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MiniReview

Health Effects of Early Life Exposure to Arsenic

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Abstract: Inorganic arsenic is a potent human carcinogen and general toxicant. More than one hundred million people are exposed to elevated concentrations, mainly via drinking water, but also via industrial emissions. Arsenic is metabolized via methylation and reduction reactions, methylarsonic acid and dimethylarsinic acid being the main metabolites excreted in urine. Both inorganic arsenic and its methylated metabolites easily pass the placenta and both experimental and human studies have shown increased risk of impaired foetal growth and increased foetal loss. Recent studies indicate that prenatal arsenic exposure also increases the risk of adverse effects during early childhood. There is a growing body of evidence that the intrauterine or early childhood exposure to arsenic also induces changes that will become apparent much later in life. One epidemiological study indicated that exposure to arsenic in drinking water during early childhood or *in utero* was associated with an increased mortality in young adults from both malignant and non-malignant lung disease. Furthermore, a series of experimental animal studies provide strong support for late effects of arsenic, including various forms of cancer, following intrauterine arsenic exposure. The involved modes of action include epigenetic effects, mainly via DNA hypomethylation, endocrine effects (most classes of steroid hormones), immune suppression, neurotoxicity, and interaction with enzymes critical for foetal development and programming.

Arsenic is a ubiquitous metalloid found in various chemical forms in soil, ground water and foods. Because arsenic in the bedrock is easily dissolved to surrounding water, inorganic arsenic is frequently present at elevated concentrations in ground water [1–3]. More than one hundred million individuals are at risk of elevated arsenic exposure, mainly via drinking water, but also via ambient air in areas with coal burning and industrial emissions. The arsenic problem in Bangladesh and West Bengal is, perhaps, the most devastating, as a substantial fraction of the many millions of hand-pumped tubewells yield drinking water with arsenic concentrations above 10 µg/l, the World Health Organization drinking water guideline [4,5]. Millions of people in Europe and the USA are also currently exposed to drinking water arsenic levels above 10 µg of As/l.

Inorganic arsenic is a well-documented potent human carcinogen, causing cancer in skin, lungs, urinary bladder, kidney and, possibly, liver [1]. In addition, chronic exposure to arsenic through drinking water is associated with detectably increased risk of several non-cancer diseases (e.g. hyperkeratosis, pigmentation changes, cardiovascular diseases, hypertension, and respiratory, neurological, liver and kidney disorders, as well as diabetes mellitus) [1,2,6]. Often, the first symptoms of exposure to arsenic in drinking water include pigmentation changes and hyperkeratosis, which reportedly appear after 5–10 years of exposure [7]. In spite of the large number of people being exposed to arsenic and the numerous studies on the health effects of arsenic, few have focused on potential developmental effects. The health effects are mostly documented at adult ages, and little is known about variation in susceptibility depending on, for example, age and gender. Such information is essential as the exposure arsenic in the environment often starts in the very beginning of life and continues for many years or even throughout life. In particular, that is true in populations exposed via arsenic-contaminated drinking water.

This report reviews available information on the exposure to arsenic in early life and the potential consequences in forms of adverse effects on foetal and infant development and survival, as well as negative health effects later in life. Most of the available information concerns exposure via drinking water, but other routes of exposure (e.g. inhalation of airborne arsenic), are likely to cause similar effects. However, the metabolism may be somewhat different after inhalation compared to the oral exposure, when the absorbed arsenic passes the liver where it is metabolized by methylation as discussed below.

Transfer of arsenic to the foetus and breast-feeding child

Arsenic readily passes the placenta in human beings [8] and in other mammals [9,10]. Studies of people exposed to arsenic via drinking water in Argentina showed similar exposure levels in the foetus as in the mother [8]. Both

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inorganic arsenic and its methylated metabolites, methylarsonic acid (MMA) and dimethylarsinic acid (DMA), pass the placenta [8,9]. Inorganic arsenic is metabolized in the body by a series of reduction and methylation reactions via one-carbon metabolism, using S-adenosylmethionine as methyl donor. The produced MMA and DMA are excreted in urine [11], but the trivalent intermediate metabolites, mainly inorganic AsIII and MMAIII, are much more reactive and have longer half-times in the tissues. A large number of studies have shown an association between the fraction of MMA in urine, probably reflecting MMAIII in the tissues, and the risk of various health effects, including cancer and atherosclerosis [12–19], but the role of arsenic metabolism in the health effects induced early in life is not clear. However, studies on pregnant mice given periodate-oxidized adenosine, known to inhibit arsenic methylation [20], showed increased developmental toxicity of arsenic [21].

