# Drinking Water and the Developing Brain

By Ellen K. Silbergeld, Ph.D.

Editor's Note: While the problem of unsafe tap water in Flint, Michigan fueled outrage and better awareness in regard to the hazards of lead in tap water, the problem has existed in city after city for years in the US and in other countries. Our author, a winner of the MacArthur Foundation "genius" grant for her work in identifying preventable causes of human disease related to environmental exposures, points out that problems extend well beyond lead. Many potentially harmful contaminants have yet to be evaluated, much less regulated. Her article examines a number of neurotoxins and related issues as they pertain to brain development.

We all have to drink water to live. But the water that we drink is not always safe, even in countries where we assume it is. Some hazards emit a disturbing odor or discolor drinking water's clarity, while others are not as easily detected. Very often drinking water is unsafe because the sources that deliver it to our homes, schools, and businesses are unprotected. Often, water is unsafe because it contains developmental neurotoxins, or DNTs. These chemicals affect brain development from the prenatal period through childhood, with long term consequences that affect motor function, learning, and behavior. They not only rob our children of their full potential, but also increase the burdens on Society, as stunted neurodevelopment can lead to lower graduation rates, increased crime, and reduced lifetime earnings.[1-5]

These economic costs have been calculated in the billions. Moreover, since cognitive attainment (as typically measured by IQ tests and similar instruments) is a continuous function (Figure 1), the population impacts of DNTs extend over a range of exposures varying in intensity but not in likelihood of occurrence. For this reason, a relatively small shift in mean or median performance can result in major impacts on the extremes of distribution. The study of lead exposures and children's IQ scores cited here, for example, demonstrates that a relatively small reduction of five points in the average IQ may result in a 1.6-fold increase in children with severe impairments (intellectual disability), as well as a decrease of more than 50 percent in the number of children with superior intellectual performance (gifted).[6] Both of these have significant impacts on Society.
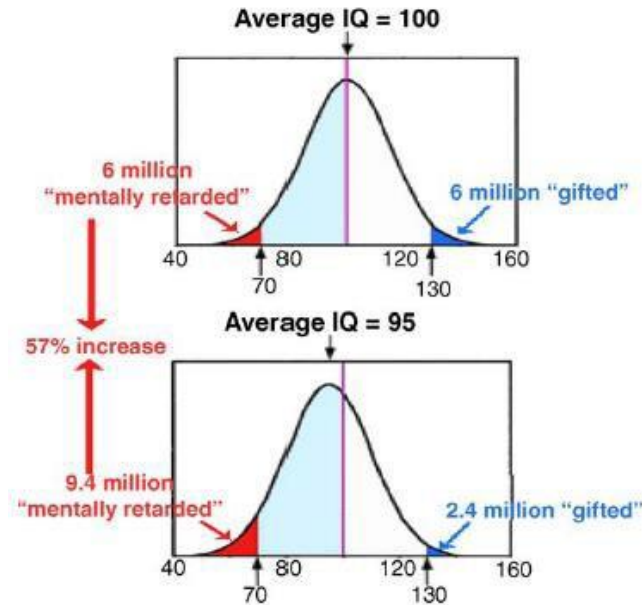
The social implications of developmental neurotoxicity: a slight shift in average IQ scores among a cohort of lead exposed children results in large increases in children with severe deficits and a loss of children with exceptionally high performance scores.

Source: Fritsch et al EFSA

Why is the developing brain so sensitive to neurotoxic hazards, and why do early exposures result in persistent deficits? To start with, humans are distinguished by a highly complex central nervous system that evolved over millions of years. The complexity of our brain requires an extended period of pre- and postnatal molecular events involving a temporal cascade of cell migration, differentiation, and communication, and the biological wiring of neuronal circuitry. Other physiological systems, including the immune and endocrine systems, also contribute to shaping and regulating brain development.

