Newsletter for the TDM and Toxicology Division of AACC

Fall 2014

Therapeutics & Toxins News

Inside this issue:

Water fluoridation: the myths and the reality

Peter L. Platteborze, PhD, DABCC, Dept. of Pathology and Area Lab Services, San Antonio Military Medical Center, JBSA-Fort Sam Houston, TX

Questions regarding the relative merits of community water fluoridation continue to make the news. Those who denounce this public health program designed to reduce tooth decay rates, have cited the CDC's recent decision to lower water fluoride levels as evidence against its safety and efficacy. However, the scientific data belies an entirely different conclusion, one that clearly shows its true effectiveness and prompted the CDC to cite it in their ten most significant public health achievements of the 20th Century. This article will discuss the history of water fluoridation, the science behind its safety and effectiveness, dispel the myths, and conclude with a discussion of recent U.S. policy changes.

Logo for Therapeutic and Toxin Newsletter

"This article will discuss the history of water fluoridation, the science behind its safety and effectiveness, dispel the myths, and conclude with a discussion of recent U.S. policy changes."

The story of water fluoridation begins in 1901 when a newly graduated dentist, Frederick McKay, moved to Colorado Springs, Colorado and was shocked at the extensive discoloration of the local residents' teeth (1). Intrigued, he began researching this uncited dental affliction and found that it was present in ~90% of the locally born children, occurred prior to the development of adult teeth and inexplicably, this "Colorado Brown Stain" was associated with a resistance to tooth decay. He correctly surmised that it was due to a compound(s) in the local drinking water but his water causation hypothesis was ridiculed by the scientific establishment of the time. McKay gained key supportive evidence in the 1920s from two observational studies in Oakley, Idaho and Bauxite, Arkansas. In both, after changing the source of the local drinking water the staining issue subsequently disappeared. Since Bauxite was a mining town owned by the Aluminum Company of America (ALCOA), their chief chemist prudently analyzed their drinking water using highly sensitive methods.

Water fluoridation: the myths and the reality

Peter L. Platteborze, PhD, DABCC, Dept. of Pathology and Area Lab Services, San Antonio Military Medical Center, JBSA-Fort Sam Houston, TX

He conclusively determined it contained very high levels of fluoride, and unsure of its meaning, sent the results to the U.S. Public Health Service (PHS).

This prompted the PHS to start a program to investigate these unusual findings. In the 1930s they completed an epidemiological survey of 345 communities scattered across the continental U.S. and concluded that, indeed, naturally high levels of fluoride in drinking water conveyed resistance to tooth decay. They also determined that the tooth discoloration; which they renamed enamel fluorosis; occurred upon chronic consumption of significant levels of fluoride. Last, the optimal level to thwart tooth decay was 1.0 ppm and its presence did not affect the appearance, taste or smell of drinking water.

In 1945 the PHS initiated a planned decade long water fluoridation clinical study in Western Michigan to determine its feasibility as a means to prevent tooth decay. They selected the city of Grand Rapids because their drinking water had a very low fluoride level and there was a correspondingly high cavity rate. With permission from the city council, they supplemented the municipal water with fluoride salts to 1.0 ppm, about ten-fold higher than the natural levels. They then closely monitored the cavity rates in the city's schoolchildren and in the nearby city of Muskegon whose fluoride-deficient drinking water was not supplemented. After just five years they were compelled to publish their results; remarkably the supplemental fluoridation had resulted in over a 60% reduction of tooth decay rates in ~29,000 schoolchildren. No changes were observed in the Muskegon negative control group. Soon thereafter other communities across North America began fluoridating their water. Fast forward to the present and more than 400 million people world-wide benefit from water fluoridation and in the U.S., 47 of the 50 largest cities fluoridate their water.

"Surface fresh water generally contains fluoride levels below 0.2 ppm but many U.S. locales have naturally occurring high fluoride levels.

Out of the 102 naturally occurring elements the halogen fluorine; symbol F and atomic number 9 in the Periodic Table; is the most electronegative and the thirteenth most abundant. Fluorides are naturally present at varying levels in the ocean, soil, plants, rocks and most food. Being one of the Earth's most common elements, high levels do not harm the environment. Surface fresh water generally contains fluoride levels below 0.2 ppm but many U.S. locales have naturally occurring high fluoride levels. The drinking water from Bauxite was recorded at 13.7 ppm and the groundwater from volcanic or mountainous areas can have even higher levels. Clinical studies have shown no significant health effects in areas where residents consumed water with natural fluoride levels of 8.0 ppm for over 15 years except for enamel fluorosis (2).