It is known that the methylation of arsenic in women is induced during pregnancy [8,22]. Studies of pregnant women exposed to arsenic via drinking water in Argentina showed that essentially all arsenic in the blood plasma and urine of the newborn babies was in the form of DMA, indicating that it is mainly this metabolite that reaches the foetus in late gestation [8]. However, the foetus is likely to be exposed to more inorganic arsenic and MMA in early gestation, before the induction of the arsenic methyltransferases.

The metabolism of arsenic is influenced by several other factors, such as age, genetic polymorphisms, nutrition, exposure to other chemicals, and in particular, the arsenic exposure level [23,24]. Even a moderately elevated arsenic exposure inhibits the methylation of arsenic, in particularly the methylation of MMA to DMA [25], implying proportionally higher MMA doses to the foetus at higher maternal arsenic exposure levels or in the tissues of the exposed child.

In contrast to the free passage of arsenic over the placenta to the foetus, the passage over the mammary gland is limited, and little arsenic is excreted in breast milk [26]. Thus, the infant is protected against arsenic exposure during the breast-feeding period, while formula prepared from the drinking water may cause considerable postnatal arsenic exposure. Our previous studies in Argentina showed a decrease in arsenic concentrations in the urine of the infants from about 80 μg/l during the first 2 days in life, as a result of foetal exposure, to less than 30 μg/l at 4 months of age [8].

Effects of arsenic on foetal development and survival

In general, foetal and early postnatal development constitutes the most vulnerable stages with regard to adverse effects of environmental toxicants [27]. Arsenic is shown to be embryotoxic and teratogenic in experimental animals; however, most studies have used high parenteral arsenic dosing, which might have involved maternal toxicity [28,29]. Only recently have experimental studies without maternal toxicity shown foetal growth retardation and neurotoxicity following oral dosing at relevant exposure levels [29]. Still, there is a need for more information on the variation in susceptibility to arsenic during embryonic and foetal development. Furthermore, there is a need for more information on the effects of combined exposures, which is likely to occur in real life. Interestingly, arsenic was found to enhance the foetal toxicity of the crop protection agent anilofos [30].

Because of the frequently used high doses of arsenic in the experimental animal studies and the profound species differences in arsenic metabolism [31], it is difficult to extrapolate the results to human beings. Therefore, human data are needed for firm conclusions and risk assessment. However, in spite of the widespread occurrence of arsenic and the numerous people exposed, there are few studies on foetal development in relation to arsenic exposure reported in the scientific literature. Several of the reported studies are either ecologic or cross-sectional in design and have potential biases in the assessment of exposure and outcomes, the latter often being obtained by interviews many years after. Increased risk of spontaneous abortion, stillbirth, preterm birth and neonatal death at elevated water arsenic concentrations was suggested in three studies in Bangladesh and West Bengal, in which 192, 533 and 202 women of childbearing age, respectively, were interviewed bout previous pregnancies [32–34]. In northern Chile, foetal and neonatal mortality rates (register data) in the town of Antofagasta were reported to be elevated during a period with increased arsenic concentration (800 μg/l) in the drinking water, compared to that in the town of Valparaíso, with essentially no arsenic in the drinking water [35]. There are also two ecological studies indicating that women drinking water with elevated arsenic concentrations during pregnancy have infants with lower birth-weight [36,37]. The studies were performed in northeastern Taiwan (up to 3600 μg/l; 85% above 50 μg/l in the drinking water), and northern Chile (on average 40 μg/l in the water) and showed 30 and 57 g lower birth-weights, respectively, in infants (weighing on average 3133 and 3398 g, respectively), compared to areas with low-arsenic exposure.