This prolonged process, starting early in gestation and continuing through adolescence, presents an extended period of vulnerability and multiple targets through which harmful exposures can interrupt and alter the developmental sequence required for a normal brain.[7,8] Moreover, since the temporal trajectory of brain development is not fully repeatable, early adverse events can have persistent impacts on brain function as well as delayed effects that may be evident only years later.
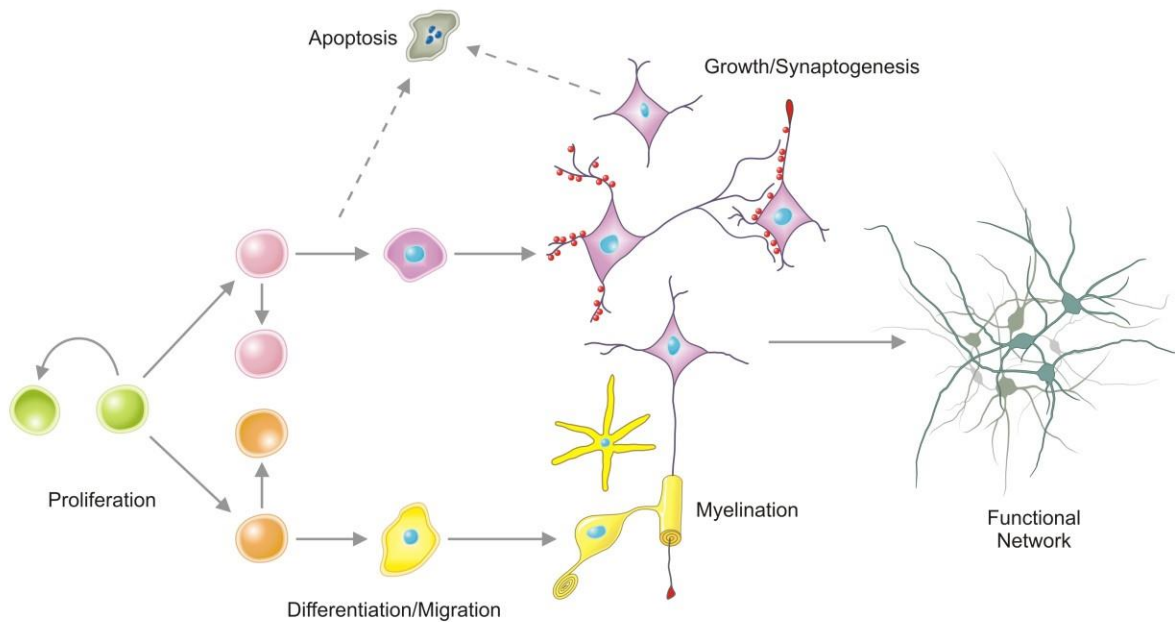
Figure 2. Molecular and cellular targets for developmental neurotoxins over development. Source: Fritsche et al EFSA

Timing and Exposure

The mechanisms by which DNTs affect neurodevelopment and the outcomes associated with these effects are strongly related to the timing of brain development and exposure.[9,10] Generally, DNT exposures early in embryonic development may kill off progenitor cells and reduce cell proliferation, or (in the case of the toxic chemical methylmercury) interfere with cell differentiation and migration. Exposures to DNTs such as pesticides may interfere with apoptosis, or cell death mechanisms essential to the pruning process of neurodevelopment. Later exposures, which have been researched most extensively for certain pesticides and lead, may interfere with intercellular communication and disrupt the establishment of functional networks and synaptic connectivity. The complexity of different timing schedules among brain regions, together with DNTs' multiple modes of action, explain why there can be both agent-specific and age-specific outcomes, resulting in distinctive impairments in cognition, behavior, and motor function.

DNTs also interact with genetics to influence the likelihood and severity of toxicity. This has been clearly demonstrated in recent studies of genetic and acquired risk factors in Autism Spectrum

Disorders.[11-13] These environment interactions include polymorphisms, or a discontinuous genetic variation, in genes and epigenetic modifications (external modifications to DNA) of gene expression. Changes in DNA methylation (a "chemical cap"), an epigenetic regulator, have been reported for lead, manganese, arsenic, and mercury.[14] Other DNTs interact with single nucleotide polymorphisms in genes that regulate metal metabolism and distribution in the body. There may also be interactions between certain DNTs and the biome of the gut, which are particularly relevant to drinking water exposure.[15]

DNTs interact with a range of other stressors and exposures that affect brain development. While coincident events and circumstances are important in understanding many outcomes of environmental exposures, this is particularly relevant to neurodevelopmental toxicology. Socioeconomic factors related to health disparities are independently associated with adverse outcomes in cognitive and neurobehavioral development. Many disadvantaged populations, especially children, are also at increased risk of exposure to environmental DNTs, including drinking water contaminants.[16-17] Moreover, children who live in high risk or underserved communities are often unable to access educational and other interventions that may ameliorate the impacts of early DNT exposures.

