Pervasive, Unsafe Exposures to Mercury and Fluoride, Developmental Toxicants that Are Biologically Plausible Causal Agents in the Jaw Epidemic

Kahn and colleagues (2020) highlight the underrecognized, modern epidemic of jaw shrinkage, including crowded teeth and constricted airways, but overlook a powerful explanatory variable: our pervasive exposures to developmental toxicants. In a landmark 2014 review on environmental causes for the epidemics of neurodevelopmental disorders, which affect 10%–15% of all US births, 11 common chemicals were recognized as neurodevelopmental toxicants (Grandjean and Landrigan 2014). Of these, we address mercury and fluoride. Both are systemic toxicants; they target certain molecular components having key roles in fundamental cellular processes—including mineral assimilation, enzyme function, energy production, and gene expression. Both are particularly harmful during fetal and childhood development. Both have been used therapeutically in medicine and oral health. Both contribute to numerous disorders that are influenced by multiple risk factors, including genetics, nutrition, and synergies, thereby yielding complex, nonlinear toxicities that are difficult to study. Both can accumulate in target tissues, such that low, chronic exposures can produce retention toxicity. Moreover, a body burden can bioaccumulate through the food chain and can also be passed from mother to child.

Mercury's broad toxicity stems from its binding affinity for sulfhydryls (-S-H), the functional group that defines thiols, such as the amino acid, cysteine. In the body, countless thiols play key roles as enzymes, cell-signal receptors and transducers, DNA and RNA transcription factors, membrane transport channels, serum transporters, microtubule components, and antioxidants—for example, glutathione. Because of their useful biochemical properties, thiols can function as regulatory switches, responding to subtle changes in the cellular environment. Indeed, cysteine is one of the most highly conserved amino acids within active sites in proteins, highlighting its functional importance. Thiols also serve structural roles within molecules and cells. Selenols (-Se-H), including selenocysteine, are the other preferred target for mercury and are vital in thyroid function, growth and development, and neuroprotection.

Significant exposures originate through dental amalgam off-gassing and dietary fish ingestion. Excessive exposures during critical windows of development may arise from the vaccine preservative, Thimerosal, and from maternal transfer, prenatally and through breast milk. Past exposures, such as to antiseptics and ophthalmic products, may contribute to retained body burden in susceptible individuals. Idiosyncratic and occult exposures may occur via breakages, spills, and casual handling.

In September 2020, the US Food and Drug Administration (FDA) issued new recommendations against the use of dental amalgams in certain "high-risk" populations including pregnant women, children, and women who are planning to become pregnant. The FDA's 2009 amalgam rule acknowledges that typical exposures to mercury vapor from amalgam are *at* the safety threshold, such that an above-average number of amalgams yields exposures in excess of safety guidelines. Moreover, the safety guideline for mercury vapor exposure, set by the US Environmental Protection Agency (EPA) in 1995, is arguably too lenient. California's equivalent standard, which explicitly considers developmental toxicity, is ten times stricter.

Fluoride, in biomolecules, displaces iodine and hydroxide and also diverts calcium and magnesium from their intended sites. Iodine displacement yields hypothyroid disorder, which is detrimental during development. Calcium serves as a constituent of bones and teeth and also functions as a second messenger in cell signaling for muscle contraction, nerve impulses, and hormone secretion. Magnesium serves as a cofactor for enzymes involved in energy production, protein synthesis, ion transport, and cell signaling, and also serves in structural roles. Via these mechanisms, fluoride disrupts gene expression and protein synthesis—for example, for collagen, proteoglycans, and matrix metalloproteinases. Fluoride accumulates in bones and teeth by displacing hydroxyls within hydroxyapatite. Fluoride promotes dental and skeletal fluorosis by inhibiting a matrix metalloproteinase necessary for growth and development.

Fluoride exposures have increased dramatically since WWII, from dental products, foods and beverages, fertilizers and pesticides, pharmaceutical products, nonstick cookware, water-repellent products, and most significantly, from community water fluoridation. Most Americans (87%) receive community water service, and of those, 73% receive fluoridated water. Formula-fed babies are a subgroup of concern.

To protect against dental caries, the US Public Health Service recommends that communities fluoridate their drinking water to a level of 0.7 milligrams per liter (mg per L) or parts per million (PPM), not to exceed the EPA's Maximum Contaminant Level of 4.0 mg per L. In a 2006 review, the National Research Council found that this limit does not protect against adverse health effects, but the EPA has yet to revise its standard.

In 1999, one of us (DCK) was invited by a Shenyang medical school team to observe dental health improvements following fluoride reductions in multiple villages in Inner Mongolia. In the high fluoride villages (4–9 PPM), most children had small dental arches and crowded, discolored teeth—that is, dental fluorosis, many with crossbites and jaw anomalies—while these

conditions were not observed in the medium (1.0 PPM) and low fluoride (0.5 PPM) villages.

US data from the ongoing National Health and Nutrition Examination Survey show that rates of dental fluorosis in adolescents have reached 65%, and furthermore, biomarkers for mercury exposure are also increasing, both with age and in the population over time.

Supplemental material

Supplemental data are available at *BIOSCI* online.

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