There are two recent fairly large cohort studies with individual exposure data in Bangladesh. Pregnancy outcome data for 2000 women, obtained from the Community Nutrition Centres (administered by BRAC, the largest non-governmental organization in Bangladesh) providing care to all pregnant women in three areas with known elevated arsenic concentrations in drinking water, showed a small but statistically significant association between arsenic concentrations in drinking water (sampled at personal follow-up interviews) and birth defects (odds ratio 1.005), but no other adverse effects [38]. A large population-based study involving a cohort of 29,134 pregnancies in Matlab, Bangladesh, evaluated the association between arsenic exposure via drinking water and foetal and infant survival data, obtained from the health and demographic surveillance system carried out by Centre for Health and Population Research, Bangladesh, since 40 years in Matlab [39]. The drinking water concentrations were obtained based on personal interviews about drinking water history and screening of arsenic concentrations in

all functioning tubewells in Matlab in a parallel study [40]. There was a fairly small but significant dose–response for foetal loss, and drinking water containing more than 50 μg/l (the national drinking water standard) during pregnancy corresponded to a relative risk of 1.14.

As there is increasing evidence that early-life exposures affecting foetal and infant environment may cause chronic disease later in life [41,42], it is obvious that more research concerning the health risks of early arsenic exposure is highly warranted, preferably using longitudinal studies that can ascertain both exposure and outcome.

Effects of arsenic on child health and development

Because of the limited transfer of arsenic to breast milk, the breast-fed infant is protected from arsenic exposure. However, both the prenatal exposure and the exposure after weaning may give rise to adverse effects on child health and development. Indeed, a significant association between maternal exposure to arsenic during pregnancy (individual water arsenic concentrations) on infant survival was observed in the above mentioned cohort study of 29,134 pregnancies in Matlab, Bangladesh [39]. Infants born to mothers who were drinking water with more than 50 μg/l during pregnancy had significantly increased mortality risks during the first year in life (relative risk 1.17), especially due to infectious diseases. The dose–response relationship indicated that the increased risk of infant mortality started already around 50 μg/l in the drinking water. While the effects in early infancy were likely due to prenatal exposure, as most of the women in the area breast-feed their infants, the effects in later infancy might have been induced by concurrent exposure via formula or semisolid food, prepared with the arsenic-contaminated water, or a combination of both pre- and postnatal exposure.

The brain is particularly vulnerable during development (i.e. during gestation and early childhood), and often the damage induced by neurotoxic agents is permanent. In the case of arsenic exposure, experimental studies have shown associations between foetal exposure and neurotoxicity and behavioural changes [29]. Rats exposed to high concentrations of arsenite (37 mg/l) in drinking water from gestation day 15 until 4 months of age showed increased spontaneous locomotor activity and alterations in a spatial learning task compared to control rats [43]. The latter effects were also found in rats exposed from postnatal day 1. Total arsenic content in brain was similar for both exposed groups and significantly different from the control group. Similarly, exposure of young rats to arsenate (5 mg/kg body weight per day) resulted in increased time to acquire operant learning and decreased acetylcholine esterase activity in some regions of the brain [44]. Even though these experimental studies demonstrate that arsenic is neurotoxic, the critical doses may be lower in human beings, considering the major species differences in metabolism of arsenic [31].

The few reported epidemiological studies concerning arsenic exposure and developmental effects in human beings are all cross-sectional in design and confronted with the fact that there may be a substantial time interval between the causative exposure or induction of lesion and the detection of outcomes (e.g. cognitive function). Neurobehavioural outcomes are influenced by the age at examination and many other co-variates, such as nutrition. The exposure to arsenic and factors influencing the susceptibility at the time of the study may be very different from that occurring prenatally or in early childhood and estimates of past exposures from questionnaires and residence data are often imprecise. Therefore, longitudinal studies are warranted for evaluation of late effects of early-life exposure. No such studies have yet been reported. A few recent cross-sectional studies have reported links between arsenic exposure and neurobehavioural deficits in school children, although the studies include few children and little information on exposure early in life. However, often it may be assumed that the exposure (e.g. from drinking water or industrial pollution), has been similar also earlier in childhood. The effects of chronic exposure to arsenic (geometric mean 63 μg As/g creatinine in urine) and lead (89 μg/l in blood) on neuropsychological development of 41 children, 6–9 years of age, living in the vicinity of a smelter in Mexico were examined were evaluated by comparing test results with those of children living in an area with lower exposure to arsenic (39 children; urinary arsenic 40 μg/g creatinine, 97 μg Pb/l), but with more prevalent undernutrition and socio-cultural disadvantages [45]. Although the average arsenic exposure was fairly high also in the control group and blood lead levels were similar in both groups, evaluation of the children using the Wechsler Intelligence Scale for Children (revised for Mexico; WISC-RM) indicated that higher levels of urinary arsenic were related to poorer performance of tests examining long-term memory and linguistic abstraction, while lower scores in WISC-RM factors measuring attention were obtained at increasing values of blood lead.

