gland.[45] In 2006, the US National Research Council found substantial evidence that fluoride exposure can impact thyroid function in some individuals. Furthermore, in pregnant women, subclinical hypothyroidism is associated with "decreased IQ of their offspring."[46]

A 2015 study found that high rates of hypothyroidism were at least 30% more likely in areas with water fluoride levels above 0.3 mg/l.[47] This was confirmed by a 2018 Canadian study that found the risk of hypothyroidism increases in adults who have iodine deficiencies and higher urinary fluoride levels.[47b]

Prematurity and Infant Mortality

The main cause of the high US infant mortality rate, when compared with Europe, is the very high percentage of preterm births in the United States. After identifying the top 20 leading causes of infant death, the CDC determined that preterm birth is the most frequent cause of infant death in the United States, accounting for 36% of infant deaths in 2007.[48] Prematurity is the #1 cause of death in the first month of life. In 2008, nearly 10,000 babies in the US died from preterm birth-related causes.[49] (See page 11.)

Preterm birth doesn't just affect the mortality of infants. A study of 674,820 individuals born in Sweden (who survived to age one) found that "low gestational age at birth was independently associated with increased mortality in early childhood and young adulthood."[50]

The severity of all the problems associated with being born early depends on the degree of prematurity. A 2012 study of 128,000 New York kids found that "each week of increased gestation from 37-41 weeks showed an added benefit in both reading and math scores."[51]

Water Fluoridation and Preterm Birth Rates

A 2009 public-health study, Relationship Between Municipal Water Fluoridation and Preterm Birth in Upstate New York, was undertaken by researchers from the Department of Epidemiology & Biostatistics at the State University of New York (SUNY), because:

> "Current literature suggests an association between periodontal disease and preterm birth. Domestic water fluoridation is thought to have lessened the burden of dental disease. Theoretically, one would expect water fluoridation to be protective against preterm birth."[52]

What was found however surprised the researchers, who did not expect fluoridated water to be positively associated with preterm birth rates – yet they had to conclude otherwise:

> "Domestic water fluoridation was independently associated with a [15%] increased risk of preterm birth in logistic regression, after controlling for age, race/ethnicity, neighborhood poverty level, hypertension, and diabetes."[52]

Results of this study were presented at the 2009 American Public Health Association Meeting, but subsequently were never published. One can't help but wonder how much other fluoride research goes unpublished, when results don't support expectations. Case in point:

> The 2007 Oregon Smile Survey showed that non-fluoridated Portland had lower rates of tooth decay. After fluoridation promoters were confronted with this reality check, they omitted Portland statistics from their next survey (2012). When a journalist compared tooth-decay rates of children living in fluoridated vs. nonfluoridated areas of Oregon, fluoridated students averaged a 9% higher decay experience than unfluoridated kids living in the Portland water district (52.03% vs. 47.81%).[53]

After the SUNY public health study, a logical next step would have been to look at available data for ecological associations elsewhere in the US. According to CDC data for 2010, in the 25 least fluoridated states (avg. 52%), the preterm birth rate averaged 116 per 1,000 births. In the 25 most fluoridated states (avg. 90%), the preterm birth rate averaged 5.8% higher: 122 per 1,000 births.[54,55]

If that difference of six births per 1,000 were extrapolated to the United States, where four million births occurred in 2010 (when 66% of the population was fluoridated), then higher levels of water fluoridation would be associated that year with about 16,000 more preterm births – each one with an annual societal economic burden of more than $50,000.[2] (The 2016 difference in preterm rates was 14% higher: 6.6% in the 25 most vs the 25 least fluoridated states.[55b])

Although this nationwide statistical association is not adjusted for age, race, poverty, and maternal disease (as the SUNY study was), nevertheless it is the best large-scale population data we have – a snapshot that supports laboratory and clinical studies showing an association between fluoridated water and preterm birth. It should not be dismissed, but after the SUNY study, no further research has been published.

Similar statistical snapshots of America in 2010 reveal that low-birthweight rates averaged 5% higher, and infant mortality rates averaged 17% higher in the 25 most-fluoridated states compared to the 25 least-fluoridated states.[56,57] (See page 11 for infant mortality rates in 2013.)

Fluoridated water's multiple correlations with *life decay* make a far more compelling case to halt fluoridation, than its single correlation with tooth decay did to start fluoridation in 1945.

