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Review

Trace elements as paradigms of developmental neurotoxicants: Lead, methylmercury and arsenic

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ABSTRACT

Trace elements have contributed unique insights into developmental neurotoxicity and serve as paradigms for such adverse effects. Many trace elements are retained in the body for long periods and can be easily measured to assess exposure by inexpensive analytical methods that became available several decades ago so that past and cumulated exposures could be easily characterized through analysis of biological samples, e.g. blood and urine. The first compelling evidence resulted from unfortunate poisoning events that allowed scrutiny of long-term outcomes of acute exposures that occurred during early development. Pursuant to this documentation, prospective studies of children's cohorts that applied sensitive neurobehavioral methods supported the notion that the brain is uniquely vulnerable to toxic damage during early development. Lead, methylmercury, and arsenic thereby serve as paradigm neurotoxicants that provide a reference for other substances that may have similar adverse effects. Less evidence is available on manganese, fluoride, and cadmium, but experience from the former trace elements suggest that, with time, adverse effects are likely to be documented at exposures previously thought to be low and safe.

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Introduction

Increased exposures to trace elements can result in undesirable consequences to human health, and as such, the developing brain has emerged to be a highly vulnerable target organ [1]. Thus, important insights into developmental neurotoxicity derive from epidemiological studies of human populations exposed to trace elements. A key advantage offered by trace elements in such studies is that valid methods for exposure assessment are widely available. Several trace elements are retained for years in the human body and are easily measured in biological samples. Of additional importance, dramatic insight into trace element toxicity has occurred in connection with tragic incidents in mass poisonings. Observational clinical studies provided documentation on adverse effects resulting from exposures during early development.

Fig. 1 shows our present understanding of developmental neurotoxicity symbolized as an iceberg. Trace elements account for about half of the industrial chemicals that have been well documented so far as developmental neurotoxicants – especially

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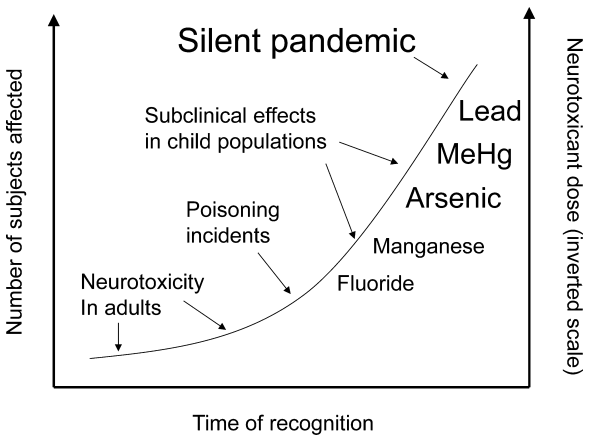

Fig. 1. Of the thousands of chemicals in current use, only a small fraction has been documented to cause developmental neurotoxicity in humans. Trace elements represent about half of the substances now known to cause developmental neurotoxicity in humans, as tip of the iceberg. Trace elements also contribute to the list of chemicals that are known to cause clinical neurological effects. Such effects are must less clear and remain poorly studied in regard to other industrial chemicals. Revised from Grandjean and Landrigan [5].

lead, methylmercury, and arsenic. This review will highlight the lessons learned from research on human health consequences of trace element toxicity affecting brain development.

One early insight arose from the discovery of fetal toxicity, proving the failed protection by the placenta that had been traditionally assumed [2]. This physiological insight was dramatically illustrated in the 1950s in Minamata, Japan, where pregnant women were unharmed by methylmercury exposure, while sufficient doses had passed through the placenta resulting in congenital poisoning of the infant [3]. The consequences of such exposures can be serious and long-lasting, as we only have one chance to develop a brain [4]. In 2010, toxic chemicals were reported as contributing to neurodevelopmental delay and neurological disease occurring in about one in six children in the US [5]. Complex developmental processes include cell multiplication, differentiation, migration, and generation of connections, with all of them occurring in a certain sequence, at a particular time. These processes are uniquely sensitive to adverse effects caused by neurotoxic chemicals, such as lead and methylmercury. Due to the limited opportunities for repair and compensation, any damage that occurs to a brain of a fetus or child will likely remain for the rest of his/her life. The consequences can therefore be dire. However, most children affected will not receive a neurodevelopmental diagnosis, and the global occurrence of adverse effects has therefore recently been termed a "silent pandemic" [6].