Another cross-sectional study of 201 children 10 years of age in Araihazar, Bangladesh, reported that the children's intellectual function on tests drawn from the Wechsler Intelligence Scale for Children, version III, was reduced in relation to exposure to arsenic in drinking water, after adjustment for socio-demographic covariates and water manganese [46]. Children with water arsenic levels above 50 μg/l achieved significantly lower performance and full-scale scores than did children with water arsenic levels below 5 μg/l. A similar investigation of 301 randomly selected 6-year-old children indicated that the children's intellectual function, evaluated using subtests of the Wechsler Preschool and Primary Scale of Intelligence, was significantly negatively associated with arsenic concentrations in drinking water [47]. With covariate adjustment, water arsenic remained negatively associated with both Performance and Processing Speed raw scores. Similarly, a cross-sectional study examining cognitive function in 49 adolescents exposed to high and 60 controls exposed to low levels of arsenic in drinking water in Taiwan found that memory and switching attention were

significantly affected by long-term cumulative exposure to arsenic after adjusting for education and sex [48].

A cross-sectional study among 351 children age 5 to 15 years in West Bengal, India, studied associations between arsenic concentrations in the children's urine and intellectual function assessed with six subtests from the Wechsler Intelligence Scale for Children as well as with the Total Sentence Recall test, the Colored Progressive Matrices test and a pegboard test [49]. There were significant associations between urinary arsenic and reductions in the adjusted scores of the vocabulary test (–12% in the upper urinary arsenic tertile), the object assembly test (–21%) and the picture completion test (–13%). There was no evidence of an association between test results and water arsenic concentrations during pregnancy or childhood.

Taken together, these studies provide strong evidence for neurobehavioural effects of arsenic exposure during childhood, although more studies are warranted to evaluate the most critical windows of exposure, the type of effects and the dose–response relationships.

Support for lasting arsenic-related neurotoxic effects is provided by follow-up of infants severely poisoned by arsenic-contaminated milk powder used for preparation of infant formula in Japan in the 1950s [50–52]. Records showed that the prepared milk contained 4–7 mg/l or more. Clinical poisoning occurred within 1 month of exposure, which corresponded to daily doses of 3–5 mg, depending on age, and total doses of approximately 60 mg arsenic. A follow-up study [53], reviewed by Dakeishi et al. [50], comparing children of about 14 years of age who, during infancy, had been given the arsenic-contaminated Morinaga milk (n = 33), with those given other brands of infant formula (n = 27) or breast-milk only (n = 48), reported a lower IQ and higher rate of severe retardation (IQ below 50) in the children given the Morinaga milk. Another follow-up study of children 14–16 years of age, including interviewing 415 children, clinical examination of 292 and psychological testing of 261 children, revealed higher prevalence of physical and mental effects, CNS disorders (e.g. epilepsy), minimal brain damage, mental retardation, as well as hearing disability and proteinuria [54] as reported in Dakeishi et al., Grandjean and Murata, and WHO/IPCS [50–52].

Late effects of early-life arsenic exposure

There is evidence from epidemiological, experimental and mechanistic studies that early-life exposure to arsenic increases the health risks later in life. A recent study by Smith et al. suggests that exposure to arsenic in drinking water during early childhood or *in utero* has pronounced pulmonary effects, greatly increasing subsequent mortality in young adults from both malignant and non-malignant lung diseases. The study compared the mortality data on lung cancer and other lung disease in Antofagasta 1989–2000 with those of the rest of Chile, focusing on persons of 30–49 years of age, who were born during or just before 1958–1970, when the town of Antofagasta had drinking water containing about 800 μg/l [55]. A new drinking water source was introduced in 1958 and first after the appearance of symptoms of arsenic poisoning, water treatment significantly decreased the water arsenic concentrations in 1970. For the birth cohort born just before the high-exposure period (1950–1957) and exposed in early childhood, the standardized mortality ratio (SMR) for lung cancer was 7.0 [95% confidence interval (CI), 5.4–8.9; $P < 0.001$] and the SMR for bronchiectasis was 12.4 (3.3–31.7). For those born during the high-exposure period (1958–1970) with probable exposure *in utero* and early childhood, the SMR for lung cancer was similar, 6.1 (3.5–9.9), while that for bronchiectasis was as high as 46 (21.1–87.7).