Link Between Preterm Birth and Brain Disorders
In 2012, researchers at the University of Adelaide discovered a possible mechanistic link between the altered brain physiology of preterm birth and subsequent neurological deficits. Their research provides the first physiological evidence that human adolescents who were born preterm have a "significantly reduced capacity for cortical neuroplasticity." Dr. Julia Pitcher of the Robinson Institute says plasticity in the brain is vital for learning and memory throughout life. "It enables the brain to reorganize itself, responding to changes in environment, behavior and stimuli by modifying the number and strength of connections between neurons and different brain areas."[58]

"The growth of the brain is rapid between 20 and 37 weeks gestation, Pitcher said. "Being born even mildly preterm appears to subtly but significantly alter brain microstructure, neural connectivity, and neurochemistry." In contrast, the brains of term-born teenagers were highly plastic.[58]

This study's findings also suggested a mechanism. Altered hypothalamic-pituitary-adrenal (HPA) axis function due to preterm birth may be "a significant modulator of this altered neuroplasticity." The HPA axis a complex neurohormone mechanism that regulates metabolic and behavioral reactions to physiological and environmental stress. It is highly susceptible to programming during fetal and neonatal development.

Animal and human studies have demonstrated that stress associated with preterm birth provokes adaptive changes in endocrine and metabolic processes that become permanently programmed via the HPA axis – affecting later health, memory, learning, executive function, and associated behavior throughout life.[59-61]

Premature birth is a stressful event, not only due to a shortened gestation period, but also because of medical interventions during the first weeks of life (painful procedures, handling, mechanical ventilation, maternal separation).

Abnormal regulation of the HPA axis is commonly associated with a range of affective and stress-related disorders. A 2012 Swedish study of more than a million individuals found that preterm birth was significantly associated with increased risk of psychiatric hospitalization in adulthood across a range of psychiatric disorders.[62]

HPA Axis and the Gut
"The gut microbiota contributes to developmental programming; a process whereby an environmental factor acting during a developmental 'window of vulnerability' can have a potentially life-long impact on physiological function," say researchers at the Brain-Body Institute at McMaster University in Ontario, Canada. The presence of gut microbiota regulates the set point for HPA axis activity.[63,64]

Findings from a 2004 study "suggest that exposure to indigenous microbiota at an early developmental stage, when brain plasticity may still be preserved, is required for the HPA system to become fully susceptible to inhibitory neural regulation."[65]

Attention-Deficit Hyperactivity Disorder (ADHD)
In a study of boys with ADHD and disruptive behavior symptoms, those scoring high on "callous unemotional traits" showed a blunted HPA axis reactivity to the experimentally induced stress.[66]

In the US, ADHD is the most common neurodevelopmental disorder of childhood. The estimated prevalence of diagnosed ADHD among children and adolescents aged 4 to 17 years was 10.2% in 2015-2016, representing a significant increase from 1997-1998.[66b] The results of a long-running study found that 29% of the children with ADHD still had ADHD as adults, and 81% of them still had at least one other psychiatric disorder, compared to 47% of those no longer with ADHD and to 35% of controls.[67] ADHD costs Americans with it about $77 billion per year in lost income.[67b]

Premature infants have significantly more severe symptoms of ADHD at school age.[68] Another statistical snapshot of America reveals that the percent of children in 2011 currently diagnosed with ADHD averaged 24% higher in the 20 states whose public drinking water was more than 85% fluoridated, compared to the 30 least fluoridated states.[54,69]

A 2015 study found that each one-percent increase in artificial fluoridation prevalence was associated with approximately 67,000 to 131,000 additional ADHD diagnoses (2003 to 2011).[70] In 2018, a major study (partially funded by the US National Institutes of Health) revealed that higher maternal levels of fluoride during pregnancy are associated with more ADHD-like symptoms in school-age children.[70b]

Prenatal Fluoride and Hyperactivity
A landmark study led by Phyllis Mullenix, PhD, found that rats exposed prenatally to fluoride exhibit higher levels of hyperactivity.[71] After her research was published in *Neurotoxicology and Teratology* (1995), Mullenix was fired from Boston's Forsyth Dental Center, where for 10 years she had been Head of the Toxicology Department. As documented by investigative journalist Christopher Bryson in *The Fluoride Deception*, Forsyth's associate director told Mullenix:

> "You are going against what the dentists and everybody have been publishing for fifty years, that this is safe and effective. You must be wrong. You are jeopardizing the financial support of this entire institution. If you publish these studies, NIDR [National Institute of Dental Research] is not going to fund anymore research at Forsyth." (Forsyth was getting about 90% of its money from NIDR.)[72]

By 2010, more than 80 animal studies had confirmed what Mullenix et al. reported.[73] Also, the Neurotoxicology Division of the EPA had found "substantial evidence" that fluoride is a chemical "toxic to the developing mammalian nervous system."