Fluoride is an essential mineral in humans; the U.S. Institute of Medicine has established Dietary Reference Intakes. Adequate Intake Levels range from 0.01 mg/day for newborns to 3 or 4 mg/day for adult females and males, respectively. The Tolerable Upper Intake Level is 0.70 mg/day for newborns and children and 10 mg/day for everyone 9 years and older. Absorption of over 10 mg/day of fluoride over many years can lead to skeletal fluorosis in which excessive calcification of bone results in stiffening of ligaments and fusion of joints and can be

Water fluoridation: the myths and the reality

Peter L. Platteborze, PhD, DABCC, Dept. of Pathology and Area Lab Services, San Antonio Military Medical Center, JBSA-Fort Sam Houston, TX

crippling (3). Symptoms of acute fluoride ingestion include nausea, emesis, tetany, coma and death. The lethal dose in most adult humans is approximately 5 – 10 g of fluoride.

Ingestion of fluoridated water results in an equivalent increase in fluoride blood and saliva levels. In humans, about half of the ingested fluoride is excreted unchanged in urine, ~6-10% in feces and from 13-23% in sweat (3). The bones and teeth contain the highest natural concentration of fluoride at levels that are from 140- to 1550- fold higher than in other tissues. Fluoride induces bone formation by stimulating osteoblasts. Analysis of biological samples is rarely done but is available at major reference laboratories via a fluoride -specific electrode.

Almost all tooth decay is due to erosion of the hard protective enamel that is primarily composed of hydroxyapatite, $Ca_{10}(PO_4)_6(OH)_2$ (4). This is commonly caused by the presence of abundant oral bacteria like *Steptococcus* (*mutans* and *sobrinus*) and *Lactobacillus* in a layer of plaque over the enamel. These species convert ingested sugar to potentially destructive organic acids. When the microbes produce sufficient acid to drive the pH below 5.5, the hydroxyapatite dissolves into calcium and phosphate ions that pass from the enamel into the plaque and saliva. This process is known as demineralization. When the pH subsequently increases some of the minerals lost can redeposit into the enamel via remineralization. Cavities occur when the rate of demineralization consistently exceeds that of remineralization over many months or years.

The ability of fluoride to reduce tooth decay is mostly due to its presence on tooth surfaces. Supplemental fluoridation causes elevated levels of fluoride in saliva and thus in the plaque which primarily interferes with the demineralization and remineralization processes. When fluoride is present in saliva and/or plaque at a pH above 4.5; a fluoroapatite, $Ca_{10}(PO_4)_6F_2$, layer forms over the surface of the enamel. This new surface layer is much more acid-resistant than the original hydroxyapatite and also forms more quickly than the latter (5). In effect the fluoride reduces the rate at which tooth enamel demineralizes by making it more acid resistant and also increasing the rate of remineralization. Even though fluoride is an excellent *in vitro* enzyme inhibitor (i.e. grey top tubes) scientists currently believe that it has minimal influence on slowing bacterial growth or their ability to metabolize sugar into acids. Fluoride has also been shown to impede the decay of exposed tooth roots which to some degree occurs in most adults over the age of 45. Beyond its impact on teeth, ingested fluoride accumulates with calcium forming denser bones so it has been prescribed to treat osteoporosis in a daily dose of 33-220 mg [3].

Fluoridation is one of many public health interventions that Americans benefit from daily to lower the prevalence of diseases. Some other interventions include fortifying salt with iodine, milk with vitamins A and D, orange juice with vitamin C, and flour with iron and B vitamins like folate.

"Fluoridation is one of many public health interventions that Americans benefit from daily to lower the prevalence of diseases."

Water fluoridation: the myths and the reality

Peter L. Platteborze, PhD, DABCC, Dept. of Pathology and Area Lab Services, San Antonio Military Medical Center, JBSA-Fort Sam Houston, TX

The general scientific consensus is that water fluoridation is the most efficient and fairest means for everyone in a community to benefit, regardless of income, education, or the ability to purchase dental care. Today it is estimated that more than 70% of all Americans have access to fluoridated water through public water systems; 12 states mandate it while the other 38 allow local government or the general public to decide (Figure 1). One of three industrial grade chemicals are typically used to supplement municipal water; they are fluorosilicic acid (H_2SiF_6), sodium fluorosilicate (Na_2SiF_6), and sodium fluoride.

