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REVIEW ARTICLE

Developmental toxicity of arsenic: a drift from the classical dose–response relationship

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Abstract

Arsenic is a well-known natural environmental contaminant distributed in food, water, air, and soil. The developmental toxicity of arsenic exposure is a significant concern in large parts of the world. Unlike acute toxic exposure, the classical dose–response relationship is not adequate for estimating the possible impact of chronic low-level arsenic exposure. The real-life risk and impact assessments require the consideration of the co-exposure to multiple toxins, individual genetic and nutritional predisposition, and the particularly vulnerable stages of the neurodevelopment. This context shifts the assessment model away from the 'one-exposure-for-one-health-effect.' We underscore the need for a comprehensive risk assessment that takes into account all relevant determinants. We aim to elaborate a model that can serve as a basis for an understanding of complex interacting factors in a long-lasting and ongoing low-level arsenic exposure, to identify, protect, and support the children at risk.

Keywords Arsenic · Toxicity · Poisoning · Treatments · Natural compound

Introduction

Arsenic is a trace element that occurs in many minerals in the Earth's crust, often together with other metals and sulfur. As a result of leaching and runoff, arsenic can leak into the soil and groundwater, and anthropogenic activities can also bring arsenic into soil and groundwater (Li et al. 2011; Singh 2006). Arsenic is on the top rank of the Substance Priority List of the U.S. Agency for Toxic Substances and Disease Registry, followed by lead, mercury, and cadmium (ATSDR 2017). The highest rank indicates its significant potential for human exposure, toxicity, and the occurring frequency at the facilities around the U.S National Priorities Sites. Human arsenic exposure is predominantly through the contaminated drinking water and food, whereas the inhalation and absorption through the skin are the minor routes (Shi et al. 2004; Tippairote et al. 2019). Reports of arsenic water contamination have come from many countries such as Bangladesh, Canada, China, India, America, Taiwan, Mexico, Poland, Japan, Nepal (Jain and Ali 2000; Smith et al. 2000), and Iran (Mosaferi et al. 2003). While the WHO standards of the maximum permissible arsenic value in drinking water was 10 µg/L (WHO 2018), a review reported that the arsenic levels in Argentina, Mexico, Taiwan, and Indo-Bangladesh exceeded such limit, at 200, 400, 50–1988, and 888 µg/L, respectively (Flora 2011). However, despite the acceptable arsenic level in local water resources, the exposure of arsenic from dietary sources was still the constitutional concern in young children (EFSA 2009). With its inherited prevalence and human toxicity potential, arsenic is a current global concern.

The main form of arsenic in water, soil, and foods is the inorganic form (Chung et al. 2014). Inorganic arsenic is a human carcinogen group 1, according to the classification by the International Agency for Research on Cancer or IARC

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(Straif et al. 2009). Acute toxic arsenic exposure leads to various dose-dependent responses ranging from mild, moderate, to lethal reactions. These symptoms include mouth dryness, diffuse skin rashes, Mee's lines in fingernails, garlicky odor breathing, weakness, muscular cramps, nausea, vomiting, diarrhea, abdominal pain, psychosis, hallucinations, delusions, delirium, seizures, neuropathy, encephalopathy, generalized vasodilation, cardiovascular collapse, hypovolemic shock, pulmonary edema, kidney failure, respiratory failure, toxic cardiomyopathy, coma, and death (Mitra et al. 2019). The exposure dosage assessment generally considers the proportions of arsenic contamination levels in the environment, exposure rate, and the individual characteristics of the victim (Gerba 2004). Taiwanese adults, who were exposed to the arsenic-contaminated well water, were at risk for increased occurrence of lung cancers for a period of at least the next 15 years. Arsenic exposure during pregnancy and childhood was linked to the increased incidence and severity of lung, cardiovascular diseases, and cancers later in life with some reports of decade-long latency periods for these conditions (Liaw et al. 2008; Marshall et al. 2007; Smith et al. 2011; Yuan et al. 2010). This cancer risk increased when their detoxification ability through methylation was low. Individuals with high methylation capacity did not suffer for the same was despite their comparable exposure dosage (Hsu et al. 2017). Various nutrients and bioactive food components influence the methylation status. The role of methylation in the arsenic detoxification and DNA methylation processes can partly explain the different cancer outcomes (Mahmoud and Ali 2019; Mondal et al. 2011). At least for the carcinogenic endpoint, the classical toxicological concept of the dose–response relationship was inadequate to appreciate the impacts of chronic, low-dose arsenic exposure (Tsatsakis et al. 2018).