Note: rat studies involving higher doses of fluoride are relevant to humans, because research shows that when rats consumed 75-125 ppm and humans 5-10 ppm fluoride in their respective drinking waters, the result was equivalent ranges of plasma fluoride levels.[74]

Fluoride, Defective Tooth Enamel, and Prematurity
A major 2011 European review of fluoride's health effects concluded: "Systemic exposure to fluoride through drinking water is associated with an increased risk of dental and bone fluorosis in a dose-response manner without a detectable threshold."[75]

Studies show that the prevalence and severity of developmental defects of enamel (DDE) in children increase significantly with the increase in fluoride levels in drinking water, as well as with the ingestion of fluoride tablets.[76-78]

Premature infants are more frequently affected by tooth enamel anomalies or defects when compared with infants born at term. An Australian study of 8,411 children found the prevalence of DDE in children and adolescents born prematurely was 56.5%, while the control group was 9.3%.[79]

Low-birthweight children more likely than their normal birthweight counterparts to have enamel hypoplasia, a form of DDE in which the tooth enamel is hard but thin and deficient in amount.[80]

Developmental enamel defects in primary teeth have been found at least twice as frequently in children with mental retardation.[81] Another statistical snapshot of America reveals that children's mental retardation rates in 1993 averaged 33% higher in the 26 states fluoridated above the average national level, compared to the 24 least-fluoridated states. Twenty years later it averaged 57% higher![82]

Genetic Factors
Animal studies show there is a genetic component in the pathogenesis of dental fluorosis and in bone response to fluoride exposure. Different strains of inbred mice demonstrate differential physiological responses to ingested fluoride.[83,84]

In human populations, African Americans appear to be more vulnerable to fluoride's toxicity. They have higher rates of dental fluorosis as well as preterm birth. A study of 83 African American and 109 White children (7-14 years old) found that even though both groups had the same water and saliva fluoride concentrations, dental fluorosis was observed in 63% of White children, but in 80% of African American children.[85]

"Approximately 50% of preterm birth has no clear medical cause, and evidence strongly suggests that genetic factors contribute to some of these cases," says Dartmouth Professor of Genetics Scott Williams, PhD. It's unknown why preterm birth happens in about 10% of pregnancies in Caucasian women nationwide, but in about 20% of pregnancies of African-American women.[86]

When a genetic predisposition is combined with mild inflammation, the rate of preterm birth profoundly increases in mice. Researchers observed aspects of the same molecular signatures in tissue samples of women who had undergone preterm birth: increases in cyclooxygenase-2 (COX-2) signaling.[87] Fluorides have well-established ability to cause and aggravate inflammation,[15] including increased expression of COX-2 in human cells.[88]

We really don't know the racial and genetic factors that determine an individual's resistance to developing fluorosis and susceptibility to fluoride's multiple mechanisms of toxicity in the body and brain.[15,16]

Fluoride Contaminates US Processed Food and Beverage Chain
Americans consume uncontrolled and unknown amounts of fluoride. Water is the predominant source of fluoride in the United States, however, a historically unprecedented array of other sources are responsible for a significant exposure to fluoride, especially in processed foods and beverages.

> In 2006, the National Research Council said manufacturers should provide information on the fluoride content of commercial foods and beverages. A decade later, fluoride content is still missing from food ingredient labels, including pet foods whose very high fluoride content has been implicated in canine bone cancer.[89,90]

Other sources of fluoride exposure include toothpaste, mouthwash, supplements, and other dental products and treatments; fluorinated pharmaceuticals, pesticides, and post-harvest fumigants. The additive effect can be substantial.

In 1993, the National Research Council admitted, "It is no longer feasible to estimate with reasonable accuracy the level of fluoride exposure simply on the basis of concentration in drinking water supply."[91] Therefore, even where fluoride levels in drinking water are claimed to be safe, mothers-to-be should take steps to minimize their consumption of fluoride to reduce the risk of premature birth – especially if they have dental fluorosis, visible proof of one's susceptibility to systemic fluoride toxicity.

Residence in the US is a risk factor for preterm birth, and more people consume artificially fluoridated water (and products made with it) in America alone than in the rest of the world combined.[92] It is high time we change our long habit of not thinking fluoride consumption wrong and realize it is a significant risk factor for premature birth and long-term neurological disabilities.