Besides iodized salt, fluoridated water is one of the cheapest and most effective public health measures ever enacted. Overall this public health program saves consumer's money, the average cost for a community to fluoridate its water supply is estimated to be ~$1 per person per year, a little less in large communities and more in small communities. This is sufficiently cost effective such that a person can consume a lifetime of fluoridated water for about the cost of a small dental filling. However, fillings are not as structurally strong as natural teeth and their median life ranges from 9 to 14 years prior to a new restoration being required. Several studies have shown that when a community ceases water fluoridation there is an associated increased rate of tooth decay. Everyone benefits from water fluoridation without the need for more expensive daily interventions which many cannot afford. By comparison, fluoride toothpaste annually costs ~$12.50 per person and the dental application of a fluoride veneer or gel costs an average of $92.

"Besides iodized salt, fluoridated water is one of the cheapest and most effective public health measures ever enacted."

It is worth noting that other parts of the developed world adjust fluoride intakes by alternative means. Countries in continental Europe often supplement their salt with fluoride while many other countries add it to milk or yogurt. None of these means is as effective as supplementing water because their dietary intake is more highly variable than water consumption.

While toxic levels cannot be achieved by drinking fluoridated water, recent studies from the CDC showed an increased prevalence of enamel fluorosis over the last two decades. While the earlier studies showed that water fluoridation led to over 60% reduction in childhood cavities; more recent investigations showed less significant reductions that only ranged from 18 - 40% (6). This prompted the U.S. Department of Health and Human Services in January 2011 to reduce the optimal level of fluoride in water to 0.7 ppm, the first change since the initial studies sixty years earlier.

The cause of both the increased enamel fluorosis and lower impact of water fluoridation in reducing cavities is directly linked to the increased consumption of other products containing fluoride. The primary source is the ingestion of fluoride from swallowed toothpaste. In the 1950s, Proctor and Gamble; sensing a major commercial opportunity; introduced Crest as the first fluoride containing toothpaste. Today nearly all toothpastes on the market contain it at high

Water fluoridation: the myths and the reality

Peter L. Platteborze, PhD, DABCC, Dept. of Pathology and Area Lab Services, San Antonio Military Medical Center, JBSA-Fort Sam Houston, TX

levels often ranging from 1000 - 1500 ppm. This caused the FDA in 1997 to require all manufacturers to place a warning label on tubes and boxes stating consumers should seek medical help if more than that used for brushing is accidentally swallowed. Many other oral hygiene products also contain substantial levels of fluoride to include mouthwashes, varnishes and gels. Additionally there are many unexpected sources like Teflon coated pans, mechanically deboned meat, rust removal products and some pharmaceuticals like the antifungal agent voriconazole. Last, there is a potential halo effect from food and beverages produced in fluoridated areas and consumed in unfluoridated ones.

Since its inception there has been a loud vocal minority opposed to water fluoridation. Dissenting voices became increasingly strident during the Cold War, largely sparked by the 1964 movie Dr. Strangelove in which insane General Jack D. Ripper called fluoridation a communist plot to poison America's water (Figure 2). This Kremlin conspiracy theory was completely fictional; in actuality many Soviet Union cities were adding fluoride to their public water supplies. Fluoridation remains controversial today, especially with the long reach of the internet. Contrary to some claims, it has not been banned anywhere.

"The World Health Organization and nearly all U.S. health agencies endorse fluoridation of community water as a safe and effective means to prevent tooth decay."

The World Health Organization and nearly all U.S. health agencies endorse fluoridation of community water as a safe and effective means to prevent tooth decay. This is based on the overwhelming weight of peer reviewed, credible scientific evidence. In fact, the safety of water fluoridation has been studied more thoroughly than any other public health measure. There have been countless assertions of harm, including heart disease, cancer, AIDS, Down syndrome, premature aging and even constipation in dogs. Over the last 40 years many human and veterinary studies have been conducted and none have shown an association between fluoridated water and any of these risks. Retired Surgeon General Dr. C. Everett Koop stated "Fluoride is not a mysterious substance… the people who oppose the fluoridation of water don't know what they are talking about." Had dentists acceded to fear mongering there would have been significantly more cavities to treat resulting in substantially greater profits. Despite this strong financial incentive dentists, have steadfastly supported water fluoridation. The amount of fluoride added during the water treatment process is strictly regulated with national standards set by the Environmental Protection Agency, American Water Works Association and the National Sanitation Foundation. Water treatment processes are also closely monitored by state and municipal agencies to further ensure safety. Customers concerned about the safety of their drinking water can purchase reverse osmosis filtration systems capable of removing the majority of fluoride and other ions.