In the context of chronic low-level arsenic exposure, growing children are more vulnerable to the toxic impacts than adults. Children who lived with their cigarette-smoking parents showed high urine arsenic levels and were considered at risk, although their parents were quite healthy (Chiba and Masironi 1992). Growing children have low body mass, large skin surface area, immature hepatic biotransformation enzyme activity, and a high tendency of hand-to-mouth behavior. These differences compromised their tolerance to toxic exposure even at low dosage (ATSDR 2007).

The prevalence of neurodevelopmental disorders, such as attention deficit and hyperactive disorders, autistic spectrum disorders, and learning disorders, is increasing worldwide and becoming the critical concern of growing children (Carballal Mariño et al. 2018). Cumulative pieces of evidence indicated that prenatal or early-life arsenic exposure, even at levels below the safety guideline, could potentially have impacts on their physiological neurodevelopmental processes (Tolins et al. 2014). Arsenic exposure during early pregnancy could alter the genome-wide DNA methylation in the offspring boys (Broberg et al. 2014). Other possible toxicological mechanisms were including the disrupted endocrine effects, immunologic suppression, neurotoxicity, and possible interactions with the enzymes that were critical for fetal development and programming (Vahter 2008). The impacts on children's intelligence and memory might become manifest later in life, and the symptoms could span from minor disruptions of functional performance to severe intellectual impairment and profounded developmental retardation.

Numerous studies and reviews are available on acute arsenic toxicity and its potential impacts on the physiology of adult humans (Abdul et al. 2015). However, comprehensive reviews on the context of neurodevelopmental impacts from chronic low-level arsenic exposure are limited.

Mechanisms of arsenic toxicity

The mechanisms of arsenic toxicity vary with respect to its chemical form (Molin et al. 2015). Arsenic primarily induces oxidative stress by oxidation–reduction reactions and induction of mitochondrial dysfunction (Prakash et al. 2016). Arsenic also interferes with the enzymatic activities of superoxide dismutase, nitric oxide synthase, and NADPH oxidase. It can bind to the sulfhydryl groups of proteins. Its inhibition of glutathione synthase and glucose-6-phosphate dehydrogenase leads to the reduction of glutathione and the NADPH pools. These combined actions compromise the free radical scavenging and worsen the oxidative stress, which further drives the damage of organelles, DNA, protein, and lipids (Kim et al. 2019; Susan et al. 2019).

The trivalent arsenicals, or arsenite, inhibit the enzymatic pathways of lipoamide regeneration that act as a vital cofactor for the pyruvate dehydrogenase complex, which converts pyruvate to acetyl-coenzyme A (acetyl-CoA) (Kurzius-Spencer et al. 2017). The reduction of the acetyl-CoA pool decreases the activity of the citric acid cycle and oxidative phosphorylation. Furthermore, the reduction of succinyl-CoA, another citric acid cycle metabolite, undermines the maturation of red blood cells. Arsenite inhibits the thiolase enzyme activity, thereby impairing fatty acid oxidation (Aposhian and Aposhian 1989). Arsenite may also block potassium channels within the heart muscles resulting in prolonged QT intervals (Mumford et al. 2007). It might also impair physiological methylation reaction and the acid–base balance (Florea and Busselberg 2008; Kim et al. 2019; Laparra et al. 2008; Paul et al. 2008; Susan et al. 2019).