A vibrant fully functioning brain is the most precious gift of life. It is inexcusable to promote, condone, or ignore any substance or policy that threatens this birthright.

Correlations Between Cognitive Scores and Gestational Age

A major study published in 2002 in the *Journal of the American Medical Association*:

"We report the first meta-analysis on the cognitive and behavioral outcomes of school-aged children who were born preterm by combining the results from case-control studies published between 1980 and November 2001...

"Among 1556 cases and 1720 controls, controls had significantly higher cognitive scores compared with children who were born preterm."

Conclusions: "Children who were born preterm are at risk for reduced cognitive test scores, and their immaturity at birth is directly proportional to the mean cognitive scores at school age. Preterm-born children also show an increased incidence of ADHD and other behaviors."[93]

Since 2001, growing evidence is finding that prenatal fluoride is associated with reduced IQ in children.

Fluoridated Water and Infant Mortality Rates

Infant and neonatal death rates averaged significantly higher in the most fluoridated states compared to the least fluoridated.[54,94]

Infant Deaths /1,000 live births for all races (2013)	30 states <80% fluoridated (avg. 58% • 2012)	20 states >80% fluoridated (avg. 93% • 2012)	% higher death rate in 20 most fluoridated states
Neonatal Deaths (under 28 days old)	3.9	4.3	10.3%
Infant Deaths (under 1 year old)	5.9	6.4	8.5%

The #2 leading cause of infant death:
"Disorders related to short gestation and low birthweight."

Infant Deaths per 1,000 live births for all races (2013)	10 least fluoridated states (avg. 35% • 2012)	10 most fluoridated states (avg. 97% • 2012)	% higher death rate in 10 most fluoridated states
Neonatal Deaths (under 28 days old)	3.6	4.3	19.4%
Infant Deaths (under 1 year old)	5.7	6.4	12.3%

References

(Titles are hot-linked to studies.)

1. Institute of Medicine (US) Committee on Understanding Premature Birth and Assuring Healthy Outcomes; Behrman RE, Butler AS, editors. Preterm Birth: Causes, Consequences, and Prevention. Washington (DC): National Academies Press (US); 2007. Appendix B, Chapters 11 & 12. (See last page.)

2. Patoine B. The vulnerable premature brain: Rapid neural development in third trimester heightens brain risks. The Dana Foundation. May 2010.

3. Slegers M. Imaging technique shows premature birth interrupts vital brain development processes leading to reduced cognitive abilities in infants. King's College London press release. May 20, 2013.

4. Ball G, Srinivasan L, Aljabar P, et al. Development of cortical microstructure in the preterm human brain. *Proc Natl Acad Sci USA*. 2013 June 4;110(23):9541–9546.

5. Born too soon: The global action report of preterm birth. World Health Organization. May 2, 2012.

6. McNeil DG. U.S. lags in global measure of premature births. *New York Times*. May 2, 2012.

7. Lynch E. New global report says US lags behind 130 other nations in preterm birth rate. March of Dimes Foundation press release. May 2, 2012.

8. Bendure V. Study finds residence in US a risk factor for preterm birth. Society for Maternal-Fetal Medicine press release. February 9, 2012.

9. Chang HH, Larson J, Blencowe H, et al. Preventing preterm births: Analysis of trends and potential reductions with interventions in 39 countries with very high human development index. *Lancet.* 2013 Jan 19;381(9862):223–234.

10. Lawn J. Best-available science will allow just 5 percent relative reduction in high-income countries' preterm birth rates by 2015. *The Lancet* press release. November 15, 2012.

11. Breaker RR. First person: How we discovered fluoride riboswitches. Yale News. December 22, 2011.

12. Breaker RR. New insight on the response of bacteria to fluoride. *Caries Res*. 2012;46(1):78–81.

13. Keeley J. Bacteria battle against toxic fluoride. Howard Hughes Medical Institute press release. December 22, 2011.

14. Kresge N. Fighting fluoride: Riboswitch helps bacteria toss out toxic fluoride. Howard Hughes Medical Institute Bulletin. May 2012. Vol. 25/#2.

15. Barbier O, Arreola-Mendoza L, Del Razo LM. Molecular mechanisms of fluoride toxicity. *Chemico-Biological Inter*. 2010 Nov 5;188(2):319–333.

16. Agalakova NI, Gusev GP. Molecular mechanisms of cytotoxicity and apoptosis induced by inorganic fluoride. *ISRN Cell Biol*. 2012:403835.