The three trace elements that have resulted in the most important insights are lead, mercury (methylmercury), and arsenic. They are also prime examples – or paradigms – of environmental chemicals, for which the development of exposure standards and policies can be followed over time and linked to expanding research and growth of the knowledge base.

Lead

Lead has been utilized for thousands of years in numerous applications, many of which resulted in environmental dissemination and human exposures. Traditionally, lead poisoning was thought of as a potentially life-threatening disease, which, in survivors, left no trace. This illusion was exposed when two pediatricians traced twenty lead-poisoned children who had at first been discharged from hospital as "recovered" [7]. Nineteen of the children had severe learning or behavioral problems and were school failures. Only five had an IQ in the normal range. More than thirty years later, a landmark study showed that increased lead exposure was a major predictor of cognitive and behavioral problems in school children in Boston [8]. This study determined the lead content of deciduous teeth as a marker of cumulated lead exposure. With time, adverse effects were documented at lower and lower lead exposures, often documented by serial blood-lead determinations. These studies took advantage of more sophisticated epidemiological designs, including larger groups of children and applying more sensitive tests of brain functions [9]. Recently, a subgroup of subjects from the original study of Boston school children was re-examined [10]. The 43 adults, now in their late 20 s, had IQ scores that were inversely associated with their childhood lead exposure. This finding echoes what Byers and Lord said more than 50 years ago: Lead toxicity does not fade away.

Gradually, the general attitude began to change, and lead toxicity increasingly was recognized as a global risk to brain development. In 2010 the European Food Safety Authority (EFSA) evaluated the cumulative evidence, at the request of the European Commission [11]. The dispassionate conclusion reads, "It was not possible to exclude a risk to the developing fetus through exposure of some pregnant female consumers". Despite the hedged language, this report represents a radical diversion from classical toxicology: There is no known safe exposure to lead, EFSA said. Soon thereafter, the conclusion that no blood lead concentration can be considered safe was echoed by other health authorities [12].

Given the discoveries on lead poisoning early in the previous century and even before that, one may wonder why it took so long for us to realize that lead exposure can harm brain development. Part of the answer is that the medical and scientific establishments were not ready to consider the "subclinical" effects of a true public health hazard [13]. Another part of the answer is that large, prospective studies using sophisticated tests only became possible beginning in the 1970s onwards. For example, modern imaging techniques have only recently allowed documentation of reductions in gray matter (cortex) volume, especially of the prefrontal cortex in adults with increased childhood lead exposures [14].

However, there is a yet a third issue that hampered scientific insight into lead toxicity. Since ancient times, lead had been looked upon as a highly useful metal. Given its economic value, any claims that lead might be toxic were not taken on face value. When lead additives were introduced as effective octane-boosters for gasoline in the 1920s, spokesman for the lead industry, Dr. Robert A. Kehoe, explained that industry leaders would make responsible decisions, but only when justified: "They have expressed themselves repeatedly not so much as being interested in opinions as being interested in facts, and if it can be shown. . . that an actual danger to the public [occurs] as a result of the treatment of the gasoline with lead, the distribution of gasoline with lead in it will be discontinued from that moment" [15]. Summing up the argument, he added: "It is a thing which should be treated solely on the basis of facts". Later referred to as Kehoe's show-me rule, his stance was strictly adhered to during subsequent decades so that very little would be accepted as "fact", unless it was in favor of the continued use of lead additives. The mere notion that a chemical substance should be considered innocuous, unless proof of the opposite could be obtained, is of course not cogent, as the consequences, if proven otherwise, may be seriously detrimental to public health.

Even today, lead exposure causes neurodevelopmental deficits that are associated with loss of IQ points [16], impairment in school performance [17], and an association with very substantial economic losses to society [18,19]. Even though lead toxicity is widely recognized today, its adverse effects still occur as a result of reckless applications of lead in the past and our unwillingness to accept that a useful metal could be so harmful. Although lead's persistence in the body allowed for reliable exposure assessment from blood anal-