Pentavalent arsenicals, or arsenate, generate toxicity through a different mechanism. The arsenate reduction reaction yields arsenite. Arsenate may compete with the phosphate groups during the conversion of adenosine

diphosphate to adenosine triphosphate, thus impairs cellular bioenergetics (Baysan et al. 2007; Kim et al. 2019).

Methylated arsenic metabolites, as well as inorganic arsenic species, can cross the blood–brain barrier and enter the brain cells (Samuel et al. 2005). These compounds also appear to enhance extracellular plaque formation (Zarazua et al. 2011) and enter the substantia nigra with the impacts on dopaminergic neuron functions (Chandravanshi et al. 2014). Such effects of arsenicals have been suggested to contribute to the pathogenesis of several neurological diseases, including neurobehavioral disorders, and also Alzheimer's disease, and Parkinson's disease (Chen 2014; Susan et al. 2019). Figure 1 summarizes all these mentioned mechanisms of arsenic toxicity.

Chronic arsenic toxicity and concurrent exposure to multiple toxins

While arsenic is ranked at the top of the ATSDR's Substance Priority list, co-exposure of this agent with other toxins is common in the real-life situation (Bora et al. 2019; Freire et al. 2018). Thus, a recent study of hair bio-element levels in Thai well-nourished children reported the frequency of high hair arsenic, lead, cadmium, mercury, and aluminum levels at 36, 25, 14, 13, and 12 percent of the participants, respectively (Tippairote et al. 2018). The co-existing of these toxins shifts the exposure outcomes and evaluations away from the 'one-exposure-for-one-health-effect' paradigm.

Among several potential toxicodynamic mechanisms, oxidative stress promotion is a primary machinery by which several heavy metals produce toxic and in some cases, neurodevelopmental consequences (Engwa et al. 2019). Co-exposure to multiple free radical-generating toxins can aggravate the underlying pathophysiologic processes and amplify the adverse outcomes (Andrade et al. 2015). A study reported the association of declined global, verbal, executive, and motor functions and skills in preschool children to their prenatal arsenic and mercury exposure, as determined by the placental levels (Neeti and Prakash 2013). There also seemed to be synergistic toxic effects between arsenic and lead (Freire et al. 2018). The presence of one element may influence the effects of others, either synergistically or antagonistically (Tippairote et al. 2017). Growing evidence suggests that early life co-exposure to metals, including lead, methylmercury, and arsenic, increases the risk for neurodevelopmental toxicity compared to single metal exposure (Sanders et al. 2015). Consequently, to comprehensively