17. Nouri MR, Titley KC. Pediatrics: A review of the antibacterial effect of fluoride. *Oral Health Journal*. January 1, 2003.

18. Feig SA, Shohet SB, Nathan DG. Energy metabolism in human erythrocytes. I. Effects of sodium fluoride. *J Clin Invest.* 1971 Aug;50(8):1731–1737.

19. Millman MS, Omachi A. The role of oxidized nicotinamide adenine dinucleotide in fluoride inhibition of active sodium transport in human erythrocytes. *J Gen Physiol*. 1972 Sep;60(3):337–350.

20. Gumińska M, Sterkowicz J. Effect of sodium fluoride on glycolysis in human erythrocytes and Ehrlich ascites tumour cells in vitro. *Acta Biochim Pol*. 1976;23(4):285–291.

21. Agalakova NI, Gusev GP. Fluoride induces oxidative stress and ATP depletion in the rat erythrocytes in vitro. *Environ Toxicol Pharmacol*. 2012 Sep;34(2):334–337.

22. Agalakova NI, Gusev GP. Fluoride-induced death of rat erythrocytes in vitro. *Toxicol In Vitro*. 2011 Dec;25(8):1609–1618.

23. Agalakova NI, Gusev GP. Excessive fluoride consumption leads to accelerated death of erythrocytes and anemia in rats. *Biol Trace Elem R*es. 2013 Jun;153(1-3):340–349.

24. Page A. Fluorosis: Crippling the innocent. *Asian Geographic Magazine*. 2010;73(4):112–117. Reports and interviews given by Prof. A.K. Susheela to the media.

25. Susheela AK. Anemia in pregnancy: An easily rectifiable problem (Guest editorial). *Fluoride* April-June 2010 43(2)104–107.

26. Susheela AK, Mondal NK, Gupta R, et al. Effective interventional approach to control anaemia in pregnant women. *Current Science*. 25 May 2010;98(10).

27. A. Susheela: A novel and effective interventional approach for prevention and control of anemia in pregnancy and low birth weight babies. Presentations: The importance of maternal nutrition for maternal health. August 31, 2010. Global Maternal Health Conference. New Delhi, India.

28. Gurumurthy SM, Mohanty S, Bhongir AV, Mishra AK, Rao P. Association of higher maternal serum fluoride with adverse fetal outcomes. *Int. J. Med. Public Health*. April-June 2011: Vol 1; Issue 2.

29. Diouf M, Cisse D, Lo CM, Ly M, Faye D, Ndiaye O. Pregnant women living in areas of endemic fluorosis in Senegal and low birthweight newborns: Case-control study. *Rev Epidemiol Sante Publique*. 2012 Apr;60(2):103–108.

30. Swanbrow D. Born to lose: How birth weight affects adult health and success. University of Michigan News. June 5, 2007.

31. Pinto-Martin JA, Levy SE, Feldman JF, et al. Prevalence of autism spectrum disorder in adolescents born weighing <2000 grams. *Pediatrics*. 2011 Nov;128(5):883–891.

32. Mecoy L. LA Biomed study increases understanding of link between low birth weights and obesity later in life. LA Biomedical Research Institute press release. June 21, 2011.

Desai M, Li T, Ross MG. Hypothalamic neurosphere progenitor cells in low birth-weight rat newborns: neurotrophic effects of leptin and insulin. Brain Res. 2011 Mar 10;1378:29–42.

33. Obesity increases the risk of preterm delivery. Karolinska Institutet press release. June 11, 2013.

Cnattingius S. Maternal overweight and obesity during pregnancy associated with increased risk of preterm delivery. The *JAMA* Network Journals press release. June 11, 2013.

34. Dutta N. Why the Govt's Iron and Folic Acid Supplementation Programme won't produce desired results (Exclusive interview with Dr A.K. Susheela). *Health.India.com.* August 6, 2013.

Video interview with A.K. Susheela. “Today Tonight” from Australia’s Adelaide 7 television news program. July 22, 2010.

35. Guarner F, Malagelada JR. Gut flora in health and disease. *Lancet*. 2003 Feb 8;361(9356):512–519.

36. Oda T, Kado-oka Y, Hashiba H. Effect of Lactobacillus acidophilus on iron bioavailability in rats. *J Nutr Sci Vitaminol (Tokyo)*. 1994 Dec;40(6):613–616.