Where It Began: Lead

Lead in drinking water was the first environmental agent to be intensively studied for developmental neurotoxicity. It was the Romans who first used lead extensively in vessels for delivering and storing water. While there are no extant medical writings associating toxicity from consumption of water thus contaminated, the Roman architect and engineer Vitruvius cautioned that "water is much more wholesome from earthenware than from lead pipes."[18]

Concerns about lead-containing water systems were raised in early modern times in Germany, Scotland, and the Massachusetts Bay Colony. Writers on medicine and natural history noted that lead and mercury could cause behavioral and neurologic dysfunctions among metal mining and smelting workers. In the 1800s, these metals were already thought to be neurotoxic to both adults and children—that is, to the developed and developing brain—suggesting an early understanding that some mechanisms of toxicity may be age-independent.

In 1977, the first report to clearly associate prenatal lead exposure from drinking water with severe mental retardation came from Glasgow when Sir Abraham Goldberg and his colleagues investigated a cluster of affected young children. Finding no clear cause, they detected prenatal lead exposure by analyzing dried blood spots collected at birth and determined that the source of lead was drinking water contaminated by storage in lead lined tanks.[19] After achieving regulatory controls on the use of lead in house paints and gasoline, public health investigators are once more assessing the importance of lead in drinking water as a source of medically significant exposures. Recent events in the US have uncovered multiple examples of highly elevated lead levels in drinking water in several cities, notably Flint, Michigan.

DNTs in Drinking Water

Most DNTs in drinking water fall into four broad categories: metals, solvents, industrial chemicals, and natural products. For DNTs such as arsenic and mercury, their presence in water also contributes to food contamination in fish and shellfish and irrigated crops. While most exposures to lead in drinking water—even to the present—results from its use in water delivery systems, other toxic metals, such as arsenic and manganese, get into drinking water from groundwater in contact with geologic formations that contain these elements. This is why arsenic represents a global risk of developmental neurotoxicity in drinking water.[20] Water-borne exposures to most other DNTs are associated with waste disposal and their use in beverage containers. Some of these DNTs, such as mercury, dioxins, and polychlorinated biphenyls, can, like lead, be bioaccumulated in fish and shellfish or taken up from irrigation water by food crops such as rice.[21]

Maternal exposure leads to fetal exposure to many DNTs. It is now well recognized that the human placenta does not protect the fetus from xenobiotic agents that circulate in maternal blood. Some DNTs, including solvents and nanomaterials, can penetrate cell layers[22]; others are actively carried across the maternal-fetal barrier by specific proteins, such as divalent metal transporters that regulate the availability of essential trace elements but can be hijacked by toxic elements.[23,24] The relationship between maternal and fetal exposures is customarily studied by comparing maternal and cord blood. However, these relationships can be more complex for certain DNTs. Lead, for example, may be mobilized from maternal bone stores into the maternal circulation in response to

hormonal changes over pregnancy,[25] and chemical compounds such as dioxins mobilized from body fat into maternal blood and breastmilk in association with changes in fat storage.[26]

One of the most potent DNTs is methylmercury, a form of the metal produced in water and soils by bacteria. The links between exposure to this compound and developmental neurotoxicity was first revealed in a catastrophic episode of methylmercury poisoning in the city of Minimata in southern Japan. Minimata more generally demonstrated the importance of prenatal exposures to DNTs and stimulated the growth of the whole field of environmental health. Up to that point, there was little knowledge of mercury effects on children. It took the tenacity of a local physician, Dr. Shoji Kitamura, who fought industrial and government authorities as well as the allegations of other physicians, who concocted the argument that the severe mental retardation and neuromotor deficits in the community were due to genetic deficiencies brought about by intermarriage within the local population.[27] To the contrary, the deficits were due to high levels of mercury in the water.

Two extraordinary observations led him to his diagnosis. The first was his reading of an old textbook on occupational diseases (D. Hunter, *Diseases of Occupation*) that included images of brain tissue from postmortem examinations of workers exposed to mercury. The anatomic damage in these images matched his own examinations of the brains of Minimata children who died early in childhood. His second observation was the dancing cats of Minimata, animals that manifested florid neuromotor and neurobehavioral deficits caused by eating scraps of the same fish consumed by pregnant women in households where infants and children were affected. This observation effectively contradicted claims of genetic insufficiency. His conclusion: Prenatal mercury exposure is associated with distinctive changes in the structure of affected brain regions, particularly the cerebellum and cerebellar cortex. To further explain this, a distinct mechanism for mercury has been proposed by Sass et al, involving immune system regulation of some of the earliest events in neurodevelopment, migration of differentiated cells to these brain regions.[28]