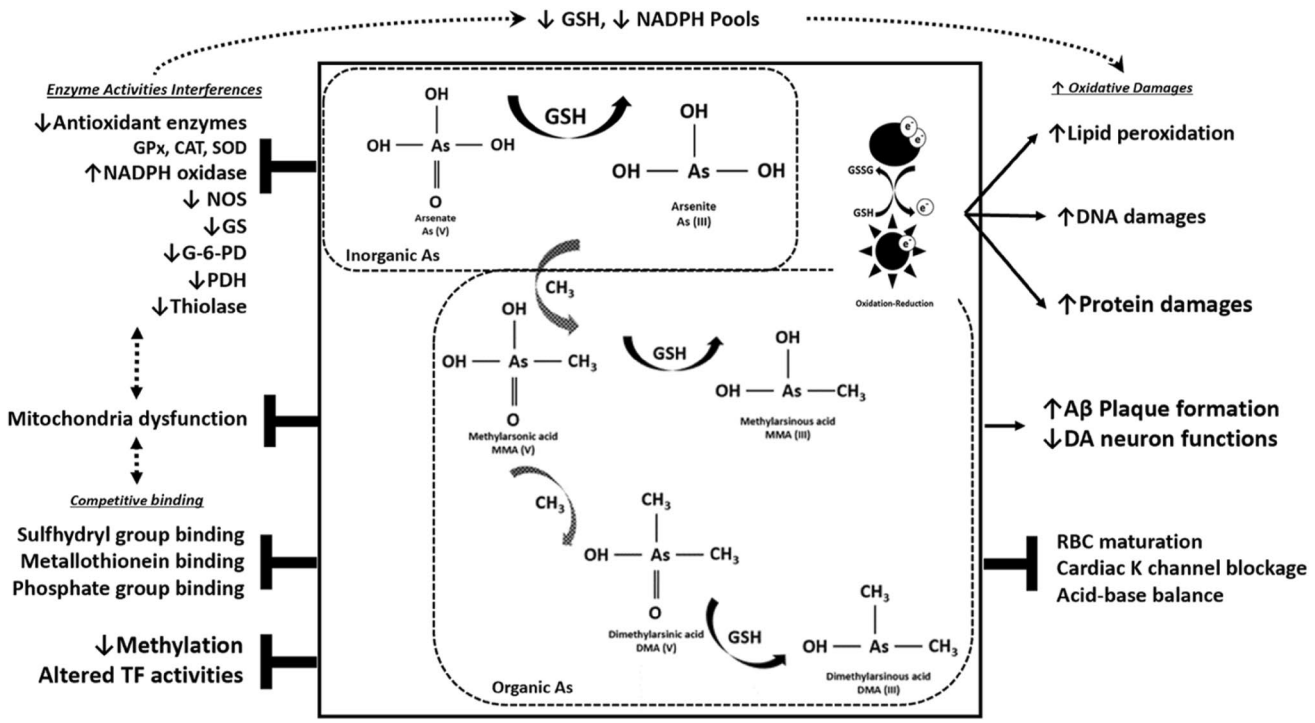

Fig. 1 The mechanisms of arsenic toxicity. *As* arsenic, *As (V)* Arsenate, *As (III)* Arsenite, *GSH* reduced glutathione, *GSSG* glutathione disulfide, *NADPH* reduced nicotinamide adenine dinucleotide phosphate, *GPX* glutathione peroxidase, *CAT* catalase, *SOD* superoxide dismutase, disorders, *NOS* nitric oxide synthase, *GS* Glutathione synthase, *G-6-PD* glucose-6-phosphate dehydrogenase, *PDH* pyruvate dehydrogenase (PDH) complex, *TF* transcription factors, *Aβ Plaque* amyloid beta plaque, *DA neuron* dopaminergic neurons, *RBC* red blood cells, *K channel* potassium channel

understand the neurodevelopmental impacts of chronic low-level exposure of arsenic, the independent assessment of arsenic is not sufficient. The consideration of concurrent exposure to other toxins is then essential.

The genetic predisposition and individual nutritional status

A prospective case–control arsenic exposure study reported the close association of arsenic methylation capacity, children's health status, and developmental outcomes (Hsueh et al. 2016). There was a strong association between arsenic methylation ability and developmental delay (Hsueh et al. 2016), and low plasma selenium and folate levels may increase the risk (Chiba and Masironi 1992; Pilsner et al. 2011). The interactions between toxic element exposure with low levels of essential elements, as measured in blood and urine samples, significantly influenced the cognitive assessment scores in a study of 95 children from the Democratic Republic of Congo (Bora et al. 2019). Individual nutritional status is a critical determinant of chronic arsenic exposure outcome.

There are complex interactions between genetic variations, gene expression pathways, and micronutrient status (Schomburg and Schweizer 2009; van Ommen et al. 2008, 2010). Several studies reported the association between low selenoenzyme activity and many variations in the single nucleotide polymorphisms (SNPs) of selenoprotein genes (Ferguson and Karunasinghe 2011). Several of the selenoprotein ameliorate cells from the free radical-induced oxidative damage through their enzymatic actions, such as glutathione peroxidase, thioredoxin reductase, and selenoprotein P (Ferguson et al. 2006; Hawkes and Alkan 2010). Many SNP variations also influence the methylation status (Alam et al. 2019; Farhud et al. 2010). Both selenoproteins and methylation status were vital defenses against arsenic toxicity (Vahter and Concha 2001).