37. Silva MR, Dias G, Ferreira CL, Franceschini SC, Costa NM. Growth of preschool children was improved when fed an iron-fortified fermented milk beverage supplemented with Lactobacillus acidophilus. *Nutr Res*. 2008 Apr;28(4):226–232.

Mitchell, J. Prebiotics and probiotics in young children. *Natural Medicine Journal*. October 2010. Vol. 2 Issue 10.

38. Naorungroj S, Wei HH, Arnold RR, Swift EJ Jr, Walter R. Antibacterial surface properties of fluoride-containing resin-based sealants. *J Dent.* 2010 May;38(5):387–391.

39. Waly NG. Assessment of salivary Lactobacillus and Streptococcus mutans counts following sodium fluoride mouthrinsing in Egyptian children. *Egypt Dent J.* 1995 Apr;41(2):1179–1188.

40. Milanesi A, Brent GA. Management of hypothyroidism in pregnancy. *Curr Opin Endocrinol Diabetes Obes*. 2011 Oct;18(5):304–309.

41. Casey BM, Dashe JS, Wells CE, et al. Subclinical hypothyroidism and pregnancy outcomes. *Obstet Gynecol*. 2005 Feb;105(2):239–245.

42. Gingery JG. Thyroid conditions raise risk of pregnancy complications: Hormone disorders linked to higher rates of preterm birth, preeclampsia. The Endocrine Society press release. May 29, 2013.

Männistö T, Mendola P, Grewal J, Xie Y, Chen Z, Laughon SK. Thyroid diseases and adverse pregnancy outcomes in a contemporary US cohort. *J Clin Endocrinol Metab*. 2013 Jul;98(7):2725–2733.

See also: Korevaar TI, Schalekamp-Timmermans S, de Rijke YB, et al. Hypothyroxinemia and TPO-antibody positivity are risk factors for premature delivery: The Generation R study. *J Clin Endocrinol Metab.* 2013 Nov;98(11):4382–4390.

43. Erdogan M, Aybike K, Ganıdagli S, Mustafa K. Characteristics of anemia in subclinical and overt hypothyroid patients. *Endocr J*. 2012;59(3):213-220.

44. Merkulova T, Keller A, Oliviero P, et al. Thyroid hormones differentially modulate enolase isozymes during rat skeletal and cardiac muscle development. *Am J Physiol Endocrinol Metab*. 2000 Feb;278 (2):E330–339.

45. Schuld A. History of the fluoride/iodine antagonism. Parents of Fluoride Poisoned Children. 2013.

46. National Research Council. *Fluoride in drinking water: A scientific review of EPA’s standards*. Effects of thyroid function. National Academies Press;2006:236.

47. Water fluoridation in England linked to higher rates of underactive thyroid: switch to other approaches in bid to protect tooth health, say researchers. *British Medical Journal* press release. February 23, 2015.

Peckham S, Lowery D, Spencer S. Are fluoride levels in drinking water associated with hypothyroidism prevalence in England? A large observational study of GP practice data and fluoride levels in drinking water. *J Epidemiol Community Health* 2015;0:1–6.

47b. Malin AJ, Riddell J, McCague H, Till C. Fluoride exposure and thyroid function among adults living in Canada: Effect modification by iodine status. *Environment International*. Volume 121, Part 1, December 2018, P. 667-674.

48. Behind international rankings of infant mortality: How the United States compares with Europe. CDC. November 2009.

Callaghan WM, MacDorman MF, Rasmussen SA, Qin C, Lackritz EM. The contribution of preterm birth to infant mortality rates in the United States. *Pediatrics*. 2006 Oct;118(4):1566–1573.

49. Preventing Preterm Births Saves Babies' Lives. March of Dimes. September 4, 2012.

50. Crump C, Sundquist K, Sundquist J, Winkleby MA. Gestational age at birth and mortality in young adulthood. *JAMA*. 2011;306(11):1233–1240.

51. Noble KG, Fifer WP, Rauh VA, Nomura Y, Andrews HF. Academic achievement varies with gestational age among children born at term. *Pediatrics*. 2012 Aug;130(2):e257–264.

Boyle C. Smart babies stay in the womb longer. *New York Daily News*. July 2, 2012.

52. Hart R, Feelemyer J, Gray C, et al. Relationship between municipal water fluoridation and preterm birth in Upstate New York, 2009. American Public Health Association Meeting and Expo. No.9, 2009.

53. Bailey-Shah S. Before you vote: Fluoride and kids' teeth – what does the data show? *KATU News*. Portland, Oregon. April 25, 2013. (*Cascadia Times*)

54. Percentage of state populations on community water systems receiving fluoridated water. National Water Fluoridation Statistics.