The above-mentioned extensive poisoning of infants in Japan by arsenic-contaminated infant formula in 1955 led to the establishment of the Hiraki Association in 1974, based on an agreement between the victim's groups, the Morinaga Milk Company and the Ministry of Health and Welfare [50]. The association has reported that by 2002, when the victims were in their 50s, about 6000 of the totally affected 13,420 individuals had established contact with the association. Of the 798 victims who had received welfare allowance, 337 suffered from mental retardation, 103 from other mental disorders, 33 from epilepsy and 129 from various disabilities. Together with the more comprehensive follow-up studies performed at 14–16 years of age, the long-lasting health effects of infant arsenic poisoning are clearly demonstrated.

The increased susceptibility in early life may not apply to all the health effects related to arsenic exposure. A recent study from Bangladesh did not find a higher risk for arsenic-related skin effects in individuals exposed since birth, or before, compared to those who started being exposed after 1 year of age [56]. If anything, individuals who had been moderately exposed from birth, or before, were less prone to develop arsenic-related skin lesions than those who were more than 1 year of age when they started using tubewell water. This was not due to lower life-time exposure among those exposed earlier in life; if anything, those individuals had slightly higher cumulative arsenic exposure than those exposed later in life.

A series of recent experimental studies have demonstrated marked increase in tumour induction in adult mice exposed to high doses of arsenic prenatally (dams exposed to 42 or 85 mg/l arsenic in drinking water during gestational days 8–18) [57,58]. Interestingly, there were marked sex differences. Female mice had ovarian and lung tumours, as well as uterine and oviduct hyperplasia, while male mice had highly elevated incidence of liver and adrenal tumours. Only when the *in utero* arsenic exposure was combined with skin application of a tumour-promoting phorbol ester TPA to the offspring, was liver tumours induced also in the females [59].

Another recent study showed that exposure of pregnant apolipoprotein E-knockout [ApoE(–/–)] mice to arsenic in the drinking water showed more than 2-fold increase in lesions in the aortic roots as well as the aortic arch in male offspring at 10 and 16 weeks of age, compared to control mice. The mice exposed to arsenic also had a 20–40%

decrease in total triglycerides, and showed a vasorelaxation defect in response to acetylcholine suggesting disturbance of endothelial cell signaling. Although the authors concluded that the results showed that *in utero* arsenic exposure induces an early onset of atherosclerosis in ApoE(–/–) mice, it is not known to what extent similar results would be obtained after exposure postnatally or in adult life.

Taken together, these studies indicate that the foetus and infant may be particularly susceptible to certain toxic effects of arsenic that may give rise to persistent health effect. Obviously, more research is needed to identify the type of effects as well as the most critical windows in development.

Late effects of early-life arsenic exposure – mechanistic evidence

The foetal and infant environment is known to be critical for the development of adverse health effects later in life. For example, it is well documented that foetal and perinatal nutrition influences organ function late in life and there is increasing evidence for similar effects of early-life exposure to toxic chemicals [60]. Thus, it is plausible that a toxic element like arsenic and its metabolites, which easily pass to the foetus, contribute to such effects. Both inorganic arsenic and the trivalent methylated arsenic metabolites are highly reactive, preferentially with sulfhydryl groups. It has long been known that arsenic inhibits numerous enzymes [3,61] (e.g. DNA repair enzymes [62]) and antioxidant-related enzymes (e.g. thioredoxin reductase [63]), one of the major stress protection systems in the placenta [64]. Arsenic also inhibits several methyltransferases, resulting in elevated homocysteine levels [19] and general inhibition of one-carbon metabolism, which is likely to critically influence the foetal environment (e.g. via DNA hypomethylation), as discussed below [65].

Arsenic induces oxidative stress, in particular oxidative DNA damage [66], as shown by increased levels of 8-hydroxy-2′-deoxyguanosine in urine of arsenic exposed individuals [67–70], and lipid peroxidation [71,72]. The oxidative stress is induced also in the placenta as indicated by increased intracellular H_2O_2 levels in a choriocarcinoma cell model [73]. The pro-oxidative effects of arsenic are compounded by the inhibition of antioxidative enzymes at elevated arsenic exposure levels. Arsenic-induced oxidative stress and apoptosis in developing rat brain cells were partly reversed by vitamins C and E [74]. Furthermore, arsenic is known to deplete intracellular glutathione [75,76]. This implies that poor nutritional status may further aggravate the pro-oxidative effects of arsenic, as shown in selenium-deficient mice [64], as well as the induction of changes of the foetal environment in a way that will lead to increased risk for adverse health effects in childhood or even adult life.