The complex interactions of diet, nutrients, toxins, genetic variations, and gene expression patterns regulate the individual responses and determine long-term effects. Studies in both animal models and human subjects reported the arsenic-induced changes of the DNA methylation patterns, histone posttranslational modifications, and microRNAs (Bjorklund et al. 2018a; Pelch et al. 2015; Rager et al. 2015). Altered gene expression patterns can direct the cellular pathways toward the carcinogenesis or disrupted neurodevelopmental processes (Bjorklund et al. 2018b).

Improvement of dietary patterns and nutritional status alleviated the chronic arsenic exposure aftermath (Sharma and Flora 2018). The specific nutrients essential in one-carbon metabolism, methylation cycles, and antioxidants showed protective effects on arsenic toxicity (Kurzius-Spencer et al. 2017). The individual nutritional status appraisal, in addition to toxic exposure assessment, is then beneficial for the comprehensive understanding of chronic arsenic exposure impacts.

The neurodevelopmental continuum

The spectrum of early-life neurotoxicant-exposure consequences appears to range from autism spectrum disorder, attention-deficit hyperactive disorder (ADHD), dyslexia, intellectual disability, learning disorder, behavioral disorders, to cognitive dysfunction (Grandjean and Landrigan 2014). Whereas substantial declines of intelligence quotient (IQ) scores are associated with significantly increased blood lead level (Reuben et al. 2017), the lesser extent of lead exposure is associated with ADHD (Tippairote et al. 2016). Different exposure levels of toxicants may lead to different impacts across this continuum. It may be inaccurate to attribute one single endpoint to the estimated developmental exposure. For example, a study presumed the protectiveness of existing arsenic reference value for developmental neurotoxicity based on the negative association between the decrements of IQ score and the arsenic levels in tap water or toenails (Tsuji et al. 2015). Without considering other possible neurodevelopmental impacts, this assumption was probably premature. The suitable approach to assess the toxic effects of low doses of chemicals should simultaneously follow the different developmental endpoints across the continuum, as in the novel model proposed by Tsatsakis et al. (2017). The 'one-exposure-for-one-health-effect' concept is consequently not valid for the continuum of neurodevelopmental outcomes of arsenic exposure.

The comprehensive risk assessment approach

The comprehensive approach to assessing chronic low-level arsenic exposure should include the appraisal of concurrent exposure to multiple toxins, individual nutritional status, together with available information of genetic predisposition to the increased individual susceptibility. The impact assessment should also extend across the neurodevelopmental continuum as much as possible. While there are many available biomarkers, the comprehensive assessment should encompass a broad spectrum of biomarkers of exposure, susceptibility, and disease (Das and Sengupta 2008; Mayeux 2004). The inclusion of intermediate or surrogate biomarkers for underlying pathophysiology of oxidative stress, inflammation, autoimmunity, mitochondriopathy, and cellular damage, is of importance. Figure 2 demonstrates this conceptual framework.