55. Martin JA, Hamilton BE, Ventura SJ, et al. Births: Final Data for 2010. *Natl Vital Stat Rep*. August 28, 2012;61(01)12, Table E.

55b. CDC (2018). Percent of Preterm Births in 2016. Page 15. Table 6.

56. Kids Count. 2013 Data Book: State Trends in Child Well-Being. Annie E. Casey Foundation. Low birthweight babies. 2010. Appendix 2. Page 44.

57. Murphy SL, Xu J, Kochanek KD. Deaths: Final Data for 2010. *Natl Vital Stat Rep*. May 8, 2013;61 (04)97, Table 22.

58. Pitcher JB, Riley AM, Doeltgen SH, et al. Physiological evidence consistent with reduced neuroplasticity in human adolescents born preterm. *J Neurosci.* 2012 Nov 14;32(46):16410–16416.

Pitcher JB. Teenagers' brains affected by preterm birth: Why being preterm could impair memory, learning. University of Adelaide press release. November 13, 2012.

59. Phillips DI, Jones A. Fetal programming of autonomic and HPA function: Do people who were small babies have enhanced stress responses? *J Physiol*. 2006 April 1;572(Pt 1):45–50.

60. Sullivan MC, Hawes K, Winchester SB, Miller RJ. Developmental origins theory from prematurity to adult disease. *J Obstet Gynecol Neonatal Nurs*. 2008 Mar–Apr;37(2):158–164.

61. Huang LT. The link between perinatal glucocorticoids exposure and psychiatric disorders. *Pediatric Research* (2011) 69, 19R–25R.

62. Nosarti C, Reichenberg A, Murray RM, et al. Preterm birth and psychiatric disorders in young adult life. *Arch Gen Psychiatry*. 2012;69(6):610–617.

63. Kunze WA, Forsythe P. Voices from within: Gut microbes and the CNS. *Cell Mol Life Sci*. 2013 Jan; 70(1):55–69.

64. Neufeld KM, Kang N, Bienenstock J, Foster JA. Reduced anxiety-like behavior and central neurochemical change in germ-free mice. *Neurogastroenterology & Motility*. Mar 2011;23(3):255–e119.

Foster JA, Neufeld KM. Gut-brain axis: how the microbiome influences anxiety and depression. *Trends Neurosci*. 2013 May;36(5):305–312.

65. Sudo N, Chida Y, Aiba Y, et al. Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice. *J Physiol*. 2004 Jul 1;558(Pt 1):263–275.

66. Stadler C, Kroeger A, Weyers P, et al. Cortisol reactivity in boys with attention-deficit/hyperactivity disorder and disruptive behavior problems: The impact of callous unemotional traits. *Psychiatry Res*. 2011 May 15;187(1-2):204–209.

66b. Xu G, Strathearn L, Liu B, Yang B, Bao W. Twenty-year trends in diagnosed Attention-Deficit/ Hyperactivity Disorder among US children and adolescents, 1997-2016. *JAMA Netw Open.* 2018;1 (4):e181471.

67. Weber M. ADHD takes a toll well into adulthood. Boston Children's Hospital press release. 3-4-2013.

67b. $77 billion in lost income is attributed to ADHD annually in the US. American Psychiatric Assoc. May 23, 2005.

68. Chu SM, Tsai MH, Hwang FM, et al. The relationship between attention deficit hyperactivity disorder and premature infants in Taiwanese: A case control study. *BMC Psychiatry*. 2012;12:85.

69. Percent of Youth Aged 4-17 Currently Diagnosed with Attention-Deficit/Hyperactivity Disorder by State (2011). National Survey of Children's Health. CDC.

70. Malin AJ, Till C. Exposure to fluoridated water and attention deficit hyperactivity disorder prevalence among children and adolescents in the United States: an ecological association. *Environmental Health* 2015;14:17.

70b. Higher levels of urinary fluoride associated with ADHD in children. University of Toronto press release. October 10, 2018.

71. Mullenix PJ, Denbesten PK, Schunior A, Kernan WJ. Neurotoxicity of sodium fluoride in rats. *Neurotoxicol Teratol*. 1995 Mar–Apr;17(2):169–177.
Full study: www.fluoridealert.org/wp-content/uploads/mullenix-1995.pdf

Fluoride and the Brain: An Interview with Dr. Phyllis Mullenix. Fluoride Action Network. 10/18/97.