It is statistically undeniable that America's dental health has improved dramatically over the last six decades as a direct result of public water fluoridation. Virtually every reputable global and national health agency endorses

Water fluoridation: the myths and the reality

Peter L. Platteborze, PhD, DABCC, Dept. of Pathology and Area Lab Services, San Antonio Military Medical Center, JBSA-Fort Sam Houston, TX

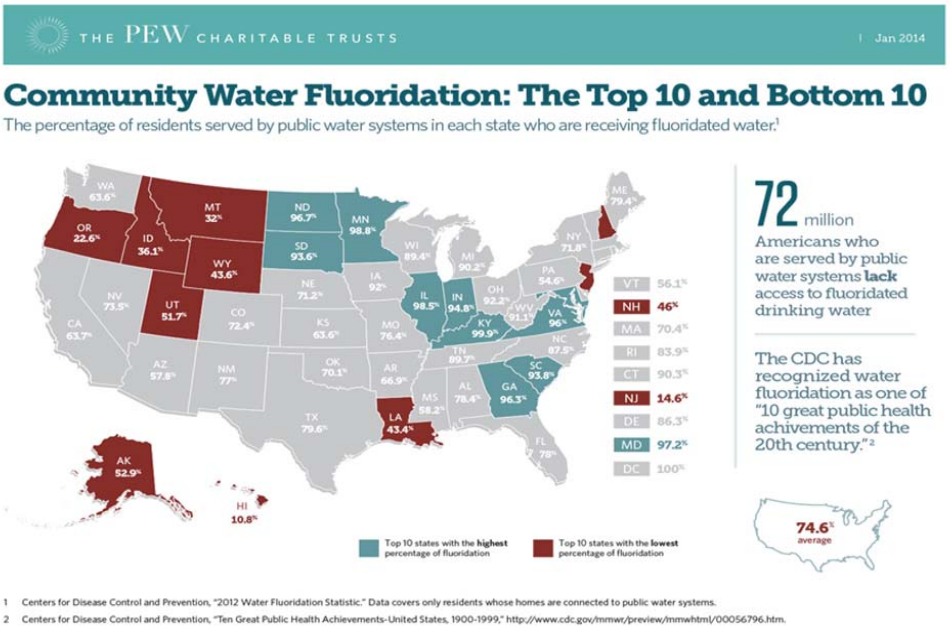
water fluoridation as safe and effective. Since its adoption in the 1950s, it has resulted in a significant improvement in the oral health of hundreds of millions of Americans and saved billions of dollars in avoided medical expenses. Tooth loss is no longer considered inevitable; adults who consume fluoridated products now typically retain the majority of their teeth for a lifetime. Based upon this impact the CDC has identified fluoridation as one of the ten great public health achievements in the 20th Century.

"Tooth loss is no longer considered inevitable; adults who consume fluoridated products now typically retain the majority of their teeth for a lifetime."

References

1. Platteborze PL. (2014). Fluoridation, making tooth decay go away. *Michigan History*. May/June: 39-44.
2. Lennon MA. (2006). One in a million: the first community trial of water fluoridation. *Bulletin of the World Health Organization*. 84: 759-760.
3. Baselt, RC. Disposition of toxic drugs and chemicals in man. 9th ed. 2011. Sea Beach, CA: Biomedical Publications. pp 698-699.
4. Hileman B. (1988). Fluoridation of water. *C&EN*. August 1: 26-42.
5. Featherstone JD. (2008). Dental caries: a dynamic disease process. *Aust Dent J*. 53: 286–291.
6. Centers for Disease Control and Prevention. (2001). Recommendations for using fluoride to prevent and control dental caries in the United States. *MMWR Recomm Rep*. 50(RR-14): 1–42.