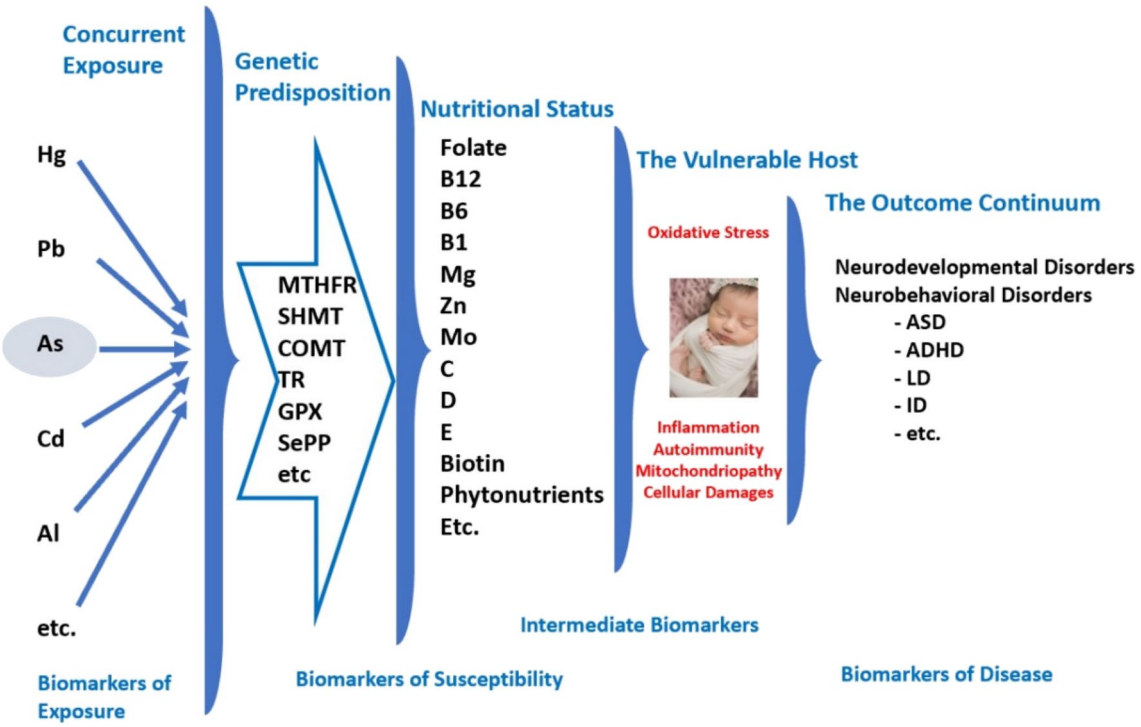

Fig. 2 The conceptual framework for assessing the neurodevelopmental impacts of chronic low-level arsenic exposure. *Hg* mercury, *Pb* lead, *As* arsenic, *Cd* cadmium, *Al* aluminium, *MTHFR* methylenetetrahydrofolate reductase, *SHMT* serine hydroxymethyltransferase, *COMT* catechol-*O*-methyltransferase, *TR* thioredoxin reductase, *GPX* glutathione peroxidase, *SePP* selenoprotein P, *ASD* autistic spectrum disorders, *ADHD* attention deficit and hyperactive disorders, *LD* learning disorders, *ID* intellectual disability

The biomarkers of exposure can be the arsenic and other element levels in the blood or urine, hair, or nail samples. Various arsenic contamination sources, such as a recent or habitual consumption of seafood or air pollution, can represent confounders as regard to a specific source. Accurate interpretation of the levels in the collected samples needs an extensive understanding of this uniqueness of an exposed individual (Tippairote et al. 2019).

In general, the blood level is not an ideal biomarker for chronic arsenic exposure due to the rapid blood clearance during the first few hours after oral ingestion (Vahter and Concha 2001). Urine arsenic levels, either total, inorganic arsenic, or methylated forms, can represent the exposure for a couple of days. Despite its relatively limited reliability, most epidemiologic studies used urine arsenic levels, preferable the 24-h collection, as the arsenic exposure indicator for arsenic-polluted area inhabitants (Minichilli et al. 2018).

Assessment of arsenic level, together with other element levels, in hair and nail samples, can represent the long-term arsenic exposure for a period of 1–12 months (Agahian et al. 1990; ATSDR 2007; Tippairote et al. 2019; Yamauchi et al. 1989). The significant hindrances of these methods are the potential incorporation of external arsenic into these samples and the inter- and intra-laboratory variation of sample collection, handling, processing, and determination of the element levels (Puchyr et al. 1998). Despite these limitations, hair arsenic level above 1 μg/g of dry hair weight indicate the acute or high-level exposure, while the levels above 0.1 or 0.2 μg/g warrant the investigation for chronic low-level exposure (Carneiro et al. 2011; Hashim et al. 2013; Park et al. 2007; Ratnaike 2003). For the nail sample, the ATSDR's upper limit of the arsenic level is 1 μg/g (ATSDR 2007).