Natural geologic sources are largely responsible for manganese contamination in drinking water. Manganese has a long history of neurotoxicity, first observed in studies of adult workers in manganese mining and smelting. After chronic occupational exposures, many of these workers were diagnosed with a Parkinsonism-like syndrome with both cognitive and neuromotor

manifestations. These similarities extend to the efficacy of L-dopa treatment. Later analyses have differentiated manganese intoxication from idiopathic Parkinsonism in terms of the brain regions and neuronal pathways affected.[29]

In children, high levels of manganese are associated with deficits in neuromotor development as well as cognitive impairments. Studies also suggest that there may be some similar adverse outcome pathways for manganese in adults and children.[30] A large study of prenatal manganese exposure—as part of a longitudinal study of environmental risk factors by child development researchers in Korea—found that both high and low manganese concentrations in maternal blood were associated with poorer performance by children tested for early learning at age six.[31] This complex dose-response curve is consistent with the observation that manganese is an essential trace element during early development, but that the range of exposures conferring benefit is narrow.

Arsenic, like manganese, is one of the few metal DNTs for which most exposures begin and largely remain associated with drinking water sourced from groundwater. But like mercury, exposures to arsenic can also occur through consumption of foods, particularly certain rice strains that can bioaccumulate the metal from irrigation water.[20] Arsenic has been less extensively studied epidemiologically for developmental neurotoxicity in children, but the available literature indicates that it is likely to be a DNT metalloid.[32]

Non Metallic DNTs

Some of the most prevalent contaminants in drinking water are generated by reactions between naturally occurring organic matter in water and disinfection agents containing chlorine or bromine. Health concerns about these byproducts, which include trihalomethanes and haloacetic acids, have focused on potential carcinogenicity. However, an important paper published in 2004 reported that early exposure of rats to dibromoacetic acid caused significant neurotoxicity.[33]

Residues of consumer products—pharmaceuticals, cosmetics, and personal care products—are also widely present in drinking water.[34] These DNTs are discharged in domestic waste water and reappear in drinking water because current methods of treatment are not adequate to remove

them. Among these DNTs are psychoactive drugs and endocrine regulators such as birth control drugs. A recent study of the anti-epileptic drug carbamazepine challenges assumptions that the concentrations of pharmaceuticals in drinking water are below the level at which effects on the brain would be expected to occur in the fetus.[35] Concentrations of estrogens in drinking water sources can be sufficient to affect the development of lower animals.[36]

In addition to drugs, other chemicals reach drinking water through household wastes. These include endocrine disrupters, both natural and man-made: a broad range of chemicals that may interfere with the body's endogenous hormone function and produce adverse developmental, reproductive, neurological, and immune effects.[37] Epidemiological and experimental studies have linked developmental neurotoxicity to pre- and early postnatal exposures to several classes of these endocrine disrupting chemicals (EDCs), including phthalates, polyhalogenated organic molecules, and perfluorinated compounds.[37] Among EDCs are chemicals that disrupt neonatal thyroid hormone function, a physiological system essential for normal brain development. Other EDCs, such as those that interact with estrogenic signaling pathways, also have anatomic effects on the brain and genitalia and impacts the normal development of sex-typic behaviors in young boys and girls.[40]

Many EDCs have been detected in watersheds in the US and the blood of almost all Americans. Others, such as bisphenol A, leach into drinking water and other beverages from containers, including baby bottles. Phthalates have been measured in beverages and in intravenous fluids delivered by plastic tubing. We have not as yet identified all the EDCs in drinking water; a recent study of surface waters downstream from the discharge of fracking wastes reported multiple interactions with receptors based on assays to detect endocrine activity.[38]

Not all DNTs are products of the chemical industry or the result of human activities. Microscopic organisms in water, including dinoflagellates and algae, can produce diverse and highly potent neurotoxins.[41] We can be exposed through contact and ingestion of water as well as inhalation of bioaerosols carrying these natural neurotoxins. We can also be exposed through the consumption of fish and shellfish that accumulate certain of these neurotoxins, such as domoic acid or saxitoxin.[42] Algal toxins are well characterized as neurotoxic to adults and have been demonstrated

to be DNTs in experimental animals and marine mammals.[43] But apart from case reports, there is scant information on health effects in children and adolescents.[44,45]

Ignorance Is Not Acceptable

Because DNTs in drinking water are often undetected, it's no surprise that studies have found that too many children and women of childbearing age in the US and elsewhere are exposed to them. Water delivery systems are complex and can involve lead and disinfectants that produce DNTs. Other types of these compounds, including pesticides, industrial products, and natural toxins, reach drinking water though a variety of environmental releases and pathways. Moreover, DNTs in water can contaminate fish, shellfish, and crops. Natural toxins, such as those produced by phytoplankton, result in highly toxic water, air, and food-borne exposures.