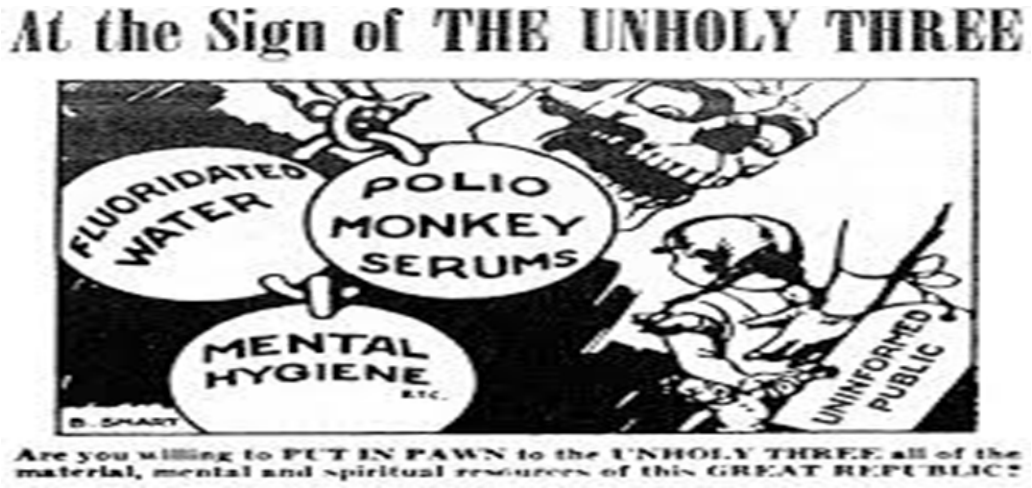
Figure 1: U.S. map illustrating percentage of residents by state who receive fluoridated water.



Water fluoridation: the myths and the reality

Peter L. Platteborze, PhD, DABCC, Dept. of Pathology and Area Lab Services, San Antonio Military Medical Center, JBSA-Fort Sam Houston, TX

Figure 2: A 1955 cartoon from opponents to water fluoridation.



"The TDM/Tox division was well represented at the Chicago National Meeting"

Notes from the Editor: Our Division Events at AACC National Meeting in Chicago

The Division meeting and lunch was held on Monday, July 28. Division awards were given out. The 2013 Young Investigator Award Recipient was: Kamisha L. Johnson-Davis, PhD. She presented the results of her research on LCMS analysis of ethanol metabolites (ethyl glucuronide and ethyl sulfate) in urine in pain management patients. These 2 metabolites are found in urine for up to 120 hours after ingestion of ethanol. Screening was done in her lab by ethanol enzymatic assay on autoanalyzers. Hand sanitizers gave false positives in such assays. LCMSMS was used for confirmation. Ethanol metabolites were found in 32%, 23%, 21% and 10% of patients who were also positive for hydrocodone, tetrahydrocannabinol, oxycodone, and methadone, respectively. 90% of samples containing ethanol metabolites were from patients who were positive for some pain medication; only 10% samples were from patients where no other pain medication was detected. Dr Johnson-Davis presented the details of here LCMSMS (using Agilent 1200 system) confirmation method. The method could detect both ethanol metabolites in a single run, with analytical ranges of 10-10,000 ng/mL. 45% of samples had ethyl glucuronide concentrations of 10,000 ng/mL or more.

The division conducted a poster walk at 2 PM on Wednesday. 45 posters were presented in TDM/Toxicology/DAU. On July 31, there was a symposium moderated by Loralie Langman of Mayo Clinic on new designer drugs. Marilyn Huestis of National Institute on Drug Abuse presented 'determining human metabolism of designer drugs with human hepatocytes and high-resolution mass spectrometry'. They use biochip and LCMSMS (TOF) to analyze new drugs and their metabolites of MW 50-1000D, concentration 0.25-5 ug/L. The second speaker, Kara Lynch of UCSF presented some case studies of novel psychoactive substances. The final speaker was Robert Kronstrand of National Board of Forensic Medicine from Sweden. He spoke on the numerous emerging designer drugs, their trends and challenges.

In summary, the division was well represented at the Chicago National Meeting.
Pradip Datta

American Association for Clinical Chemistry
Improving healthcare through laboratory medicine

Editorial Board

Please contact Dr. Pradip Datta at pradip.datta@siemens.com if you are interested in joining the editorial board or if you have ideas or article contributions for this newsletter.