Reports from the arsenic-polluted area suggested that the skin lesions, such as skin hyperpigmentation, or palmoplantar hyperkeratosis, are the frequent and early signs of chronic low-level arsenic exposure (Khan et al. 2003; Mandal and Biswas 2004; Puchyr et al. 1998). The clinical diagnosis of neurodevelopmental disorders required the recognition of the signs and symptoms of the specific conditions as outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (APA 2013).

A proposed risk management plan

A new paradigm of risk management will depend on the findings from a comprehensive assessment of concurrent exposure levels, susceptibility, and potential developmental impacts. At the public level, there should be a program to

raise the awareness of potential adverse neurodevelopmental consequences of chronic low-level arsenic exposure (Das and Sengupta 2008; Hanchett et al. 2002). The parents' participation is critical for initiating the exposure control measures of potential arsenic and other toxic metal contamination sources (Caldwell et al. 2006). The practical knowledge of the potential exposure sources, preventive strategies, and monitoring procedures is essential (Chowdhury et al. 2006; Hassan et al. 2005; Khan et al. 2006).

Following the exposure control arrangements, the immediate priority should be a correction of all existing nutritional deficiencies, promotion of healthy arsenic biotransformation, and, when possible, enhancing physiologic excretion pathways. However, there has been documented co-occurrence of high exposure to arsenic, lead, mercury, cadmium, and aluminum, together with low hair levels of selenium, zinc, molybdenum, sulfur, and phosphate, also in well-nourished children (Tippairote et al., 2018). Such micronutrient deficiency compromises the toxin biotransformation processes. The support of methylation and antioxidant capacity are vital to mitigate the arsenic toxicity (Bhattacharya 2017; Flora 2011; Mondal et al. 2011; Ratnaike 2003; Tippairote et al. 2019). Encouraging healthy modifiable lifestyle interventions, such as healthy eating, adequate hydration, avoid constipation, regular exercise, ensure good sleep quality, is also beneficial for improving nutrient assimilation, enhancing the excretion through urine, skin, and bile routes, and preventing the reabsorption of toxins (Jones and Quinn 2010; Skröder Löveborn et al. 2016; Vahter 2002).

Following the processes as mentioned above, the justification of whether to do chelation therapy depends on the documented evidence of the degree of ongoing oxidative damages and the amount of toxic retention in tissues. There is still no established consensus on the clinical usefulness of the chelating agents such as dimercaptosuccinic acid, 2,3-dimercapto-1-propanesulfonic acid (DMPS), or d-penicillamine on chronic low-level arsenic exposure (Guha Mazumder 2015; Mazumder 2008; Sun et al. 2006), although DMPS, which can be given orally, has been recommended in poisoned cases, by some researchers (Aaseth et al. 2015; Guha Mazumder et al. 2001).

Concluding remarks

The developmental toxicity from arsenic exposure is the prioritized concern for the growing children worldwide due to its inherited toxicity and high prevalence. Unlike the acute arsenic toxicity, the classical dose–response relationship is not adequate for risk assessment in chronic low-level arsenic exposure. The real-life exposure and impact assessments require the consideration of the co-exposure to multiple toxins, individual genetic and nutritional predisposition, and the continuum of neurodevelopmental outcomes. This context shifts the assessment model away from the 'one-exposure-for-one-health-effect'. This proposed risk assessment and management model should serve as a basis for an understanding of these complex interacting factors in ongoing low-level arsenic exposure. The overview perspective should help to formulate actionable plans to identify, prevent, protect, and support the children at risk.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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