While technology allows us to contemplate voyages to faraway planets and create devices to purchase things with a wave of the phone, we remain largely ignorant of the nature and extent of DNTs in our water, food, and other consumer products. Our knowledge of toxic agents such as methylmercury, arsenic, and lead is largely drawn from devastating effects of population exposures that we haven't prevented.[46] Recent discoveries about endocrine disruptors (perfluorinated compounds (PFCs, for example) illustrate the magnitude of our failure to identify the neurotoxicity of chemicals commonly found in drinking water.[39] Through a survey of workers' blood levels, PFCs were accidentally discovered to be highly persistent and, because of their multiple uses, likely to be almost ubiquitous in human blood samples. Several toxicological studies have reported adverse impacts of these chemicals on brain development, while epidemiological studies indicate associations between prenatal exposures to PFCs and deficits in early childhood development in the US and other countries.[37]

We depend upon toxicological studies to identify potential DNTs among the thousands of existing chemicals in use here and abroad, prior to human exposure. However, our current approaches are widely acknowledged to be inadequate. Testing methods are expensive and often criticized for their lack of specificity and failure to detect the multiple mechanisms involved.[47] That critical outcomes include deficits in learning and social behavior challenges methods utilizing animal models and cells for identification of potential DNTs.

As a result, we have not progressed much from the discovery of lead as a cause of intellectual disability in infants, and mercury as the cause of severe neurotoxicity in young children. In these instances, investigations that identified preventable environmental exposures were only pursued because no other cause was identified. The cases of lead in Glasgow and mercury in Minimata were exceptional, too, because of their severity and the persistent and extraordinary detective work of local physicians. This is not reassuring.

Since then, epidemiological studies of outcomes related to developmental neurotoxicity among children exposed pre- and postnatally have helped us to define the risks of a limited number of DNTs, especially at low-level exposures. The problem is that most of this research continues to focus on a limited set of well-characterized agents and does not adequately lead to studies that will identify the number or variety of DNTs in drinking water and elsewhere.[26] Still, advances are coming from longitudinal studies underway in Europe, Korea, and Japan. Some of this epidemiological research has already contributed critical new knowledge about known toxicants and may reveal additional compounds for further study.[48]

Knowledge of toxic chemicals in our air is much further along than in our drinking water. In the US and many other countries, we have established monitoring systems for airborne hazards and now control many of them at the source of release. We don't do this for drinking water. For a more complete knowledge of exposure to DNTs from this source, we need a national system for environmental monitoring and exposure assessment. Most of the available data on chemicals and other substances in water come from studies by the United States Geological Survey, rather than from the Environmental Protection Agency, and these surveys are not generally designed to assess population exposures. The recent scandal over lead in Flint has revealed the extent to which drinking water needs to be monitored. To prevent developmental neurotoxicity in the years ahead, we must do much better.

Bio

Ellen K. Silbergeld, holds a Ph.D. in environmental engineering from John Hopkins University, where she is a professor in epidemiology, environmental health sciences, and health policy and

management. Her research and professional activities bridge science and public policy, with a focus on the incorporation of epidemiology and mechanistic toxicology into environmental and occupational health policy. Her areas of current focus include the health and environmental impacts of industrial food animal production; cardiovascular risks of arsenic, lead, and cadmium; and immunotoxicity of mercury compounds. She has served as a science advisor for the Environmental Protection Agency, Department of Energy, Centers for Disease Control, National Institute of Environmental Health Sciences, Occupational Safety and Health Administration, and international organizations, including the World Bank, United Nations Environment Programme, World Health Organization, Pan American Health Organization, Food and Agriculture Organization, and the International Labour Organization. She has served as editor-in-chief of *Environmental Research* and has published more than 450 peer-reviewed articles, monographs, and reviews. She is the recipient of a lifetime achievement award from the Society of Toxicology, the Barsky Award from the American Public Health Organization, and a MacArthur Foundation "genius" award.

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