Recent research has shown that arsenic is a potent endocrine disruptor interacting with most classes of steroid hormones [77–81]. Such interaction is likely to occur at very low concentrations and to have long-term consequences particularly if induced early in life. Arsenic has been shown to disrupt glucocorticoid receptor-mediated transcription in a very complex fashion. Low concentrations of arsenic (0.1–0.7 μM) stimulated transcription in rat hepatoma cells of both the endogenous tyrosine aminotransferase gene and the reporter genes containing tyrosine aminotransferase glucocorticoid response elements. At slightly higher concentrations (1–3 μM), the effects of As became inhibitory [78]. Arsenic was also found to alter gene regulation by the closely related mineralocorticoid, progesterone and androgen steroid receptors at concentrations [77]. Very low doses were found to enhance hormone-mediated gene transcription, whereas slightly higher but still non-cytotoxic doses were suppressive. Arsenic also interacts with the more distally related oestrogen receptor [79,82–84]. Interaction of arsenic with oestrogen receptor-α and oestrogen-associated functions has previously been reported [85–88]. The above-mentioned transplacental mouse studies by Waalkes' research group [58], in which pregnant mice were given drinking water with to 45 or 85 p.p.m. arsenic from gestation days 8–18, provide evidence that arsenic-induced aberrant oestrogen receptor signaling may affect early-life genetic programming leading to tumour formation, possibly also other effects, much later in adulthood. The intrauterine arsenic exposure increased oestrogen receptor-α transcript and protein levels in the female foetal lung [82]. Furthermore, the insulin growth factor system, which is influenced by oestrogen receptor, was activated in the foetal lung and α-foetoprotein, epidermal growth factor receptor, L-myc and metallothionein-1 were all overexpressed. Gene expression analysis of the male liver showed overexpression of oestrogen receptor-α, potentially through hypomethylation of the promoter region of the gene, and cyclin D1, as well as feminized expression pattern of several cytochrome P450 genes [89].

There is increasing evidence during recent years that arsenic acts via epigenetic effects at very low exposure levels, mainly by interfering with DNA methylation [90–93]. Arsenic causes mainly induction of hypomethylation, possibly by inhibition of DNA methyltransferases [93], but hypermethylation of promoter of gene p53 and p16 in arsenic-exposed people has also been reported [94]. Sub-μM arsenic concentrations were found to inhibit both DNMT1 and DNMT3A in human keratinocytes [92]. As DNA methylation is an important mechanism of the foetal programming [41,95], arsenic-induced changes in DNA methylation may have severe consequences for the development of health effects both before and after birth. Indeed, recent studies by Waalkes' research group showed that newborn male mice, born to dams exposed to high concentrations of arsenic in drinking water from gestation days 8–18, had a significant reduction in methylation globally in GC-rich (guanidine and cysteine) regions [96]. There was also enhanced expression of genes encoding for glutathione production and aberrant expression of genes related to insulin growth factor signalling pathways and cytochrome P450 enzymes. Further studies using lower exposure levels are warranted.

The mechanisms of action of low doses of arsenic reviewed above imply risk of changes during critical periods in early

life that may lead to permanent health effects, some of which may not be apparent or even detectable, until much alter in childhood or adult life.

Conclusions

Arsenic is a potent carcinogen and general toxicant, which easily passes the placenta. There is convincing evidence that arsenic induces a number of effects in the foetus, some of which result in foetal loss or growth retardation. There is a growing body of evidence that some of the changes induced in foetal or infant life lead to detectable adverse health effects later in childhood as well as in adult life. Potential modes of action involved include epigenetic effects, mainly DNA hypomethylation, interaction with steroid hormones (e.g. oestrogens, immune suppression, neurotoxicity and inhibition of numerous enzymes). However, in most cases, the exposure, for example, via drinking water or air continue even after early childhood and cross-sectional studies later in life has not identified critical windows of exposure. A few epidemiological and mechanistic studies indicate that the foetus is highly susceptible to arsenic and that adverse effects that give rise to health disorders later in life may occur at fairly low exposure levels.

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