72. Bryson C. The Fluoride Deception. *Seven Stories Press*;2004:22.

73. Connett P, Beck J, Micklem HS. The case against fluoride: How hazardous waste ended up in our drinking water and the bad science and powerful politics that keep it there. *Chelsea Green Publishing*; 2010:148-150.

74. Mullenix PJ. Central nervous system damage from fluorides: The neurotoxicity of fluoride. Fluoridation.com. September 14, 1998.

75. Critical review of any new evidence on the hazard profile, health effects, and human exposure to fluoride and the fluoridating agents of drinking water. European Union's Scientific Committee on Health and Environmental Risks (SCHER). 16 May 2011. Abstract.

76. Ekanayake L, van der Hoek W. Dental caries and developmental defects of enamel in relation to fluoride levels in drinking water in an arid area of Sri Lanka. *Caries Res*. 2002 Nov-Dec;36(6):398–404.

77. Wong HM, McGrath C, Lo EC, King NM. Association between developmental defects of enamel and different concentrations of fluoride in the public water supply. *Caries Res*. 2006;40(6):481–486.

78. Hiller KA, Wilfart G, Schmalz G. Developmental enamel defects in children with different fluoride supplementation – a follow-up study. *Caries Res*. 1998;32(6):405–411.

79. Hall RK. Prevalence of developmental defects of tooth enamel (DDE) in a pediatric hospital department of dentistry population (1). *Adv Dent Re*s. 1989 Sep;3(2):114–119.

80. Masumo R, Bårdsen A, Astrøm AN. Developmental defects of enamel in primary teeth and association with early life course events: a study of 6–36 month old children in Manyara, Tanzania. *BMC Oral Health*. 2013;13:21.

81. Bhat M, Nelson KB. Developmental enamel defects in primary teeth in children with cerebral palsy, mental retardation, or hearing defects: a review. *Adv Dent Res*. 1989 Sep;3(2):132–142.

82. State-Specific Rates of Mental Retardation – United States, 1993. CDC. *Morbidity and Mortality Weekly Report (MMWR)*. January 26, 1996;45(03):61–65. Table 1: Prevalence rate of mental retardation, by state for children (6–17 years old) per 1,000 population, 1993.

Osmunson B. Comment and advisory: EPA. March 13, 2011. Likely and possible harm to the brain and IQ from fluoride:60. Effect of fluoride on the brain: estimating IQ drop:176–179.

MacArthur JD. Fluoridated Water's Association with Mental Retardation and Intellectual Disability.

83. Everett ET. Fluoride's effects on the formation of teeth and bones, and the influence of genetics. *J Dent Res*. 2011 May;90(5):552–560.

Everett ET, McHenry MA, Reynolds N, et al. Dental fluorosis: variability among different inbred mouse strains. *J Dent Res*. 2002 Nov;81(11):794–798.

84. Mousny M, Banse X, Wise L, Everett ET, et al. The genetic influence on bone susceptibility to fluoride. *Bone*. 2006 Dec;39(6):1283–1289.

85. Martinez-Mier EA, Soto-Rojas AE. Differences in exposure and biological markers of fluoride among White and African American children. *J Public Health Dent*. 2010 Summer;70(3):234–240.

86. Hertel D. Dartmouth researchers aim to discover the unknown causes of premature birth. Geisel School of Medicine press release. July 18, 2013.

87. Miller N. Scientists prevent preterm birth caused by gene-environment interactions. Cincinnati Children's Hospital Medical Center press release. August 27, 2013.

88. Ridley W, Matsuoka M. Fluoride-induced cyclooxygenase-2 expression and prostaglandin E2 production in A549 human pulmonary epithelial cells. *Toxicol Lett*. 2009 Aug 10;188(3):180–185.

89. Dog food comparison shows high fluoride levels. Environmental Working Group. June 26, 2009.

90. Glasser G. Dogs, cats, osteosarcoma, dysplasia and pet food fluoride. National Pure Water Assoc.

91. Committee on Toxicology. Health Effects of Ingested Fluoride. Washington DC: *National Academy Press*;1993:128.

92. Countries that fluoridate their water. Fluoride Action Network. August 2012.

93. Bhutta AT, Cleves MA, Casey PH, Cradock MM, Anand KJ. Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. *JAMA*. 2002 Aug 14; 288(6):728–737.

94. Xu J, Murphy SL, Kochanek KD, Bastian BA. Deaths: Final Data for 2013. *Natl Vital Stat Rep*. 2016 Feb 16;64(2):98. Table 22.

Footnote #1: