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SCIENTIFIC OPINION

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Update of the risk assessment of inorganic arsenic in food

EFSA Panel on Contaminants in the Food Chain (CONTAM) | Dieter Schrenk | Margherita Bignami | Laurent Bodin | James Kevin Chipman | Jesús del Mazo | Bettina Grasl-Kraupp | Christer Hogstrand | Laurentius (Ron) Hoogenboom | Jean-Charles Leblanc | Carlo Stefano Nebbia | Elsa Nielsen | Evangelia Ntzani | Annette Petersen | Salomon Sand | Christiane Vleminckx | Heather Wallace | Lars Barregård | Diane Benford | Karin Broberg | Eugenia Dogliotti | Tony Fletcher[†] | Lars Rylander | José Cortiñas Abrahantes | Jose Ángel Gómez Ruiz | Hans Steinkellner | Tuuli Tauriainen | Tanja Schwerdtle

Correspondence: contam@efsa.europa.eu

Abstract

The European Commission asked EFSA to update its 2009 risk assessment on arsenic in food carrying out a hazard assessment of inorganic arsenic (iAs) and using the revised exposure assessment issued by EFSA in 2021. Epidemiological studies show that the chronic intake of iAs via diet and/or drinking water is associated with increased risk of several adverse outcomes including cancers of the skin, bladder and lung. The CONTAM Panel used the benchmark dose lower confidence limit based on a benchmark response (BMR) of 5% (relative increase of the background incidence after adjustment for confounders, $BMDL_{05}$) of 0.06 μg iAs/kg bw per day obtained from a study on skin cancer as a Reference Point (RP). Inorganic As is a genotoxic carcinogen with additional epigenetic effects and the CONTAM Panel applied a margin of exposure (MOE) approach for the risk characterisation. In adults, the MOEs are low (range between 2 and 0.4 for mean consumers and between 0.9 and 0.2 at the 95th percentile exposure, respectively) and as such raise a health concern despite the uncertainties.

KEYWORDS

benchmark dose (BMD), epidemiological studies, inorganic arsenic (iAs), margin of exposure (MOE), risk assessment

[†]until 30.9.2021.

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SUMMARY

In 2009, the EFSA Panel on Contaminants in the Food Chain (CONTAM) adopted a Scientific Opinion on the presence of arsenic in food. The European Commission (EC) has asked the European Food Safety Authority (EFSA) for an update of the hazard assessment of inorganic arsenic (iAs) because new studies have become available on the toxic effects of iAs since the publication of the 2009 Opinion. Using the revised exposure assessment on iAs issued by EFSA in 2021 an updated risk assessment of iAs for human health should be performed. The EC has also asked for risk assessments on small and complex organoarsenic species and on the combined exposure to inorganic and organic arsenic which will be provided in separate Opinions.

Arsenic is a metalloid, widely present in the environment because of both natural occurrence and anthropogenic activity. Arsenic occurs in various organic and inorganic forms. In food and feed, inorganic arsenic species are predominantly in the +3 or +5 oxidation state, present as thio complexes or, as the oxo anions arsenite and arsenate. During sample preparation and analysis iAs bound to thio groups in peptides or proteins in food is converted to arsenite and arsenate. Hence, data on occurrence are nearly exclusively recorded as these two analysed species. The sum of the quantified arsenite and arsenate in food (in mg As/kg wet weight) is often referred to as iAs. In natural water and drinking water, arsenic habitually appears as arsenite and arsenate, whereas organic arsenic forms are rare in water. In humans, iAs is rapidly and to a great extent (45%–80%) absorbed after ingestion, widely distributed in the body to almost all organs. It readily crosses the placental barrier. iAs is metabolised by reduction, oxidative methylation, thiolation and glutathiolation. The degree of methylation is crucial for its toxic effects in humans. Inorganic arsenic is eliminated via the urine in the form of iAs and its methylated metabolites, with a half-life of around 2–3 days.

The toxicokinetics of iAs in laboratory animals differ considerably from those in humans, particularly regarding their methylation capacity. Therefore, toxicity data resulting from animal experiments are not a suitable basis for human health risk assessment.

There is no universally accepted biomarker for chronic exposure to iAs. Measurements of total arsenic in blood or urine represent not only iAs but also organic As species and are thus of limited value. Specific measurements of iAs, and its methylated metabolites, or the sum of iAs, and its methylated metabolites, also named total urinary inorganic arsenic (u-tiAs), provide more appropriate estimates of iAs exposure. Inorganic arsenic accumulates in hair and nails. Thus, As in hair and nails is also used as biomarker for chronic iAs exposure.

Chronic exposure to iAs is associated with increased DNA damage (DNA breaks and oxidatively induced DNA base modifications) and clastogenic events in somatic cells from exposed individuals. Chronic exposure to iAs in utero or adult life is also associated with epigenetic changes that may lead to aberrant gene expression.

Inorganic arsenic is itself a weak inducer of gene mutations, but efficiently induces chromosomal aberrations, micronuclei and aneuploidy *in vitro* and *in vivo*. Inorganic arsenic does not directly interact with DNA, but it induces oxidative stress, which is believed to play a role in the formation of DNA base oxidation as well as both DNA single and double strand breaks. The production of oxidative clustered DNA lesions is likely responsible for iAs induced double strand breaks.

Inorganic arsenic and its metabolites interfere with the DNA damage response by inhibiting DNA repair and by interfering with cell cycle control- and apoptotic pathways. The inhibition of DNA repair systems leads to accumulation of DNA damage induced by both exogenous and endogenous sources. This phenomenon likely contributes to the co-mutagenic effects observed when iAs is combined with exposure to other DNA-damaging agents. Methylation of iAs, particularly to trivalent methylated species, should be regarded as an activation process that forms more reactive species, which exert stronger cyto- and genotoxic effects.

In animal studies, increases in tumour incidence upon exposure to iAs via drinking water have been observed. However, the results of these studies with respect to tumour sites and effective doses are inconsistent and do not provide a robust basis for risk assessment.

For hazard assessment only human studies were considered. The studies encompassed study subjects with exposure to long-term low to moderate levels of iAs, defined as concentrations of arsenic in water of less than ~ 150 µg/L, or biomarker concentrations estimated to result from equivalent doses.

The evidence from epidemiological studies can be considered as sufficient and causal for associations between low to moderate exposure to iAs (defined as above) and cancers of the skin, bladder and lung, skin lesions other than skin cancer, spontaneous abortion, stillbirth, infant mortality, congenital heart disease, respiratory disease, chronic kidney disease, neurodevelopmental effects, ischemic heart disease and carotid artery atherosclerosis. However, since the epidemiological studies on skin lesions were performed in low and medium income regions (Bangladesh, China) and nutrition and health status are important modifying factors, it is difficult to translate these risks to populations with more adequate nutrition such as in Europe.

The evidence from epidemiological studies performed in Bangladesh is sufficient to assume a causal association between low to moderate exposure to iAs and decreased birth weight. However, the results for this effect from other countries (Chile, Taiwan, Mongolia, Mexico, US) are inconsistent. Moreover, the average birth weight in Europe is much higher and undernutrition is less common, putting the relevance of the evidence from Bangladesh for a European population in doubt.

There is insufficient evidence for an association between low to moderate exposure to iAs, and breast, prostate, kidney, liver, pancreatic and gallbladder cancer, male fertility, neurotoxicity, stroke and hypertension, glucose metabolism, diabetes and metabolic syndrome.

Data from studies were considered for dose–response modelling if the studies had a low level of overall risk of bias. In addition, data had to show a statistically significant association with iAs as a continuous variable and/or a statistically significant trend test and/or a statistically significant increase of risk in the upper exposure category. For modelling of quantile data, results for at least three exposure categories in total were required.

For studies meeting these criteria, iAs concentrations in drinking water (measured as total As) were transformed into total daily iAs dietary exposures (applying default or reported water intakes and adding region specific exposure estimates to account for the contribution from food). When total urinary iAs concentrations (sum of iAs and its methylated metabolites) were reported these were transformed into daily iAs dietary exposures per kg bw per day by applying default factors for urine volume or creatinine excretion.

The results used for dose–response analysis are the adjusted incidences and resulting number of cases based on the adjusted risk ratios reported in these studies and the provided (cohort studies) or estimated (case–control studies) population sizes. As benchmark response (BMR), a relative increase of 5% of the background incidence (estimated from the lowest exposure category) after adjustment for confounders was used.

The results from 20 epidemiological studies fulfilled the validity criteria for BMD modelling and the results from these benchmark dose (BMD) calculations were considered further for the selection of an appropriate Reference Point. For the six cohort studies the follow-up time varied between 3 and 12 years.

Low benchmark dose lower confidence limits (BMDLs) (≤ 0.17 μg iAs/kg bw per day) based on a BMR of 5% relative increase of the background incidence after adjustment for confounders were calculated for skin cancer, lung cancer, bladder cancer, respiratory disease, skin lesions, chronic kidney disease and ischemic heart disease.

The CONTAM Panel used the BMDL based on a BMR of 5% (relative increase of the background incidence after adjustment for confounders, $BMDL_{05}$) of 0.06 μg iAs/kg bw per day obtained from a case–control study on skin cancer (squamous cell carcinoma) carried out in the US, as a reference point (RP) because the study was considered to be of good quality with a low risk of bias. Exposure categories were based on u-tiAs. The results from a second skin cancer case–control study on basal cell carcinoma with a population from Hungary, Romania and Slovakia support the choice for an RP based on skin cancer for hazard assessment.

The CONTAM Panel concluded that an RP of 0.06 μg iAs/kg bw per day should also be considered to cover lung cancer, bladder cancer, skin lesions, ischemic heart disease, chronic kidney disease, respiratory disease, spontaneous abortion, stillbirth, infant mortality and neurodevelopmental effects.

Inorganic As is a genotoxic carcinogen. Both thresholded and non-thresholded mechanisms could apply for the different genotoxic effects of iAs and its trivalent and pentavalent methylated metabolites. Therefore, the CONTAM Panel concluded that it is appropriate to apply a margin of exposure (MOE) approach for risk characterisation rather than establishing a health-based guidance value. There are no precedents in EFSA for identification of an MOE of low concern, when using a BMDL derived from human cancer data. Therefore, the Panel decided not to determine a value for an MOE of low concern.

The RP of 0.06 μg iAs/kg bw per day for skin cancer is in the range of the mean dietary exposure estimates for iAs in adults (0.03–0.15 μg iAs/kg bw per day), and below any of the 95th percentile exposure estimates in adults (range = 0.07–0.33 μg iAs/kg bw per day). Therefore, in adults, the MOEs range between 2 and 0.4 for mean consumers and between 0.9 and 0.2 at the 95th percentile exposure, respectively.

Based on the conditional uncertainty analysis and considering both studies on skin cancer, the probability that the mean exposure scenario exceeds the associated BMDs range from unlikely (likelihood ≈ 0.17) to likely (likelihood ≈ 0.86).

An MOE of 1 would correspond to an exposure level that is associated with a 5% increase relative to the background incidence for skin cancer, based on the available data. The CONTAM Panel concludes that this MOE raises a health concern.

The CONTAM Panel notes that dietary iAs exposure is higher in the younger age groups and therefore the respective MOEs are smaller. However, this does not necessarily indicate that children are at greater risk, because the effects are due to long-term exposure and most of the epidemiological studies are conducted in adults who would also have had higher dietary exposure during early life. Therefore, the CONTAM Panel concludes that children are covered by this risk characterisation.

Although risk characterisation is based on the results of relatively large epidemiological studies, susceptible individuals of higher genetic risk may not be adequately represented in these studies. Therefore, dietary exposure to arsenic may be of greater concern for such individuals than for the general population.

According to the report from EFSA from 2021, across the different age classes, the main contributors to the dietary exposure to iAs (LB) were 'Rice', 'Rice-based products', 'Grains and grain-based products (no rice)' and 'Drinking water'. Particular foodstuffs indicated for the young population (e.g. 'Cereal-based food for infants and young children' and 'Biscuits, rusks and cookies for children') made a relevant contribution in the dietary exposure to iAs in this age group.

The CONTAM Panel notes that an EFSA guidance on the use of human data for risk assessments is needed, in particular on BMD modelling of epidemiological data and for a quantitative risk assessment for genotoxic carcinogens based on epidemiological data. The Panel recommends investigating the relevance of arsenic-induced epigenetic alterations for iAs associated disease risk. The mechanisms of induction of DNA double strand breaks by arsenic should be investigated to clarify its mode of interaction with DNA. Additional research should explore the mechanisms underlying genomic instability caused by iAs. The health effects of pre- and perinatal exposure to arsenic and how arsenic-induced alterations occurring during early life can impact the development of certain diseases in adult life should be further elucidated. The role of inter-individual variations in susceptibility to arsenic-related health conditions should be investigated with a focus on arsenic biotransformation and differences in DNA repair. Moreover, the CONTAM Panel notes that several recommendations regarding the dietary exposure assessment for iAs, which are still valid, were made in the 2021 EFSA scientific report.

1 | INTRODUCTION

1.1 | Background and Terms of Reference as provided by the requestor

1.1.1 | Background

In 2009, the EFSA Panel on Contaminants in the Food Chain (CONTAM) adopted a Scientific Opinion on the presence of arsenic in food. Arsenic occurs naturally in soil and ground water. Inorganic arsenic may cause cancer of the skin, urinary bladder and lungs and EFSA calculated $BMDL_{01}$ values for these effects between 0.3 and 8 μg/kg bw per day, highlighting a possible risk to consumers on the basis of the estimated exposure. However, for the organic arsenic forms EFSA indicated that arsenobetaine, which is the major form of arsenic in fish and most seafood, is widely assumed to be of no toxicological concern. Arsenosugars and arsenolipids are mainly metabolised in humans to dimethylarsinate (DMA(V)), but sparse information is available regarding their toxicity. For other organoarsenic compounds no human toxicity data are available. Because of the lack of data, arsenosugars, arsenolipids, methylarsenate (MMA(V)) and dimethylarsinate (DMA(V)) could not be considered in the risk characterisation.

In its 2014 scientific report on dietary exposure to inorganic arsenic in the European population,[1] EFSA identified grain-based products as the main contributor to the exposure and also rice, milk and dairy products as important contributors. The heterogeneity of the food consumption data, the conversion of total arsenic to inorganic arsenic and the treatment of left censored data represented important uncertainties in the exposure assessment.

Commission Recommendation (EU) 2015/1381[2] recommended Member States to monitor during 2016, 2017 and 2018 the presence of arsenic, preferably by determining the content of inorganic and total arsenic and, if possible, other relevant arsenic species, in a wide variety of food, and to provide these data to EFSA on a regular basis at the latest by October 2018.

The newly available occurrence data have been used for an updated consumer exposure assessment for inorganic arsenic, which was endorsed by the CONTAM Panel of 24–25 November 2020.

Since the publication of the 2009 Opinion on arsenic in food new studies have become available on the toxic effects of inorganic arsenic and it is therefore appropriate to update the hazard characterisation. Taking into account the new exposure assessment and new information on the adverse health effects, a new risk assessment should be performed for the risks for human health related to inorganic arsenic in food. Since the publication of the 2009 Opinion on arsenic in food new studies have become available on the toxic effects of organic arsenic. Furthermore, it has become clear that dimethylmonothioarsenate (DMMTA, thio-DMA(V)) is formed from methylarsenate (MMA(V)) due to the application of sulphate fertilisers, and that this substance could be more toxic than methylarsenate (MMA(V)). It is therefore appropriate to update the hazard identification and characterisation of organic and inorganic arsenic. On the basis of the available occurrence data for organic arsenic or literature information on organic arsenic in food, the exposure could be estimated in order to carry out an assessment for the risks for human health related to organic arsenic in food. In view of different properties of the organoarsenic species, arsenobetaine, arsenosugars and arsenolipids, it is appropriate to assess the organic arsenic species in 2 further separate opinions: an Opinion on small organoarsenic species and an Opinion on arsenobetaine, arsenosugars and arsenolipids, which should also include other relevant complex organoarsenic species. After finalising the risk assessments on inorganic and organic arsenic, also the combined exposure to inorganic and organic arsenic should be assessed.

1.1.2 | Terms of Reference

In accordance with Art. 29 (1) of Regulation (EC) No 178/2002 the Commission asks EFSA for

- an updated consumer risk assessment for inorganic arsenic in food, taking into account
  - the updated exposure assessment, endorsed by the Panel in November 2020.
  - newly available scientific information
- a consumer risk assessment for organic arsenic in food, taking into account
  - newly available scientific information
  - occurrence data for organic arsenic in food
  - literature data on the occurrence of organic arsenic in food
- a consumer risk assessment on the combined exposure to inorganic and organic arsenic, taking into account
  - the risk assessment on inorganic arsenic in food
  - the risk assessments on organic arsenic in food

[1]EFSA (European Food Safety Authority), 2014. Scientific report of on the dietary exposure to inorganic arsenic in the European population. EFSA Journal, 12(3), 3597.
[2]Commission Recommendation (EU) 2015/1381 of 10 August 2015 on the monitoring of arsenic in food. OJ L 213, 12.8.2015, p. 213.

1.1.3 | Interpretation of the Terms of Reference

The present Opinion is the first of in total four scientific opinions covered by the ToR from the EC (see Section 1.1). It is an update of the previous EFSA Opinion on inorganic arsenic (iAs) in food (EFSA CONTAM Panel, 2009) which has been used as a starting point for the assessment. In this Opinion the adverse effects of the food relevant iAs species arsenite and arsenate are evaluated. In addition, potential genotoxic effects of their major human metabolites (see Table 1 in Section 1.2.1 on Chemistry for a list of compounds covered) are assessed. The risks of iAs in food are characterised using the scientific report on chronic dietary exposure to arsenic (EFSA, 2021).

1.2 | Additional information

1.2.1 | Chemistry of inorganic arsenic relevant to its presence in food

The metalloid arsenic (atomic number, 33; relative atomic mass, 74.92) occurs in group 15 of the periodic table along with nitrogen and phosphorus. Consequently, the chemistry of arsenic is similar in many respects to that of these two elements. The most stable arsenic species found under normal environmental conditions contain the arsenic atom in oxidation state +5; under reducing conditions arsenic species can occur with the arsenic atom in oxidation state −3 and + 3.

In food and feed, arsenic is usually found in combination with other elements such as oxygen, sulfur, carbon and hydrogen. From a chemical point of view arsenic combined with oxygen and sulfur is called inorganic arsenic, whereas arsenic combined with carbon and hydrogen is referred to as organic arsenic.

Inorganic arsenic in food and feed comprises species mainly in the +3 or + 5 oxidation state, present as thio complexes or, primarily, as the oxo anions arsenite and arsenate. During sample preparation and analysis iAs bounds to thio groups in peptides or proteins in food is converted to arsenite and arsenate and hence data are nearly exclusively recorded as these two actually measured species. The sum of the quantified arsenite and arsenate in food (in mg As/kg wet weight) is often referred to as iAs. In oxygenated conditions, such as found in drinking water, the arsenic is present mainly as arsenate.

In natural water and drinking water, arsenic habitually appears in inorganic forms (arsenite and arsenate); organic arsenic forms are rare in water, as they are the result of biologically activity (EFSA, 2021).

After ingestion iAs metabolised by humans (see Section 3.1.1) by a series of reduction, methylation and conjugation processes. Arsenate, as well as human iAs metabolites relevant to this Opinion are listed in Table 1 below.

TABLE 1 Inorganic arsenic species and their major human metabolites relevant for the present assessment.

Name[a]	Abbreviation	Chemical structure[b]
Inorganic arsenic (sum of arsenite and arsenate)		
Arsenite	iAs(III)	$As(O^-)_3$
Arsenate	iAs(V)	$O=As(O^-)_3$
Methylarsonate, monomethylarsonic acid	MMA(V)	$CH_3AsO(OH)_2$
Methylarsonite, monomethylarsonous acid	MMA(III)	$CH_3As(OH)_2$
Dimethylarsinate, dimethylarsinic acid[c]	DMA(V)	$(CH_3)_2AsO(OH)$
Thio-dimethylarsinate, thio-dimethylarsinic acid, dimethylmonothioarsinate	Thio-DMA(V), DMMTA(V), DMTA(V)	$(CH_3)_2AsS(OH)$
Dimethylarsinite, dimethylarsinous acid	DMA(III)	$(CH_3)_2AsOH$
MMA (sum of MMA(III) and MMA(V))		
DMA (sum of DMA(III) and DMA(V))		

[a]The names for the fully protonated forms (monomethylarsonic acid and dimethylarsinic acid) are often used in the literature although the species are usually measured as the anion, namely monomethylarsonate or dimethylarsinate).

[b]Arsenic species are drawn in their fully protonated form.

[c]Also named cacodylic acid.

1.2.2 | Analytical methods

In its previous Opinion (EFSA CONTAM Panel, 2009) the CONTAM Panel summarised that several suitable methods are available for the measurement of total arsenic and arsenic species in food and biological samples. For the determination of total arsenic following mineralisation, hydride generation atomic absorption spectrometry (HG-AAS) and inductively coupled plasma mass spectrometry (ICP–MS) are sensitive, reliable and commonly used methods. Speciation analysis for iAs consists of three main aspects: extraction, separation and detection (e.g. Petursdottir et al., 2015). Inorganic arsenic species are frequently extracted with methanol, water or a mixture of both. The higher extraction efficiencies observed for mildly acidic extractions might be due to acid hydrolysis causing a release of degradation

products from arsenic species in the protein and lipid fractions. As an alternative the extraction procedure can be based on microwave-assisted alkaline solubilisation of the sample. Here arsenate and arsenite are solubilised and at the same time arsenite is oxidised to arsenate allowing subsequent determination of (combined) iAs as arsenate by anion exchange high-performance liquid chromatography (IEX-HPLC). Concentrations of iAs in food are generally presented in mg As/kg wet weight. After each extraction method separation by anion exchange columns are routinely applied to efficiently separate iAs from DMA and MMA. Due to excellent compatibility with ion exchange HPLC, excellent detection limits and linear range capable of quantifying low ng/L as well as high mg/L concentrations in the same run ICP–MS is the detection technique most widely used. Since arsenic has only one isotope, isotope dilution methods cannot be applied to improve detection specificity. However, ICP–tandem mass spectrometer is increasingly applied combining high sensitivity with high specificity. Here arsenic is detected in the MS/MS mode with oxygen introduced into the collision/reaction cell to shift As^+ from mass 75 to mass 91 through the formation of $^{75}As^{16}O^+$ in the cell (e.g. Stetson et al., 2020).

1.2.3 | Previous assessments

In 2009, the EFSA CONTAM Panel assessed the risks to human health related to the presence of arsenic in food (EFSA CONTAM Panel, 2009). The Panel noted that the main adverse effects reported to be associated with long-term ingestion of iAs in humans are skin lesions, cancer, developmental toxicity, neurotoxicity, cardiovascular diseases, abnormal glucose metabolism and diabetes. A provisional tolerable weekly intake (PTWI) of 15 μg/kg bw was established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 1983 (FAO/WHO, 1983). Since then, data have shown that oral exposure to iAs causes cancers of the lung and urinary bladder in addition to skin, and a range of other adverse effects had also been reported at exposures lower than in the studies reviewed by JECFA. Therefore, the CONTAM Panel concluded that the JECFA PTWI was no longer appropriate. The CONTAM Panel identified cancers of the urinary bladder, lung and skin, and skin lesions, as the most relevant endpoints for providing an appropriate Reference Point to be used in the risk characterisation. Dose–response data from key epidemiological studies were modelled using a benchmark response of 1% extra risk. A limitation in all the available studies was that total dietary exposure to iAs was not measured, and in most studies the concentration of arsenic in drinking water was used as the exposure metric. A range of benchmark dose lower confidence limit ($BMDL_{01}$) values between 0.3 and 8 μg/kg bw per day was identified for cancers of the lung, skin and bladder, as well as for skin lesions. Since dietary exposure to iAs was within the range of the $BMDL_{01}$ values, the possibility of a risk to some consumers could not be excluded. In 2009, the CONTAM Panel also evaluated organic forms of arsenic, concluding that arsenobetaine is not of toxicological concern and that arsenosugars, arsenolipids, methylarsonate and dimethylarsinate could not be considered in the risk characterisation, because of the lack of data.

In 2011, the JECFA reviewed its PTWI of 15 μg/kg bw set in 1983 for iAs (FAO/WHO, 2011). The JECFA noted that the quantitative assessment of cancer risk from iAs is limited, for instance because of the lack of information on total exposure in epidemiological studies. The JECFA calculated a BMDL for a 0.5% increased incidence of lung cancer seen in an epidemiological study (Chen et al., 2010a) using several assumptions to estimate exposure from drinking-water and food with differing concentrations of iAs. A $BMDL_{0.5}$ of 3.0 μg/kg bw per day (range of 2.0–7.0 μg/kg bw per day) for lung cancer based on the range of estimated total dietary exposure was calculated. The Committee noted that since the PTWI of 15 μg/kg bw established previously was in the region of the $BMDL_{0.5}$, it was no longer appropriate, and in consequence the PTWI was withdrawn.

In 2012, the International Agency for Research on Cancer (IARC) assessed the carcinogenicity of arsenic and arsenic compounds (IARC, 2012). They noted that trivalent arsenicals do not react directly with DNA, but cause oxidative DNA damage, DNA strand breaks and/or alkali labile sites. Pentavalent arsenic causes DNA strand breaks and DNA-protein crosslinks attributed to the dimethylarsinic (DMA) peroxy radical. Other possible modes of action include induction of genomic instability, probably via reactive oxygen species (ROS), inhibition of DNA-repair and co-mutagenesis with other compounds. The IARC concluded that there was sufficient evidence in humans for the carcinogenicity of mixed exposure to iAs compounds, including arsenic trioxide, arsenite and arsenate, which cause cancer of the lung, urinary bladder and skin. Arsenic and iAs compounds were also associated with cancer of the kidney, liver and prostate. There was sufficient evidence in experimental animals for the carcinogenicity of dimethylarsinic acid, calcium arsenate, sodium arsenite and limited evidence in experimental animals for the carcinogenicity of sodium arsenate, gallium arsenide, arsenic trioxide and trimethylarsine oxide. There was inadequate evidence in experimental animals for the carcinogenicity of monomethylarsonic acid and arsenic trisulfide. Overall, there was sufficient evidence in experimental animals for the carcinogenicity of iAs compounds. Taking into account all of the evidence the IARC classified arsenic and inorganic arsenic compounds as carcinogenic to humans (Group 1), dimethylarsinic acid and monomethylarsonic acid as possibly carcinogenic to humans (Group 2B), and arsenobetaine and other organic arsenic compounds not metabolised in humans, as not classifiable as to their carcinogenicity to humans (Group 3). The IARC noted that elemental arsenic and inorganic arsenic species share the same metabolic pathway namely: arsenate → arsenite → methylarsonate → dimethylarsenite. Thus, independent of the mechanisms of action and the metabolite being the actual carcinogen, different iAs species should be considered as carcinogenic.

In 2015, the German Federal Institute for Risk Assessment evaluated the risks for consumers related to arsenic in rice and rice products (BfR, 2014). The estimated exposures of the different age groups were compared with the lower value of the $BMDL_{01}$ value range of 0.3–8 μg/kg bw per day calculated for iAs by EFSA (EFSA CONTAM Panel, 2009) to characterise possible risks. Comparing chronic exposure estimates of adults with the EFSA $BMDL_{01}$ value resulted in MOEs of 37–1000 (average consumption) and 12–320 (95th percentile) for the adult population. For adult consumers only, the MOEs ranged from 11 (average) to 889 (95th percentile). For children aged over 0.5 years, MOEs of 9 to 500 and 2–143 were calculated at the mean and 95th percentile, respectively. For children aged from 0.5 to 1 year, MOE values ranged from 1 to 22. Based on the outcome of the assessment, the BfR concluded that health impairments regarding the risk of cancer are possible and that iAs in food should be reduced to the unavoidable minimum.

In 2016, the UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT, 2016) published a statement on potential risks from arsenic in the diet of infants aged 0 to 12 months and children aged 1 to 5 years. The COT noted that the EFSA had calculated $BMDL_{01}$ values ranging from 0.3 to 8.0 μg/kg bw per day based on cancers of the lung, skin and urinary bladder, and on skin lesions (EFSA CONTAM Panel, 2009), while the JECFA established a BMDL of 3.0 μg/kg bw per day for a 0.5% increased incidence of lung cancer (FAO/WHO, 2011). The COT concluded that the JECFA BMDL should be used in the risk characterisation because it was based on more robust and recent data than that available to EFSA. Taking into account the quality of the key data, the COT concluded that an MOE of 10 or more compared to the JECFA BMDL would be considered as a low health concern.

In 2016, the U.S. Food and Drug Administration (FDA) issued an assessment of health risks from iAs in rice and rice products for public comment (US FDA, 2016). The quantitative estimates of cancer risk focused on lung and bladder cancer, which provided the best evidence of cancer at relatively low levels of exposure. The predicted cancer risks attributed to lifetime consumption of arsenic in rice and rice products was 39 cases per million people (10 cases of bladder, 29 of lung cancer) as compared to combined lung and bladder cases from all causes over a lifetime of 90,000 cases per million people. The modelling predicted that risk increases almost proportionally with daily rice servings and if the amount of rice would be increased by one serving daily, lifetime cancer risk would increase to 74–183 cases per million people, depending on the type of rice consumed. Eliminating rice and rice products from the diets of infants and children (until age 6) could reduce lifetime cancer risk by 6% and 23%, respectively. The FDA also noted evidence that fetuses may have increased susceptibility to adverse effects via maternal uptake of iAs. Exposure during infancy and early childhood could have neurotoxic effects, although it was not clear if these effects would be lasting.

In 2021, the EFSA again assessed chronic dietary exposure to iAs (EFSA, 2021). The results from this assessment are used for the present Opinion and are described in detail in Section 3.4.1 on Occurrence data used in the present assessment and Section 3.5.1 Exposure assessment used for the present Opinion.

1.2.4 | Legislation

Council Regulation (EEC) No 315/933[3] stipulates that food containing a contaminant in an amount unacceptable for public health shall not be placed on the market, that contaminant levels should be kept as low as can reasonably be achieved and that, if necessary, the European Commission may establish maximum levels (MLs) for specific contaminants. These maximum levels are laid down in the Annex I of Commission Regulation (EU) 2023/915.[4] Table 2 presents an excerpt of the table where the MLs for iAs as listed in Annex I to Regulation 2023/915.

TABLE 2 Maximum levels for inorganic arsenic in food as laid down in Regulation (EU) No 2023/915.

3.4	Arsenic	Maximum level (mg/kg)	Remarks
		Inorganic arsenic (sum of $As^{(III)}$ and $As^{(V)}$)	The maximum level for inorganic arsenic applies to products listed in 3.4.1–3.4.4
3.4.1	Cereals and cereal based products		Rice, husked rice, milled rice and parboiled rice as defined in Codex Standard 198–1995
3.4.1.1	Non-parboiled milled rice (polished or white rice)	0.15	
3.4.1.2	Parboiled rice and husked rice	0.25	
3.4.1.3	Rice flour	0.25	
3.4.1.4	Rice waffles, rice wafers, rice crackers, rice cakes, rice flakes and popped breakfast rice	0.30	
3.4.1.5	Rice destined for the production of food for infants and young children[a]	0.10	

[3]Council Regulation (EEC) No 315/93 of February 1993 laying down Community procedures for contaminants in food. OJ L 37, 13.2.1993, p. 1–5.

[4]Commission Regulation (EU) 2023/915 of 25 April 2023 on maximum levels for certain contaminants in food and repealing Regulation (EC) No 1881/2006 OJ L 119/103, 5.5.2023, p. 103–107.

TABLE 2 (Continued)

3.4	Arsenic	Maximum level (mg/kg)	Remarks
3.4.1.6	Non-alcoholic rice-based drinks	0.030	
3.4.2	Infant formulae, follow-on formulae and food for special medical purposes intended for infants and young children[a] and young child formulae[b]		The maximum level applies to the product as placed on the market
3.4.2.1	Placed on the market as powder	0.020	
3.4.2.2	Placed on the market as liquid	0.010	
3.4.3	Baby food[a]	0.020	The maximum level applies to the product as placed on the market
3.4.4	Fruit juices, concentrated fruit juices as reconstituted and fruit nectars[c]	0.020	
		Total arsenic	The maximum level for total arsenic applies to products listed in 3.4.5
3.4.5	Salt	0.50	

[a]Food as defined in Article 2 of Regulation (EU) No 609/2013 of the European Parliament and of the Council of 12 June 2013 on food intended for infants and young children, food for special medical purposes and total diet replacement for weight control and repealing Council Directive 92/52/EEC, Commission Directives 96/8/EC, 1999/21/EC, 2006/125/EC and 2006/141/EC, Directive 2009/39/EC of the European Parliament and of the Council and Commission Regulations (EC) No 41/2009 and (EC) No 953/2009. OJ L181, 29.6.2013, p. 35.

[b]'Young-child formulae' refers to milk-based drinks and similar protein-based products intended for young children. These products are outside the scope of Regulation (EU) No 609/2013 (Report from the Commission to the European Parliament and the Council on young-child formulae (COM(2016) 169 final) https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A52016DC0169&qid=1620902871447).

[c]Food as defined in Council Directive 2001/112/EC of 20 December 2001 relating to fruit juices and certain similar products intended for human consumption. OJ L 10, 12.1.2002, p. 58.

Harmonised requirements for arsenic in drinking water are set by Council Directive 98/83/EC[5] on the quality of water intended for human consumption and by the new Directive (EU) 2020/2184[6] of the European Parliament and of the Council on the quality of water for human consumption, which entered into force on 12 January 2022 and which will repeal Council Directive 98/83/EC from 13 January 2023.

Both directives stipulate that Member States shall set limit values of 10 µg/L for arsenic in water intended for human consumption.

In Commission Directive 2003/40/EC[7] establishing the list, concentration limits and labelling requirements for the constituents of natural mineral waters and the conditions for using ozone-enriched air for the treatment of natural mineral waters and spring waters, a maximum limit of 0.010 mg/L is established for total arsenic.

The Codex Alimentarius Commission (Codex) has adopted maximum levels for iAs of 0.2 mg/kg in polished rice[8] and of 0.35 mg/kg in husked rice (paddy rice from which the husk only has been removed, also known as brown rice or cargo rice).[9]

2 | DATA AND METHODOLOGIES

The current update of the EFSA risk assessment on iAs, was developed applying a structured methodological approach, which implied developing a priori the protocol or strategy of the full risk assessment. The protocol in Annex A of this Opinion contains the method that was proposed for covering all the steps of the risk assessment process.

The CONTAM Panel used its previous risk assessment on iAs in food (EFSA CONTAM Panel, 2009) as a starting point for drafting the current Opinion.

2.1 | Collection and appraisal of data collected from public literature

2.1.1 | Collection of data

Several comprehensive literature searches were conducted to identify scientific literature relevant to the assessment. Web of Science (Core collection: Science Citation, Index, Emerging Sources Citation Index, Current Chemical Reactions, Index

[5]Council Directive 98/83/EC of 3 November 1998 on the quality of water intended for human consumption. OJ L 330, 5.12.1998, p. 32.

[6]Directive (EU) 2020/2184 of the European Parliament and of the Council on the quality of water for human consumption of 16 December 2020. OJ 435, 23.12.2020, p. 1–62.

[7]Commission Directive 2003/40/EC establishing the list, concentration limits and labelling requirements for the constituents of natural mineral waters and the conditions for using ozone-enriched air for the treatment of natural mineral waters and spring waters of 16 May 2003. OJ L 126, 22.5.2003, p. 34.

[8]https://www.fao.org/news/story/it/item/238558/icode/

[9]https://www.fao.org/news/story/en/item/419100/icode/

Chemicus)[10] and Pubmed (NLM)[11] were identified as sufficient and appropriate to serve as sources of information for literature for the present assessment. The structure, syntax and terms used for the searches have been designed and conducted by the Working Group (WG) with the support of an information specialist. Controlled vocabulary, when available, (i.e. MeSH) and natural vocabulary were used to represent the key elements of the searches. The language of the original studies has been limited to English. The obtained references were imported to EndNote (Clarivate Analytics).[12] Deduplication was performed using automatic and manual procedures. Since this Scientific Opinion is an update of the Scientific Opinion of EFSA on arsenic in 2009, the literature search was restricted to papers published from 1 January 2009 onwards. In addition, a search for previous assessments (risk and exposure assessments of governmental and international bodies) was carried out. During the development of the Opinion, additional publications for the different sections were collected by applying a 'snowballing approach'[13] and considered for the assessment where relevant.

Finally, a public consultation on the draft Opinion was carried out from 24 July 2023 to 10 September 2023 and the comments and documents were considered for finalising the Opinion.

The first literature search was carried out on 14 of April 2021 to identify papers on the following key topics:

A) ADME: Arsenic AND ADME AND (Humans OR Animals) AND Reviews
B) Toxicity:
   - Arsenic AND (Toxicity AND Animal)
   - Arsenic AND (Cytotoxicity OR Genotoxicity) AND (*In vitro* OR *In vivo*)
C) Epidemiological studies: Arsenic AND Epidemiological studies AND Humans

ADME results have been limited to review papers as this was deemed sufficient to address the terms of reference. For all other sections primary research was considered as well. The period covered in this search was 1st of January 2010 to 14th of April 2021. The search strings for each database are described in detail in Table B.1 of Annex B. The number or results of the searches are reported in Table 3 below.

TABLE 3 Number of hits of the search on key topics covering the period of 2010–2021.

Search	PubMed	Web of science	PubMed and web of science combined after de-duplication
ADME	701	434	858
Toxicity	4079	3430	4536
Epidemiological studies	4,468	2822	4870

Abbreviation: ADME, Absorption, Distribution, Metabolism and Excretion.

An additional search was performed in September 2021 to identify papers on epigenetic and transgenerational effects of arsenic not sufficiently covered with the search terms previously applied. This was done as the WG agreed the search terms applied in the first overall search were insufficient to cover all publications relevant for this field. The search was conducted covering the period of 1st of January 2010 to 20th of September 2021. The search string is reported in Annex B in Table B.2. The number of results of the searches is reported in Table 4 below.

TABLE 4 Number of hits of the search on epigenetic and transgenerational covering the period of 2010–2021.

Search	PubMed	Web of science	PubMed and web of science combined after de-duplication
Epigenetic and transgenerational effects	54	178	169

The first comprehensive literature search carried out on 14th April 2021 was repeated on 10 December 2021 to cover also the publication period of 1st of January 2009 to 31st of December 2009 (not covered in the first literature search). It was repeated again on 15 July 2022 to cover also the period 14th of April 2021 to 18th of July 2022. Notably, the key topics of these two repeated searches were the same except that only studies related to epidemiology were considered (search terms and key topics of these searches are therefore not presented in the Annex B). This is because it was agreed at the 119th CONTAM Panel that for the risk characterisation of iAs animal data do not need to be considered. This was decided because of the known toxicokinetic differences between laboratory animals and humans which limit their use for assessing human health effects of iAs (EFSA CONTAM Panel, 2009). The abundance of human data available together with the notion that for human health risk assessment human data should be used preferably were further arguments for basing crucial parts of the assessment on human data only.

The results of the two repeated searches are reported in Tables 5 and 6 below.

[10]Web of Science (WoS), formally ISI Web of Knowledge, Thomson Reuters. https://thomsonreuters.com/thomson-reuters-webof-science/
[11]https://www.ncbi.nlm.nih.gov/
[12]EndNote X6, Thomson Reuters. https://endnote.com/
[13]Identifying articles that have been cited in articles found in a search (see Jalali & Wohlin, 2012).

TABLE 5 Number of hits of the search on epidemiological studies covering the period of 2009–2010.

Search	PubMed	Web of science	PubMed and web of science combined after de-duplication
Epidemiological studies	125	277	170

TABLE 6 Number of hits of the search on epidemiological studies covering the period of 2021–2022.

Search	PubMed	Web of science	PubMed and web of science combined after de-duplication
Epidemiological studies	563	465	727

2.1.2 | Evaluation of data

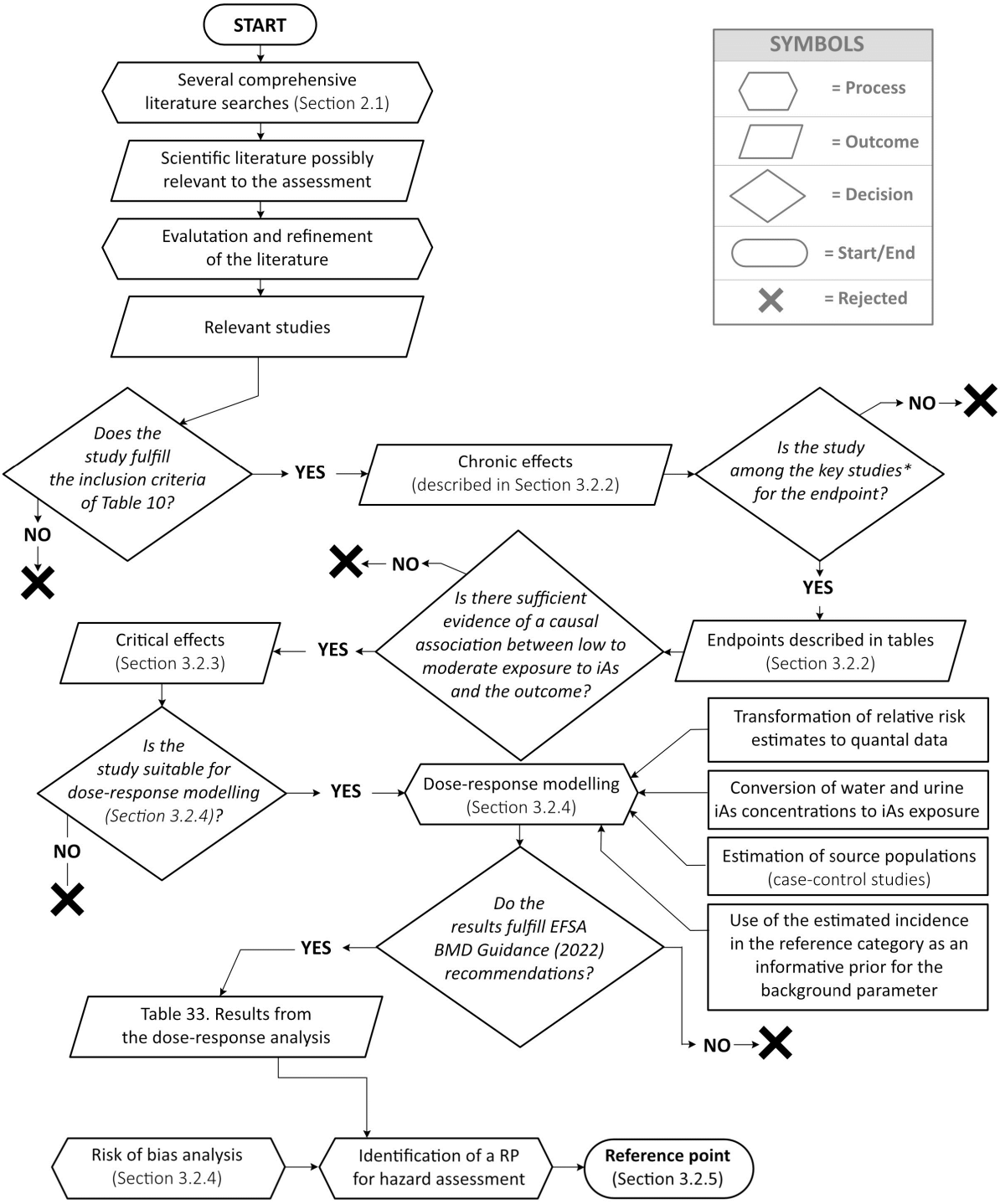
For the pre-evaluation, the scientific literature obtained was screened based on title and abstract, applying expert judgement. Publications obviously irrelevant for the present mandate were excluded from further consideration. These were publications for example dealing with the use of arsenic in medical or technical applications, publications on arsenic in geology, effect on arsenic on plants, wild animals or ecosystems or publications where arsenic was used as a compound to validate test systems. From the first search the pre-evaluation resulted in a total of 4539 potentially relevant studies (human and animal). From these only human data, and animal data on carcinogenicity, genotoxicity and epigenetic changes and *in vitro* data on genotoxicity and epigenetics were considered further (see Section 2.1.1 above). Publications dealing with arsenic trioxide were also not further considered because of the difference in the toxicokinetics between arsenic trioxide and arsenic present in food and drinking water. Human studies covering mixtures of arsenic and other contaminants or compounds potentially ameliorating arsenic mediated effects (which were in particular intervention studies) were also excluded from analysis as these were considered not relevant for the risk characterisation of iAs. In the updated search on key topics covering the period 2009–2010, 81 studies were considered possibly relevant in the pre-evaluation. In the updated search on key topics covering the period 14th of April 2021 to 18th of July 2022, 160 studies were considered possibly relevant after the pre-evaluation. For the search on epigenetic and transgenerational effects carried out in 2021, the pre-evaluation by experts resulted in 64 possibly relevant papers on the specific topic. For the final evaluation and refinement of the scientific literature to be considered for the assessment, the abstracts were again assessed and evaluated by relevant domain experts from the CONTAM working group.

2.1.3 | Transformation of data from epidemiological studies and benchmark dose calculations

The transformation of data from epidemiological studies for use in benchmark dose (BMD) assessments is described in detail in Section 3.2.4 Dose–response analysis.

2.1.4 | Overview of methodology applied

Figure 1 provides an overview of the methodology applied for the present risk assessment. After collection and evaluation of the literature (see Sections 2.1.1 and 2.1.2) selection criteria were applied, after which causal association was scrutinised, the suitability for BMD modelling was evaluated after which dose response modelling was carried out. Before conducting BMD modelling the relative risk estimates were transformed to quantal data. Additionally, the iAs concentrations were converted to exposures, taking into account default values and estimating source populations for case–control studies. This was followed by a risk of bias analysis of the studies from which the most relevant valid BMDL could be derived. Finally, a Reference Point based on the BMD modelling, expert knowledge and an MOE to estimated exposure levels in Europe were established.



*The studies which comply with the inclusion criteria.

FIGURE 1 Flowchart on the methodology applied for risk assessment.

3 | ASSESSMENT

3.1 | Hazard identification and characterisation

3.1.1 | Toxicokinetics

This chapter gives a short summary of the crucial steps in the toxicokinetics of iAs upon ingestion by humans. A more detailed review can be found in the previous CONTAM Opinion on arsenic (EFSA CONTAM Panel, 2009) as well as recent reviews (e.g. Roy et al., 2020; Thomas, 2021).

In humans, soluble iAs is rapidly and well absorbed after ingestion (45%–80%). After absorption, arsenic is widely distributed to almost all organs and readily crosses the placental barrier. In blood arsenic is distributed between plasma and erythrocytes. Here it is mainly bound to SH-groups in proteins and low-molecular-weight compounds such as glutathione (GSH) and cysteine. The major metabolic pathways of iAs in humans include oxidation, reduction, methylation, thiolation and glutathiolation of arsenic. Methylation capacity is crucial for arsenic toxicity. Elimination through urine in the form of iAs and its methylated metabolites occurs with a half-life of around 2–3 days (Buchet et al., 1981b). Average values for the major urinary species following iAs intake are 10%–30% iAs (sum of arsenite and arsenate), 10%–20% MMA (sum of MMA(III) and MMA(V)) and 55%–75% DMA (sum of DMA(III) and DMA (V)). Notably there is high inter-species, inter-population and inter-individual variability for arsenic methylation and also other aspects of toxicokinetics. Susceptibility factors include life stage, sex, nutritional status (e.g. Kurzius-Spencer et al., 2017; López-Carrillo et al., 2016; Xu, Drobná, et al., 2016), microbiota (e.g. Coryell et al., 2019) and genetic polymorphisms related to arsenic metabolism genes and transporter genes (e.g. EFSA CONTAM Panel, 2009; Schuhmacher–Wolz et al., 2009). Most studies concentrate on the polymorphisms of *arsenite-methyltransferase* (*AS3MT) and glutathione-S-transferases* (GST) especially *GSTO1 (glutathione S-transferase omega 1)* (e.g. Antonelli et al., 2014; Caceres et al., 2010; De Loma et al., 2018; Engström et al., 2011; Fu et al., 2014; Gao et al., 2015; González-Martínez et al., 2018).

3.1.1.1 | *Metabolism*

The metabolism of iAs in the humans has been proposed through three different, likely interlinked, pathways (Figure 2). The classical pathway suggests a process of sequential reduction and oxidative methylation steps. Following ingestion, the first step of metabolism is a reduction of As(V) to As(III): 50%–70% of arsenate is rapidly reduced to arsenite (most likely facilitated by GSH) in blood and the liver (Aposhian et al., 2004; EFSA CONTAM Panel, 2009; Rehman & Naranmandura, 2012). Then As(III) undergoes a cycle of oxidative methylation reactions and reduction reactions that sequentially couple a methyl group to an As atom in the trivalent form (Figure 2A). Methylation takes place mainly in the liver, although most organs are capable of methylating arsenic (e.g. bladder, kidneys). Arsenite methyltransferase (AS3MT) catalyses the transfer of the methyl group from S-Adenosylmethionine (SAM) to arsenite and MMA(III), resulting in MMA(V) and DMA(V).

The second proposed pathway suggests that arsenic either binds to certain proteins (Figure 2C) or conjugates with glutathione (Figure 2B) and these intermediates are subsequently methylated by AS3MT. Arsenic triglutathione (ATG) is methylated to monomethylarsonic diglutathione (MMAG) and dimethylarsinic glutathione (DMAG). MMAG and DMAG are further reduced to MMA(III) and DMA(III) and then oxidised to the respective pentavalent forms.

Thio-DMA(V) is the pentavalent sulfur analogue of DMA(V) and a metabolite of organic as well as inorganic arsenicals. Thio-DMA(V) was first identified as a mammalian arsenic metabolite in urine from a sheep naturally consuming large amounts of arsenosugars through seaweed (Hansen et al., 2004). It has been discussed that thio-DMA(V) may have been misidentified as DMA(III) in human urine samples before and, therefore, might have escaped detection in many samples to date (Hansen et al., 2004). Indeed, thio-DMA(V) has later been identified a later study in human urine after exposure to iAs-contaminated drinking water (Raml et al., 2007). In this study investigating the urine of 75 inorganic arsenic-exposed women in Bangladesh, thio-DMA(V) has been shown to be a common metabolite, being detected in 44% of the samples. Although thio-DMA(V) has been identified as human iAs metabolite the metabolic mechanism of the formation is not fully understood so far. Like DMA and MMA, thio-DMA(V) also directly occurs in food, e.g. in rice.

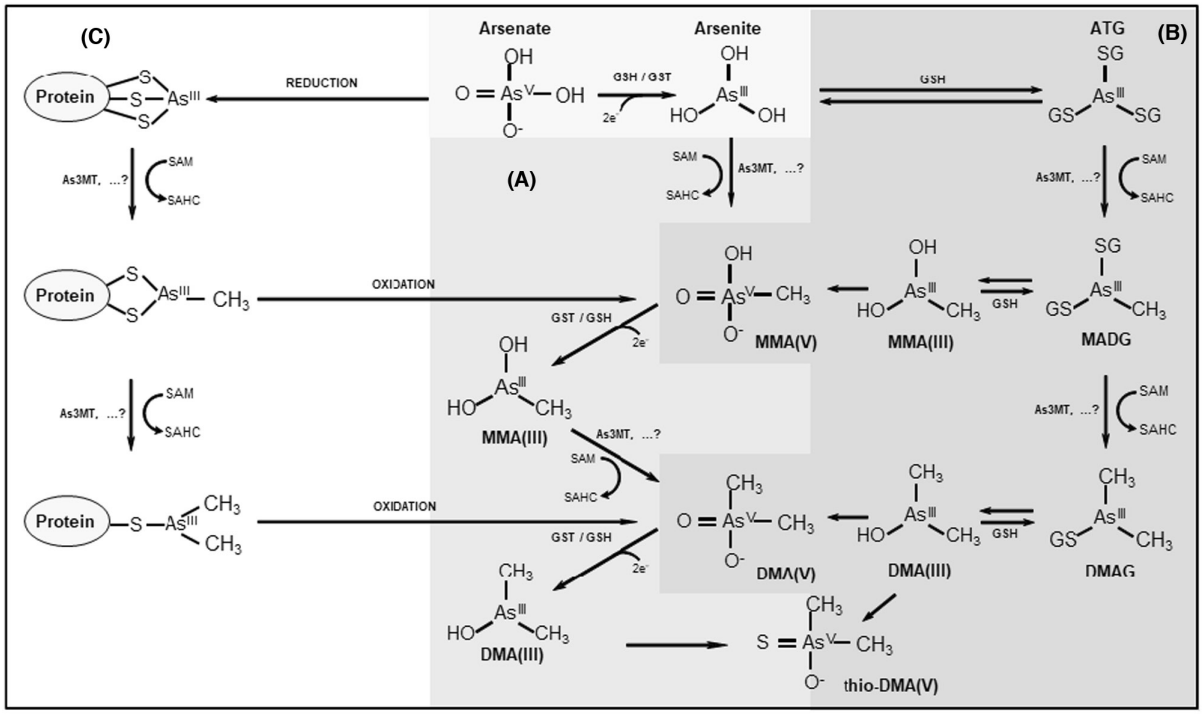


FIGURE 2 Simplified schemes of the originally proposed human iAs metabolism pathway (A), the two more recently proposed alternative pathways (B, C) as well as a possible conjunction of the pathways. ATG, Arsenic triglutathione; MMA(V), monomethylarsonic acid; MMA(III), monomethylarsonous acid; DMA(V), dimethylarsinic acid); DMA(III), dimethylarsinous acid; MMAG, monomethylarsonic diglutathione; DMAG, dimethylarsinic glutathione; thio-DMA(V), thio-dimethylarsinic acid; GSH, glutathion-S-transferases; AS3MT, arsenite methyltransferase; SAM, S-Adenosylmethionine; SAH, S-Adenosylhomocysteine. Scheme modified from Hartwig and Schwerdtle (2009), © Blackwell Publishing Ltd/Wiley.

3.1.1.2 | *Interspecies variability in inorganic arsenic toxicokinetics*

In 2009, the CONTAM Panel concluded that experimental animals differ considerably from humans with regard to iAs metabolism and other aspects of toxicokinetics. Thus, the results of toxicity studies in animals do not provide a suitable basis for hazard assessment (EFSA CONTAM Panel, 2009).

This paragraph highlights briefly important interspecies differences in iAs toxicokinetics.

Animals differ in their ability to methylate inorganic As (Vahter, 1999). Additionally, Vahter (1999) showed that the methylated metabolites are produced in different ratios in humans compared to most mammals and that humans excrete more MMA(V). Marmoset monkeys do not methylate iAs, whereas rodents (hamsters, mice), rabbits and dogs show high methylating capacity, reaching up to 80% urinary DMA(V). The lower urinary excretion of DMA in rats is not an indication of low iAs methylation capacity but results from the specific retention of DMA(V) in rat erythrocytes. Primary rat hepatocytes have been shown to methylate iAs better than cultured primary human hepatocytes and keratinocytes (Styblo et al., 2000).

Since 2009, no toxicokinetic studies contradicting the previous conclusions have been identified. Thus, the conclusion still stands that results of toxicity studies in animals do not provide a suitable basis to assess the risks to human health related to iAs ingestion because of considerable interspecies differences in the toxicokinetics of arsenic.

3.1.1.3 | *Transfer to human milk*

In contrast to the rapid transfer of As to the fetus, little As is excreted in human milk following iAs ingestion (EFSA, 2021; EFSA CONTAM Panel, 2009). A small study reported median levels around 0.31 μg/L of tAs in US mothers, with a maximum of 0.62 μg/L and detectable arsenic in only five of the nine samples of breast milk analysed. Arsenic exposure of the mothers was not assessed (Carignan et al., 2015). The average concentration of arsenic in human milk of 60 Swedish mothers was 0.55 μg/L (SD = 0.70 μg/L) with the highest concentration measured being 4.6 μg/L (Björklund et al., 2012). Arsenic concentration in human milk was positively correlated with fish consumption, but external arsenic exposure was not assessed. Speciation analysis of milk from this study showed no content of inorganic As or its methylated metabolites in the human milk. Other studies have shown that following the consumption of fish, a small percentage of arsenolipids are transported to the milk of nursing women (Stiboller et al., 2017; Xiong et al., 2020).

Different studies support the assumption that even in areas with drinking water containing relatively high to moderate concentrations of arsenic, only small amounts appear to pass through mammary glands to human milk (Carignan et al., 2015; Concha, Vogler, Lezcano, et al., 1998; Concha, Vogler, Nermell, & Vahter, 1998; Signes-Pastor et al., 2018). Overall, the available studies indicate that after ingestion of inorganic arsenic, little arsenic is transferred to human milk.

3.1.2 | Biomarkers

3.1.2.1 | *Biomarkers of exposure*

In its previous Opinion (EFSA CONTAM Panel, 2009) the CONTAM Panel noted that total arsenic in urine is a common biomarker of arsenic exposure as most arsenic compounds originating from oral arsenic intake of food and water are excreted via urine within a few days. Urine collected over 24 h is preferred for biomonitoring of arsenic. However, because of difficulties in obtaining 24-h urine samples, first-morning or spot urine samples are usually used for biomonitoring of arsenic. Fish and other seafood can contain relatively high concentrations of arsenobetaine and other organic arsenic compounds, which are considered much less toxic than iAs and are also excreted in the urine (Taylor, Li, et al., 2017). Consequently, consumption of even small amounts of seafood can result in high urinary concentrations of total arsenic making it difficult to assess iAs exposure. Total urinary arsenic is therefore often not a suitable biomarker of exposure. Specific measurements of iAs, and its methylated metabolites (e.g. MMA and DMA), or the sum of iAs and its methylated metabolites, also named total urinary inorganic arsenic (u-tiAs), provide more appropriate estimates of exposure (e.g. Middleton et al., 2016). In urine samples where arsenobetaine levels are low (e.g. arsenic intake is not from fish consumption), DMA typically contributes to > 50% of total arsenic in the urine (Buchet et al., 1981a; Colín-Torres et al., 2014; Cubadda et al., 2012; Fillol et al., 2010; Tam et al., 1979). However, the sum of iAs and related metabolites (u-tiAs) might be affected by ingestion of DMA which can occur as such in food including rice but also by ingestion of arsenosugars via seaweed, which can be metabolised into DMA and other methylated arsenic compounds compromising the assessment of iAs exposure (Taylor, Li, et al., 2017). Thus, study participants need to refrain from consumption of all seafood for several days before sampling to achieve reliable results. Urinary arsenic concentrations are often adjusted to creatine to control for variations in urine flow rates. This may lead to incorrect conclusions because of differences in muscle mass between individuals and, in particular, between women and men (Nermell et al., 2007). Therefore, it has been proposed to normalise to the specific gravity of the urine rather than adjusting for creatinine levels (Nermell et al., 2007).

Levels of total arsenic in blood are also of limited value when estimating exposure to iAs because it is cleared from the blood within a few days after ingestion (Buchet et al., 1981a; Middleton et al., 2016). The exception to this is where there is constant exposure to arsenic, for example by using the same water supply or where rice is a staple food in the diet (Meharg et al., 2014; Signes-Pastor, Gutiérrez-González, et al., 2021).

Under conditions of constant high exposure to iAs, the concentration of total arsenic in the blood reaches a steady state, better reflecting exposure to iAs although diurnal variation also exists (Signes-Pastor, Gutiérrez-González, et al., 2021). High levels of iAs in the drinking water correlate with elevated total arsenic concentrations in blood (Arikan et al., 2015; Rodrigues et al., 2015). Unlike urinary arsenic, which reflects excretion, arsenic in blood is a measure of internal exposure and thus reflects actual tissue burdens. However, blood arsenic concentration also correlates positively with frequency of fish consumption, making it unsuitable as a biomarker of exposure to iAs (Miklavcic et al., 2013; Snoj Tratnik et al., 2019).

Inorganic arsenic is the major form in hair and nails with MMA and DMA combined making up < 20% of total arsenic in this biomatrix. Because trivalent arsenicals have high affinity for sulfhydryl groups they bind to keratin in hair and nails (Shen et al., 2013). Inorganic arsenic therefore tends to accumulate in hair and nails and because they grow slowly, arsenic concentrations in hair and nails are considered reasonable biomarkers for long-term exposure to iAs (Signes-Pastor, Gutiérrez-González, et al., 2021).

The CONTAM Panel reviewed the literature published since the previous Opinion (EFSA CONTAM Panel, 2009) and concluded that there is no new information that alters the view that there is no universally accepted biomarker for chronic iAs exposure. If continuous iAs exposure is stable over time, urinary arsenic may be used as a biomarker provided that arsenic species or u-tiAs are analysed. Hair and, in particular, toenails are probably the best biomarkers of long-term exposure to iAs. However, also these are imperfect because arsenic in hair and nails may not exclusively originate from iAs and there are studies showing a correlation between seafood consumption and total arsenic in hair and nails (Taylor, Goodale, et al., 2017).

3.1.2.2 | *Markers of genotoxicity*

Since the previous Opinion, additional biomonitoring studies investigating genotoxic damage in cells from individuals either occupationally or environmentally exposed to arsenic have been published using different markers. The marker most frequently investigated was the frequency of micronuclei (MN) in peripheral blood lymphocytes. In this Section only relevant studies conducted on populations exposed orally to iAs via an environmental source were reviewed. Details of the studies are presented in Table 7.

Most biomonitoring studies have been conducted in areas containing high levels of arsenic in soils and waters because of their geological constitution and/or vicinity to mining sites. In these studies, the drinking water arsenic concentration reported for the control population (so called 'unexposed' individuals) is < 10 μg/L. Chronic ingestion of contaminated drinking water (arsenic concentration > 50 μg/L) in some populations, including children, from Argentina (Bartolotta et al., 2011) and India, particularly from West Bengal (Bandyopadhyay et al., 2016; Chatterjee et al., 2018; Paul et al., 2014; Paul, Bhattacharjee, et al., 2013; Paul, Das, et al., 2013) and Assam (Roy et al., 2016), was reported to be associated with significant increases of MN frequency in lymphocytes and also in urothelial (Bartolotta et al., 2011; Chatterjee et al., 2018; Paul, Bhattacharjee, et al., 2013; Paul, Das, et al., 2013) and buccal (Chatterjee et al., 2018) cells. A cross-sectional study (Paul, Das,

et al., 2013) was conducted in West Bengal where individuals with arsenicosis[14] and unexposed individuals were recruited before and after reduction in the level of exposure via drinking water. In the arsenicosis group, a five-fold decrease in arsenic concentrations in drinking water led to a significant decline of MN frequency in urothelial cells (three-fold decrease) and lymphocytes (2.5-fold decrease) and of the number of individuals with dermatological disorders. In a cross-sectional study from exposed and unexposed individuals from the same area (Paul, Bhattacharjee, et al., 2013) an ~60-fold decrease in arsenic concentrations in drinking water led to a significant decline (~ three-fold decrease) of MN frequency in urothelial cells of exposed individuals. Still there was a significant difference compared to the control population (1.3–1.5-fold increase). In these two cross-sectional studies the follow-up individuals had consumed drinking water with reduced levels of arsenic for at least 5 years indicating that a partial reduction of cytogenetic damage may occur when the oral exposure decreases. Two studies investigated chromosomal aberrations (CA) in populations from West Bengal (Banerjee et al., 2010) and a mining district in Mexico (Tovar-Sanchez et al., 2016), exposed to arsenic via drinking water, showing a significantly higher frequency of CA in lymphocytes as compared to unexposed individuals.

One study (Banerjee et al., 2013) examined the genotoxic impact of exposure to high arsenic in rice in humans. This cohort study from West Bengal (India) involved 417 subjects not otherwise significantly exposed to arsenic through drinking water (not more than 20% of total dietary exposure). Significantly higher frequencies of MN in urothelial cells were associated with consumption of cooked rice with >200 μg/kg arsenic as staple food as compared to lower exposure groups. Several potential confounders were analysed (age, gender, tobacco usage, bodyweight, drinking water arsenic, drinking water intake and study sub-area). The only covariates of significance in predicting MN, were cooked rice arsenic ($p < 2.2$ e-16) and, to a much lower extent, tobacco usage ($p = 0.022$). It is of note that for this study population the authors estimated that 200 μg/kg total arsenic is equivalent to ~180 μg/kg iAs in rice and, on the basis of the mean cooked rice intake (560 g/day) and mean body weight of participants (51.3 kg), to a mean daily intake of iAs of ~2.0 μg/kg bw, raising concerns for the health risks of populations consuming rice as a staple food.

MN and CA are frequently associated with cancer and inflammation-driven diseases (reviewed in Fenech et al., 2021). The study by Banerjee et al. (2008) was the first to provide evidence that individuals chronically exposed to arsenic via drinking water with hyperkeratosis[15] present a significantly higher frequency of CA than exposed individual without hyperkeratosis. No significant difference in the level of DNA damage as detected by the alkaline elution method was observed between the two groups but an *in vitro* challenge assay[16] showed that upon induction of DNA damage, the repair capacity in the exposed individuals with premalignant hyperkeratosis was significantly less than that of individuals without skin lesions. A deficiency in DNA repair was proposed as the main driver of arsenic carcinogenicity. More recently, Paul et al. (2011, 2014) confirmed these findings by showing a correlation between higher incidence of CA and higher arsenic concentration in the biological tissues (hair and nails) of patients with blood cancer from areas heavily contaminated with arsenic when compared to healthy controls from non-contaminated areas (Paul et al., 2011) and a higher frequency of MN in exposed individuals with skin lesions as compared to subjects without skin lesions (Paul et al., 2014). These studies highlight the possibility that MN and CA formation in humans is not only a marker of induced DNA damage but also of genetic susceptibility and disease initiation and progression (Bonassi et al., 2008; Fenech et al., 2020).

Navasumrit et al. (2019) carried out a birth cohort study on 205 pregnant women residing in arsenic-contaminated areas in Hanam province (Vietnam) to evaluate potential genotoxic effects of in utero arsenic exposure in newborns. Toenails and urine samples were collected during pregnancy and umbilical cord blood samples immediately after birth. Oxidative/nitrative DNA damage (8-hydroxydeoxyguanosine (8-oxodG) and 8-nitroguanine), DNA strand breaks and MN were measured in cord blood. Evidence has been provided that cord blood arsenic concentrations reflect chronic As exposure of the fetus during pregnancy (Rodrigues et al., 2015; Guan et al., 2012). In the study by Navasumrit et al. (2019) cord blood arsenic concentration was significantly associated with that of maternal toenail arsenic suggesting an association between fetal and maternal iAs exposure via drinking water. Maternal toenail arsenic level was significantly associated with all markers of genetic effects measured in cord blood while cord blood arsenic levels were associated with increased DNA strand breaks and MN frequency but not with oxidative DNA damage. All these effects were dose dependent.

Two meta-analyses (Annangi et al., 2016; Dong et al., 2019) were carried out to review the biomonitoring studies where MN frequency was used as marker of genotoxicity in human populations exposed environmentally or occupationally to arsenic. Annangi et al. (2016) limited the review to studies (three on occupational and seven on environmental exposure) where peripheral blood lymphocytes were analysed while Dong et al. (2019) considered studies (25 on different sources of exposure) dealing with three human cell types, i.e. lymphocytes, buccal and urothelial cells. Both analyses, concluded that environmental chronic exposure to iAs via contaminated water is associated with increased MN frequency among exposed individuals. The subgroup analysis carried out by Dong et al. (2019) showed that when the exposure source was occupational or other than drinking water, no increase in MN frequency was observed in all three types of cells tested.

Telomere dysfunction is an important mechanism to generate chromosomal instability commonly found in several disease processes including cancer (McNally et al., 2019). Some studies addressed the potential association of arsenic exposure with alteration of telomere structure but with equivocal results. Significant increase in telomere length in leukocytes was reported in arsenic-exposed communities from Mexico (Villarreal et al., 2019) and Northern Argentina (Li et al., 2012);

[14]A chronic health condition arising from prolonged ingestion (not less than 6 months) of arsenic above a safe dose, usually manifested by characteristic skin lesions, with or without involvement of internal organs.

[15]A condition characterised by an increased thickness of the stratum corneum, the outer layer of the skin.

[16]Cells are exposed to a DNA damaging agent *in vitro* to investigate how they respond.

a slight increase, not statistically significant, in children from West Bengal (Chatterjee et al., 2018) and lack of association in people from Bangladesh (Zhang et al., 2018). Future studies are needed to establish the mechanisms underlying lengthening of telomeres and its potential contribution to arsenic-induced cancer risk.

Besides clastogenic effects, other markers of DNA damage were positively associated with the level of exposure via arsenic-contaminated water. DNA breaks (both single and double-strand breaks) as detected by alkaline elution were significantly higher in airway cells (Dutta et al., 2015) and in lymphocytes (Roy et al., 2016) of exposed populations from Indian regions and in lymphocytes from environmentally exposed Mexican children and adults (Jimenez-Villarreal et al., 2017; Sampayo-Reyes et al., 2010; Tovar-Sanchez et al., 2016) as compared to control groups. Elevated levels of oxidative stress-induced damage (e.g. 8-oxodG, 8-nitroguanine) in urine, plasma or saliva, were detected in populations from highly contaminated areas (Dutta et al., 2015; Hinhumpatch et al., 2013; Mar Wai et al., 2019; Navasumrit et al., 2019; Pei et al., 2013). 8-oxodG is considered a marker for oxidative stress derived from oxidatively generated damage to 2′-deoxyguanosine via a mechanism that has not yet been clarified (Evans et al., 2016). Only one study found no evidence that exposure to arsenic increases levels of plasma protein carbonyls or 8-oxodG (Harper et al., 2014). In a Thai population, arsenic exposure in utero was associated with increased levels of urinary 8-nitroguanine in newborns which significantly correlated with increased expression of inflammatory genes in cord blood (Phookphan et al., 2017). A follow-up study showed that these arsenic-exposed children had increased urinary 8-nitroguanine and significantly higher levels of 8-oxoguanine in saliva DNA corresponding well to decreased expression of human 8-oxoguanine DNA glycosylase 1 (hOGG1), the major DNA glycosylase for the excision of 8-oxoguanine DNA base lesions (Hinhumpatch et al., 2013). In a large prospective cohort study (788 participants) in Taiwan (Tsai, Kuo, et al., 2021) the levels of urinary 8-oxodG and N7-methylguanine showed a positive association with cumulative well-water exposure to arsenic and urinary arsenic species.

Inorganic arsenic induces DNA damage and the formation of MN and CA in various cell types *in vitro* as well as *in vivo* (see Section 'Genotoxicity'). Here, a large number of studies where these genotoxicity markers have been investigated in somatic cells (i.e. lymphocytes, urothelial and buccal cells) of people environmentally exposed to high levels of arsenic in adulthood as well as in early life were reviewed. Although some studies present limitations (e.g. small population size, lack of dose–response relationship, no evaluation of potential confounders), overall, they consistently indicate that chronic environmental exposure via contaminated water is associated with increased DNA damage (DNA breaks and oxidatively induced DNA damage) (levels of As in the range of 10–40 μg/L) and clastogenic events (levels of As > 50 μg/L) in somatic cells from exposed individuals. A well conducted birth-cohort study (Navasumrit et al., 2019) showed that these effects are also induced in newborns after in utero arsenic exposure. Table 7 shows an overview of the studies on markers of genotoxicity published since 2009.

TABLE 7 Markers of genotoxicity in cells from exposed individuals.

Reference	Test system	Population size (*n*) case/control	As exposure (mean)	Results	Additional information
Banerjee et al. (2010)	CA in lymphocytes Serum oxidative stress enzymes activities	50 exposed (34 with skin lesions; 16 without) 41 unexposed from West Bengal (India)	Concentration in water (μg/L): exposed, 218.17; unexposed, 6.92; chronic exposure: more than 10 years	Significantly higher incidence of CA in exposed versus unexposed individuals Catalase and myeloperoxidase activity higher in exposed versus unexposed individuals at low levels of exposure	Levels of As measured in urine, nails and hair
Bartolotta et al. (2011)	MN assay in buccal cells	27 exposed to high levels, 32 exposed to low levels from rural and urban areas of Argentina	Concentration in water (μg/L): exposed to high levels > 50 versus exposed to low levels < 50, serving as controls	Significant increase of MN frequency in the exposed group of both rural and urban populations versus controls	No effect of age and gender
Sampayo-Reyes et al. (2010)	Alkaline comet assay in peripheral blood leukocytes	84 exposed (adults and children): low exposed ($n = 42$); medium exposed ($n = 26$); high exposed ($n = 19$) from Northern Mexico	Concentration in water (μg/L) Low exposed, 12.1; medium exposed, 16; high exposed, 45.6	A positive association was found between the level of exposure and DNA breaks (% of DNA in tail)	Correlation of the total urinary As content of the exposed individuals with the As content in drinking water Influence of AS3MT Met287Thr polymorphism on DNA break induction
Banerjee et al. (2013)	MN assay in urothelial cells	304 exposed 113 unexposed from West Bengal (India)	Concentration in cooked rice (mg/kg): exposed from > 100 up to > 300; unexposed ≤ 100; not significantly exposed to arsenic through drinking water	Significantly higher MN frequency in all groups with a mean As concentration in cooked rice > 200 μg/kg versus lower exposure group (≤ 100–≤ 200)	Strong correlation between grouped urinary As and cooked rice As data Information on possible confounding factors available
Hinhumpatch et al. (2013)	8-oxodG in salivary DNA and urines by HPLC hOGG1 gene expression by RT-PCR in saliva	Children: 40 exposed/20 unexposed from Ron Phibul District (Thailand)	Concentration in water (μg/L): drinking water: exposed 5.66/unexposed 0.4; Non-drinking water: exposed 39.96/ unexposed 2.97; In utero and continuous exposure	Significantly higher levels of salivary 8-oxodG in exposed children; levels of urinary 8-oxodG excretion and salivary hOGG1 expression significantly lower in exposed children	Analysis of As in drinking water, saliva, nails and urines. Information on possible confounding factors available
Paul, Das, et al. (2013)	MN assay in urothelial cells and lymphocytes	189 arsenicosis/171 unexposed from West Bengal (India) recruited at two time points, (2005–06 and 2010–11)	Concentration in water (μg/L): Exposed: 190.1 (2005–2006)/37.94 (2010–2011) Unexposed: < 10	Decrease of As exposure resulted in significant decline of MN frequency in urothelial cells and lymphocytes No changes of MN frequency in unexposed individuals at the two recruitment times	Decrease of As exposure resulted in significant decline in the number of individuals having dermatological disorders and in the severity of each dermatological outcome
Paul, Bhattacharjee, et al. (2013)	MN assay in urothelial cells	145 exposed/60 unexposed (2004–2005); 128 exposed/54 unexposed (2010–2011)	Concentration in water (μg/L): 348.23 (2004–2005)/ 5.60 (2010–2011)	Decrease of As exposure resulted in a significant decline in the MN frequency No changes of MN frequency in unexposed individuals at the two recruitment times	

TABLE 7 (Continued)

Reference	Test system	Population size (*n*) case/control	As exposure (mean)	Results	Additional information
Pei et al. (2013)	8-oxodG by Elisa in urines and leukocytes	75 exposed/12 unexposed from China	Concentration in water (μg/L): exposed from 27.2 to 35.6 from normal to severe skin lesions	Chronic exposure to low levels selectively induces oxidatively induced DNA damage of peripheral blood polymorphonuclear cells	Urinary As levels were increased in the severe skin lesion group compared with the normal group. Information on confounding factors available
Harper et al. (2014)	8-oxodG in urines by Elisa Protein carbonyls by Elisa in plasma	378 participants from Bangladesh	Concentration in water (μg/L): five exposure categories from < 10 to > 300	None of the measures of As exposure was significantly associated with protein carbonyl or 8-oxodG levels	Water, blood and urinary As concentrations were measured. Information on possible confounding factors available
Paul et al. (2014)	MN assay in lymphocytes	157 exposed (75 WOSL; 82 WSL)/ 88 unexposed individuals from West Bengal (India)	Concentration in water (μg/L): exposed WOSL 186.74; WSL 195.66 / unexposed: 4.37	Significant increase of MN frequency in both subpopulations of exposed individuals (higher in WSL versus WOSL) versus unexposed individuals	As levels measured in water, urine, nails, hair and blood samples Promoter hypomethylation of ERCC2 and decrease in CAK activity
Dutta et al. (2015)	Alkaline comet assay in airway cells 8-oxodG in plasma by Elisa	142 chronically exposed women/ 131 unexposed women from West Bengal, India	Concentration in water (μg/L): exposed 11–50; unexposed < 10	Significantly higher levels of DNA breaks (comet tail moment) in airway cells from exposed versus unexposed women. Increased levels of 8-oxodG in plasma of exposed women	Elevated inflammation markers in exposed women
Bandyopadhyay et al. (2016)	MN assay in lymphocytes	Children (5–15 years): 67 exposed/49 unexposed from West Bengal (India)	Concentration in water (μg/L): exposed, 45.01; unexposed, 6.22; chronic exposure: since birth	MN frequency significantly higher in exposed versus unexposed individuals	Significant association of MN frequency in exposed individuals with reduced LINE-1 methylation
Roy et al. (2016)	MN assay in exfoliated buccal cells Comet assay in lymphocytes	138 individuals divided into four groups. Group I ($n = 54$) non chewer, unexposed. Group II ($n = 32$) chewers, unexposed. Group III ($n = 24$) exposed, non-chewers. Group IV ($n = 28$) chewers, exposed	Concentration in water (μg/L) exposed Group III, 43; Group IV, 43; unexposed Group I, 2 and Group II, 3	Statistically significant increase of MN frequency for Group II, III and IV as compared to controls (Group I); Group IV the highest incidence of MN. DNA breaks (% of tail DNA) gradual significant increase among the groups. Strong positive correlation between the exposed population and the frequency of binucleated cells	Amount of chewing tobacco had significant positive correlation with MN frequency and in the percentage of tail DNA
Tovar-Sanchez et al. (2016)	Alkaline comet assay and CA in whole blood samples	22 exposed, 20 unexposed from Mexico	Concentration in water (μg/L): exposed 60, unexposed (not detected)	DNA breaks (tail length) and CA were positively and significantly correlated with As concentrations in whole blood samples. Terminal deletions registered the highest determination coefficient	Check for metal concentration (Pb, As, Cu, Zn, Cd) in drinking water. As was the only metal with a significant difference in blood samples between exposed and control. Information on confounding factors available

(Continues)

TABLE 7 (Continued)

Reference	Test system	Population size (*n*) case/control	As exposure (mean)	Results	Additional information
Jiménez-Villarreal et al. (2017)	Two-tailed comet assay in lymphocytes	76 exposed, 112 unexposed from Mexico	Concentration in water (μg/L): exposed 14.3/unexposed 7.7	Significantly higher frequency of DSB (comet tail length) in exposed to higher levels of As versus control group	Information on nutritional status and lifestyle variables
Phookphan et al. (2017)	8-nitroguanine by Elisa in urines	Children (6–9 years): 40 exposed, 41 unexposed; prenatally and early childhood exposed, from Thailand	Concentration in water (μg/L): 8.38 and 78.05 for drinking and non-drinking water, respectively. Levels of As in drinking and non-drinking water in the control sites were 12.5- and 13.4-fold lower	The level of urinary 8-nitroguanine was significantly higher in exposed newborns and children, by 1.4- and 1.8-fold, respectively	Hypomethylation of inflammatory genes (COX2, EGR1 and SOCS3)
Chatterjee et al. (2018)	MN assay in buccal and urothelial cells, and lymphocytes	Children (5–15 years): 68 exposed/52 non exposed from West Bengal (India)	Concentration in water (μg/L) exposed 50.8 and unexposed 6.2; chronic exposure since birth	Significantly higher MN frequency in all the three cell types in As exposed children versus unexposed children	Correlation between urinary As and MN frequency in lymphocytes and urothelial cells
Mar Wai et al. (2019)	8 – oxodG in urines by Elisa	198 pregnant women in the third trimester of pregnancy from Myanmar	Concentration in water (μg/L): 0.02–198, exposure for at least 6 months	Higher urinary As concentrations were significantly associated with higher 8 – oxodG levels	Urinary As concentrations were significantly correlated with drinking water As concentrations
Navasumrit et al. (2019)	8-oxodG, 8-nitroguanine by immunoassays, alkaline comet assay and MN assay in cord blood	205 pregnant women recruited during 2010–2012 from Haman Province, Vietnam	Concentration in toenail (μg/g): three groups were identified: low < 0.5, medium 0.5–1 and high > 1 Concentration in water (μg/L): low exposed group < 10; high exposed group ~ 60	Maternal toenail As level was significantly associated with all markers of early genetic effects. Cord blood As levels associated with DNA strand breaks (tail length, tail moment, %DNA in tail) and MN frequency	Cord blood As level significantly increased with maternal As exposure The group of women with high exposure had a significant reduction in arsenic methylation capacity
Tsai, Kuo, et al. (2021)	8-oxodG and N7-MeG by LC–MS/MS in urines	788 participants were enrolled in a prospective cohort study in Taiwan between 1991 and 1994, with follow-up between 2011 and 2014	Concentration in well water (μg/L): low < 24.30, high > 24.30; cumulative exposure (concentration in well-water multiplied by the duration of artesian water consumption) low < 874.2, high > 874.2	The levels of 8-oxodG and N7-MeG have a significantly positive association with cumulative artesian well-water As exposure and urinary As species levels after adjusting for age, sex and cigarette smoking	Non-statistically significant mediation effects of 8-oxodG were observed. Higher risk of bladder cancer for participants with As exposure and urinary 8-OHdG levels higher than the median

Abbreviations: 8-OHdG, 8-hydroxy-2′-deoxyguanosine; 8-oxodG, 8-hydroxydeoxyguanosine; As, arsenic; AS3MT, arsenic(III)methyltransferase; CA, chromosomal aberration; CAK, CDK-activating kinase; Cd, cadmium; COX2, cytochrome c oxidase subunit II; Cu, copper; DNA, deoxyribonucleic acid; DSB, double strand break; EGR1, early growth response factor 1; ERCC2, excision repair cross-complementation group 2; Elisa, enzyme-linked immunosorbent assay; HPLC, high-performance liquid chromatography; hOGG1, human 8-oxoguanine DNA glycosylase 1; LC–MS/MS, liquid chromatography–tandem mass spectrometry; LINE-1, long interspersed nucleotide element-1; MN, micronucleus; *n*, number; N7-MeG, N7-methylguanine; Pb, lead; RT-PCR, reverse transcriptase-polymerase chain reaction; SOCS3, suppressor of cytokine signalling 3; WOSL, without skin lesions; WSL, with skin lesions; Zn, zinc.

3.1.2.3 | *Markers of epigenetic changes*

An extensive body of research highlights the epigenetic effects of iAs and its human metabolites. These effects have been shown in *in vitro* cell cultures and in *in vivo* animal models exposed to iAs (see comprehensive reviews from Bustaffa et al., 2014; Bhattacharjee et al., 2020; Cardoso et al., 2020). Here, we provide a brief overview of the most relevant studies published since 2009 on ex vivo data, obtained in human populations exposed to iAs primarily via contaminated drinking water.

Changes in DNA methylation have been the most extensively studied epigenetic alterations while changes in histone post-translational modifications (PTMs), chromatin structure and micro-RNA (miRNA) expression have begun to receive increasing attention.

S-adenosylmethionine (SAM) is the main donor of methyl groups during the methylation of both trivalent arsenic species and DNA. DNA demethylation events upon iAs exposure are therefore expected because of the high demand imposed on DNA methyltransferase (DNMT) enzymes during the arsenic biotransformation process while the occurrence of localised hypermethylation is more challenging to explain mechanistically (reviewed in Reichard & Puga, 2010). In recent years, technological advancements, including methylation-sensitive deep sequencing and microarrays, have allowed to characterise DNA methylation changes globally with sequence-level sensitivity. Epigenome-wide association studies (EWAS) have confirmed significant associations between in utero or adult life arsenic exposure and epigenetic dysregulation of global DNA methylation levels in blood. These EWAS include birth cohorts in the United States (Bozack et al., 2018; Green et al., 2016; Koestler et al., 2013), Bangladesh (Broberg et al., 2014; Cardenas, Houseman, et al., 2015; Gliga et al., 2018; Kile et al., 2014), Mexico (Rojas et al., 2015) and Taiwan (Kaushal et al., 2017), and studies in adults in the United States (Bozack et al., 2020; Liu et al., 2014), Bangladesh (Argos et al., 2015; Demanelis et al., 2019), Argentina (Ameer et al., 2017) and China (Guo et al., 2018) where exposure to iAs was primarily through drinking water. However, when analysed in detail, the results of these EWAS are largely inconsistent. As reviewed in Argos et al. (2015) and Bozack et al. (2020), the analysis of these studies shows great differences in the identity and number of CpGs identified and a very limited overlap between significant loci. In addition, some of these studies present small sample sizes resulting in limited statistical power particularly when interrogating a large number of CpG sites. Differences between the populations studied (e.g. age, sex, genetic background, nutritional status), the type of tissue examined (e.g. whole blood, cord blood), levels of iAs exposure (ranging from 23 μg/g creatinine [Kaushal et al., 2017] to > 302 μg/g creatinine urinary arsenic [Argos et al., 2015]), differential residual confounding and methods for quantifying DNA methylation might explain the limited replication among EWAS. Moreover, most studies lack data on functional changes in gene expression.

Most of the investigations into the effects of arsenicals on histone PTMs have been performed *in vitro*, in which changes in both global and gene-specific histone PTM patterns have been observed (reviewed in Bailey & Fry, 2012). Few studies have been conducted in humans. Changes in both methylation and acetylation of histones have been shown in association with arsenic exposure and these associations differed in a sex-specific manner (Chervona et al., 2012; Howe et al., 2016). A critical role of miRNA in iAs-induced tumorigenesis and carcinogenesis has been proposed based on many *in vitro* studies showing that dysregulated expression of miRNA occurs in arsenic-induced malignant cell transformation (reviewed in Cardoso et al., 2018). A few studies conducted in human populations confirm that arsenic species may modulate miRNA expression (Banerjee et al., 2017, 2019; Pérez-Vázquez et al., 2017; Zeng et al., 2019).

Despite the limitations presented above, some relevant aspects of iAs effects on the epigenome have emerged which are:

- Changes in DNA methylation are reported in populations exposed to a wide range of iAs levels including low levels (ranging from 23 to > 302 μg/g creatinine urinary As). It is of note that a genome-wide examination of cord blood isolated from newborns from a birth cohort in New Hampshire (Koestler et al., 2013) showed that low levels of prenatal As exposure (maternal urinary total As: median 4.1 μg/L, interquartile range 1.8–6.6) may affect the methylation of CpG islands. The DNA methylation status of several of these CpG islands had linear relationships with maternal urinary total inorganic As.
- There is a growing body of evidence indicating that iAs induces epigenetic dysregulation in a sex-specific manner (Broberg et al., 2014; Niedzwiecki et al., 2015; Pilsner et al., 2012). These alterations, if functional, may account for differential susceptibility to iAs-induced disease in males and females, a feature observed in various cohorts exposed to iAs.
- Several reports indicate that in utero arsenic exposure alters DNA methylation potentially altering fetal developmental programming, which may result in a higher risk of disease later in life. For instance, Rager et al. (2014), by analysing the methylation profile of newborn cord blood samples from a Mexican pregnancy cohort exposed to arsenic by drinking water (from 0.456 to 236 μg/L), identified 16 genes that showed a correlation between iAs-associated changes in DNA methylation and mRNA expression, seven of which were associated with differences in birth outcomes such as gestational age (GA) and head circumference (HC).
- iAs-induced DNA methylation changes have been detected in critical genes for disease development such as tumour suppressor genes and DNA repair genes (Bhattacharjee et al., 2018; Hossain et al., 2012; Intarasunanont et al., 2012, Kile et al., 2012; Lambrou et al., 2012, Majumdar et al., 2010; Pilsner et al., 2012; Smeester et al., 2011). However, in many cases, the functional consequences of these changes or their causal relationship with disease have not been established.
- Altered epigenetic marks can be metastable, and thus the effects of altered gene expression and disease risk have the potential to be transgenerational. In a rat model Nava-Rivera et al. (2021) have recently provided multigenerational (up to F3) evidence of changes in global DNA methylation in gonadal tissue upon parental arsenic chronic exposure.

It is of concern that iAs-induced epigenome alterations in the early life of an individual may affect the health of later generations.

The existing reports of epigenetic changes mediated by iAs in exposed human populations highlight the need for further research. In particular, the relevance of these alterations to disease risk in exposed populations needs to be addressed. The interplay between multiple epigenetic components and non-epigenetic alterations that likely work together to mediate the toxic effects of arsenicals also requires to be further investigated.

3.1.3 | Genotoxicity

As summarised in the previous EFSA Opinion (EFSA CONTAM Panel, 2009) the evidence available at that time on the genotoxic effects of iAs included:

- negative mutation assays in bacterial cells; weak (or insignificant) mutagenic activity in mammalian cells *in vitro*;
- clastogenic (micronuclei, chromosomal aberrations, sister chromatid exchanges) and aneugenic effects mostly at high doses in mammalian cells *in vitro*;
- induction of DNA damage (DNA strand breaks, oxidative base modifications and apurinic/apyrimidinic (AP) sites) in mammalian cells *in vitro*;
- enhancement of genotoxicity, mutagenicity and clastogenicity of other DNA damaging agents in mammalian cells *in vitro* by interfering with DNA damage response processes;
- *in vivo* induction of micronuclei and chromosomal aberrations in mouse peripheral blood lymphocytes and in mouse bone marrow.

The data published since 2009 mainly refer to further analysis of DNA damage and clastogenic effects induced by iAs both *in vitro* and *in vivo*. The findings are summarised below, and further details are presented in Table 8 (*in vitro* studies) and Table 9 (*in vivo* studies).

3.1.3.1 | *In vitro genotoxicity*

Inorganic arsenic species

Most studies published after 2009 deal with the characterisation of DNA damage induced by iAs species. The comet assay has been widely applied because it is a rapid and sensitive technique able to measure multiple classes of DNA damage in individual cells. The standard alkaline comet assay, that allows to detect single (SSB) and double-strand breaks (DSB) and alkali-labile sites (apurinic/apyrimidinic sites), has been used in a variety of cells in culture of rodent or human origin, either primary or transformed. In general, arsenite and arsenate were confirmed as good inducers of DNA breaks and alkali-labile sites at subtoxic concentrations (Benhusein et al., 2016; Catanzaro et al., 2010; Jiang et al., 2013; Li et al., 2014; Naranmandura, Carew, et al., 2011; Singh et al., 2011; Xu, McClain, et al., 2016). The induction of oxidative DNA base damage by iAs was further supported by studies where the formamidopyrimidine-DNA glycosylase (Fpg)-modified comet assay was associated with the use of mouse cell lines defective in the DNA glycosylase specific for removal of 8-oxoguanine, OGG1 (Bach et al., 2014, 2015). The use of Fpg in the comet assay allows for the detection of 8-oxoguanine in addition to certain imidazole ring-opened purines and abasic sites (Karakaya et al., 1997). From these studies, OGG1 emerged as a relevant DNA repair enzyme for arsenic-induced toxicity and genotoxicity. In addition, in OGG1 defective cells chronically exposed to arsenic, the overexpression of the metabolising enzyme arsenic-methyltransferase (As3MT) was identified as an adaptive mechanism that protects from cell death but leads to accumulation of high levels of DNA damage due to their repair defect (Bach et al., 2015). The alkaline comet assay does not distinguish SSB from DSB. The induction of DSB by iAs was suggested by some studies where the level of phosphorylated H2AX, measured either by western blotting or by the foci assay, was used as a marker of DSB (Kopp et al., 2018; Okamura & Nohara, 2016; Xie et al., 2014). The induction of γH2AX foci can result from different types of DNA lesions including DNA adducts, abasic sites, strand breaks and replication or transcription blocking lesions (Watters et al., 2009). In 2009, Ying et al., provided unequivocal evidence that arsenite induces DSB by confirming the increase in the number of γH2AX foci with the analysis of DSB by pulse field gel electrophoresis (PFGE) that allows to look directly to DSB. Another confirming evidence was presented by Xie et al. (2014) by using the neutral comet assay that detects only DSB (Xie et al., 2014). DSB are the most lethal DNA lesions, and it is of note that arsenic induces this type of damage at subtoxic concentrations as low as 5 μM (Xie et al., 2014; Ying et al., 2009). In addition, Ying et al. (2009) showed that these DSB are replication-dependent and homologous recombination (HR) is required for their repair. Based on these findings, they hypothesised that these breaks arise from collapse of replication forks due to the large number of lesions and inhibition of DNA repair induced by arsenic. A study in yeast (Litwin et al., 2013) confirms the induction of DSB by arsenic and shows that arsenic may also cause DSBs independent of replication and transcription. On the basis of these findings the authors suggested 'a direct genotoxic mode of arsenic action'.

The source and mechanisms of ROS production by iAs have been addressed in some studies (Catanzaro et al., 2010; Ebert et al., 2014; Li et al., 2014; Naranmandura, Carew, et al., 2011). In general, long-term cell exposure and/or high concentrations

of sodium arsenite were required to measure a significant increase in the levels of intracellular ROS. In line with these findings, no production of ROS was detected in rat liver submitochondrial particles and liver cells (RLC-16) upon exposure to low levels of arsenite[l] (Naranmandura, Xu, et al., 2011). Even if there is no direct evidence of arsenic-induced ROS at subtoxic doses, indirect evidence has been reported. Arsenic was shown to increase glutathione levels upon short-term exposure to low concentrations (Benhusein et al., 2016; Naranmandura, Carew, et al., 2011). Activation of p38/Nrf2 pathway and upregulation of glutamate-cysteine ligase catalytic subunit (GCLC) expression have been proposed as the underlying mechanisms (reviewed in Ran et al., 2020). While these *in vitro* studies confirm that arsenic exposure has a regulatory role on glutathione synthesis they are not in agreement with *in vivo* studies showing that arsenic exposure can reduce glutamate and cysteine levels and inhibit glutathione synthesis (reviewed in Ran et al., 2020). Further experiments are required to assess the regulatory role of arsenic on glutathione synthesis.

Arsenic can also induce generation of reactive nitrogen species (RNS) (reviewed in Gurr et al., 2003). The mechanisms involved are still poorly understood. Recently, As-induction of peroxynitrite through superoxide and nitric oxide production, has been shown to contribute to As-induced DNA repair inhibition (Zhou et al., 2019).

The induction of cell cycle alterations and perturbations of mitosis with associated aneuploidy and/or chromosomal damage (CA and MN) by iAs was confirmed in a wide repertoire of immortalised cell lines (Ganapathy et al., 2019; Jiang et al., 2013; Leffers et al., 2013; Unterberg et al., 2014) and in primary fibroblasts but not in primary epithelial cells (Xie et al., 2014). Clastogenic effects were reported at subtoxic doses (Ganapathy et al., 2019; Leffers et al., 2013; Unterberg et al., 2014).

Several lines of evidence indicate that arsenic exposure leads to compromised DNA repair (reviewed in Tam et al., 2020). This is likely to account for the enhancement by arsenite of the mutagenicity of other DNA-damaging agents. In the last decade the molecular mechanisms of arsenic-induced disruption of DNA repair have been further investigated. Besides the nucleotide excision repair (NER), the first DNA repair pathway shown to be inhibited by arsenic and its metabolites, the base excision repair (BER) and several players of the DNA damage response (DDR) were shown to be additional targets of arsenicals. Nollen et al. (2009) showed that in human skin fibroblasts arsenite affects the expression of the DNA damage recognition protein, XPC, resulting in decreased protein level and diminished assembly of the NER machinery within the cells after local UVC-irradiation. In line with this finding Holcomb et al. (2017) showed that in *in vitro* cultures of human fibroblasts and mouse keratinocytes arsenite exerts a concentration-dependent inhibition of the removal of UV photoproducts and a significant reduction of XPC protein levels. Cells exposure to arsenite was shown to decrease the activity, expression or protein level of key players in BER such as the DNA glycosylase, OGG1, DNA ligase IIIa and XRCC1 as analysed in cell extracts (Ebert et al., 2011). In addition, the main DNA polymerase of BER, Pol β, was shown to play an important role in repairing arsenite-induced DNA damage and maintaining chromosomal integrity (Lai et al., 2011). Global Poly(AP-ribosyl)ation, predominantly mediated by PARP1 and critical for immediate initiation of DDR, was previously shown to be markedly inhibited by arsenite (Hartwig et al., 2003). Ding et al. (2009) showed that arsenite suppresses the repair of UVR-induced 8-oxoguanine, inhibits PARP-1 activity in cells in culture and interacts with the PARP-1 zinc finger domain (Ding et al., 2009). The authors proposed that arsenite-induced inhibition of PARP-1 activity by contributing to oxidative DNA damage might account for the reported co-carcinogenic activities of arsenic in UVR-induced skin carcinogenesis. Arsenite was also shown to compromise ubiquitination of FANCD2, a key player of inter-strand DNA cross link (ICL) repair, thus causing diminished recruitment of FANCD2 to ICL DNA damaged sites in the cells and inhibition of DNA ICL repair in arsenite-treated cells in culture as shown by sensitisation to DNA ICL agents (Jiang et al., 2017). The abilities of arsenic to disrupt zinc fingers, to dysregulate ubiquitination and suppress gene expression may all negatively impact on the DDR and potentially contribute to the enhancement of mutagenic and carcinogenic effects by arsenicals (reviewed in Muenyi et al., 2015).

Human metabolites of inorganic arsenic species

Our current understanding of the significance of iAs biomethylation indicates that at least some of the toxic effects of iAs exposure depend on formation of methylated metabolites containing trivalent arsenic. As summarised in the previous EFSA Opinion (EFSA CONTAM Panel, 2009), several studies indicate that the trivalent methylated arsenic species are more cyto- and genotoxic than both their pentavalent counterparts and the iAs species. Similarly, they are more potent inhibitors of the activities of GSH reductase and of thioredoxin reductase. The genotoxicity of methylated arsenic species does not involve direct covalent interaction with DNA. Indirect processes such as generation of ROS and inhibition of DNA repair might be the underlying mechanisms (reviewed in Thomas et al., 2001 and Thomas, 2021). Since 2009, additional evidence has been obtained regarding the generation of free radicals by these arsenical species. In rat liver RLC-16 cells, MMA(III) generates ROS primarily in mitochondria likely accounting for its higher cytotoxic effect as compared to DMA(III) that generates ROS in other organelles (Naranmandura, Xu, et al., 2011). This contrasts with the lack of generation of ROS by iAs(III) that is less cytotoxic in this cell system. Similar results were reported by the same group (Rehman et al., 2014) in human myeloid leukaemia HL-60 cells where MMA(III) and DMA(III), but not iAs(III), increased oxidative stress and induced loss of mitochondrial membrane potential and apoptosis. Consistent with these data ROS generation by MMA(III) was confirmed in a variety of cells (Dopp et al., 2010; Tokar et al., 2013; Xu et al., 2017). The decreasing order of cytotoxicity from trivalent to pentavalent arsenic species, MMA(III) ≥ DMA(III) > iAs(III) ≫ iAs(V) ≫ DMA(V) > MMA(V), was confirmed in two human cell lines, on the basis of the 24 h IC_{50} values, by using real time cell-electronic sensing analysis on a large number of trivalent and pentavalent arsenic species (Moe et al., 2016). MMA(III) toxicity was also significantly higher than that of iAs(III) in human brain cells *in vitro* (Yoshinaga-Sakurai et al., 2020).

Ebert et al. (2011) addressed the issue of potential interference of methylated arsenical species with DNA repair enzymes showing that they affect BER by several mechanisms. The analysis of cell extracts from treated human lung cells showed that OGG1 activity was mostly affected by DMA(V), DNA ligase III protein level by arsenite and XRCC1 protein content by MMA(V). The trivalent methylated metabolites exerted strong effects on the investigated BER proteins but only at cytotoxic concentrations.

To understand the role of speciation and methylation in the toxicity of arsenic, studies were conducted with arsenic methylation proficient and deficient cell lines (Dopp et al., 2010). The non-methylating UROtsa cells were shown to accumulate higher amounts of MMA(III) in the cytosol and to be less prone to arsenic-induced cytotoxicity than the methylating hepatocytes where arsenic compounds are more distributed into the cell organelles. Induction of DNA breaks was detected in both cell types at concentrations as low as 5 μM MMA(III). The authors noted that this concentration lies within the concentration range of arsenic in urine in humans (5 μM iAs (III) = 650 μg/L). A correlation between DNA damage induction and free radical formation was reported although a significant increase of DNA breaks was already detected at relatively low ROS levels. The use of the hOGG1-modified comet assay confirmed the induction of guanine base oxidation upon MMA(III) exposure of mouse bone marrow, spleen, thymus cells (Xu, McClain, et al., 2016) and activation of the DNA damage response, as detected by increased γH2AX fluorescence, in mouse thymus cells (Xu et al., 2017). No significant induction of DNA breaks was reported in HepG2 liver cells after exposure to DMA(V) (Benhusein et al., 2016) in line with a lower DNA-damaging capacity by pentavalent species. The clastogenic activity of methylated arsenic species, MMA(III), MMA(V) and DMA(V), was confirmed by the micronucleus assay at non cytotoxic/slightly cytotoxic concentrations (Bartel et al., 2011; Meyer et al., 2015) and resulted to be higher than that of iAs (Bartel et al., 2011). Interestingly, when MMA(III)-induced chromosomal aberrations were measured in freshly prepared splenic lymphocyte cultures upon exposure in different cell cycle phases (Kligerman et al., 2010), a significant increase was only detected when cells were treated in late G1- or S-phase but not in G0- or G1-phase. The authors concluded that MMA(III)-induced cytogenetic damage is short-lived.

Among methylated As metabolites, thio-DMA(V) was the latest to be identified as a human metabolite and shown to be present in food. Consequently, limited data on toxicity were available until 2009. Bartel et al. (2011) carried out a toxicological characterisation of thio-DMA(V) in cultured human lung A549 cells showing that it is highly cytotoxic, does not induce DNA breaks and produces a small but significant increase of bi- and multi-nucleated cells at slightly cytotoxic doses. Increased frequency of bi- and multi-nucleated cells was also reported by Leffers et al. (2013) in UROtsa cells for both thio-DMA(V) and DMA(V) at incipient cytotoxic concentrations, indicating cell cycle arrest and disturbance in mitosis. Neither increase of micronuclei frequency nor of bi- or multi-nucleated cells was reported by Unterberg et al. (2014) after long exposure times (from 7 to 21 days) of UROtsa cells to subtoxic doses of thio-DMA(V), while arsenite was confirmed to be clastogenic at subtoxic doses. The toxic mode of action of thio-DMA(V) was further characterised in human bladder cells (Ebert et al., 2014) confirming its high cytotoxicity and the lack of induction of DNA breaks and oxidative base modifications. Interestingly, thio-DMA(V) specifically inhibited H_2O_2-induced cellular poly(ADP-ribosyl)ation (at a 35,000-fold lower concentration than arsenite), suggesting that, by inhibiting DNA repair, it might promote genotoxicity. Thio-DMA(V) was also among the most toxic arsenic compounds in human bladder cancer EJ-1 cells, similar to trivalent DMA(III) (Naranmandura, Carew, et al., 2011). Cellular exposure to thio-DMA(V) resulted in reduced protein expression of p53 and p21, increased DNA breaks, as measured by the alkaline comet assay, and increased intracellular hydroxyl radicals. The authors concluded that *in vitro* thio-DMA(V) is the most toxicologically potent arsenic species, and it might be relevant to arsenic-induced carcinogenicity in the urinary bladder.

Cell transformation

Previous work showed that MMA(III) and DMA(III) can transform human urothelial cells in culture (Bredfeldt et al., 2006). Waalkes' laboratory confirmed the oncogenic potential of MMA(III) in a cell transformation assay in both methylation-deficient (prostate) and proficient (liver) cells that acquired cancer cell characteristics concurrently with oxidative stress induction during chronic MMA(III) exposure (up to 30 weeks) (Tokar et al., 2013). In a previous work the same laboratory (Kojima et al., 2009) showed that iAs can also induce a malignant phenotype in prostate methylation-deficient cells but without generation of oxidative damage while MMA(III) does so more rapidly and with ROS induction, suggesting different underlying mechanisms. Several studies report that cell transformation induced by long-term arsenic exposure involves epithelial-to-mesenchymal transition (EMT) (Chang & Singh, 2019; Wang et al., 2013), which plays a role in tumour progression and metastasis.

Table 8 provides an overview of the *in vitro* genotoxicity tests with arsenic.

TABLE 8 *In vitro* genotoxicity tests with arsenic species.

Reference	Test system	Cells	Concentration/treatment time	Results	Additional information
Ding et al. (2009)	8-oxodG measurement by HPLC-ED and in situ immune fluorescence; PARP-1 activity by in situ immune fluorescence	Human keratinocyte cell line (HaCaT)	Sodium arsenite 2 μM (24 h)	Enhancement of UVR-induced 8-oxodG and suppression of UVR-induced PARP-1 activation (lowest dose tested 0.2 μM)	No data on cytotoxicity. Exposure to 1–3 μM arsenite: no increase of 8-oxodG Inhibition of PARP-1 activity significantly increases UVR-induced 8-OHdG formation Mass spectrometry analysis reveals that arsenite can occupy the first zinc finger of PARP-1 (PARPzf)
Nollen et al. (2009)	Western blotting and gene expression analysis of cell extracts	Tert-immortalised human diploid skin fibroblasts (VH10hTert)	Sodium arsenite 1, 5, 10 μM (24 h) MMA(III) 0.1, 1, 1.3 μM (24 h)	Inhibition of XPC expression and protein levels for both arsenicals. Diminished association of XPC to sites of local UVC damage Viability > 80%	Cell viability: cell number and colony forming ability Inhibition of XPE expression
Ying et al. (2009)	γ-H2AX foci Pulse field gel electrophoresis (PFGE)	Chinese hamster cells (AA8)	Sodium arsenite from 5 to 50 μM (24 h)	**Positive:** concentrations as low as 5 μM could induce gH2AX foci (IC50 = 18.6 μM)	Cell viability: clonogenic assay 50 μM arsenite produces a similar amount of DSBs as a 6 Gy dose of ionising radiation as estimated by PFGE. The occurrence of homologous recombination (HR) confirmed by Rad 51 foci and cell recombination assay HR defective cells are hypersensitive to arsenite Arsenite inhibits SSB repair
Catanzaro et al. (2010)	Alkaline comet assay	Primary cultures of rat astrocytes	Sodium arsenite 2.5, 5, 10, 30 μM (24 h)	**Positive**: significant increase of DNA breaks (tail length) at 10 μM for 24 h (> 70% viability)	Cell viability: trypan blue exclusion test Cells treated with 30 μM for 24 h were all ghost (small heads and large tails), likely apoptotic cells Absence of ROS production by CM-H_2DCFDA
Dopp et al. (2010)	Alkaline comet assay	Non-methylating cells: UROtsa transformed human urothelial cells; methylating cells: primary human hepatocytes	As(III), MMA(III), iAs(V), MMA(V) for 1 h; range of doses tested not reported	**Positive:** significant induction of DNA breaks (tail moment): primary human hepatocytes at 5 μM MMA(III) (LC50 = 20μM) and 50 μM iAs(III) (not cytotoxic up to 5 mM); UROtsa cells at 5 μM MMA(III) (LC50 = 83μM) and 5 μM iAs(III) (LC50 = 5000 μM) for 1 h **Negative:** in human hepatocytes iAs(V) and MMA(V) did not induce DNA breaks at doses up to 500 μM; they were not tested in urothelial cells	Cell viability: trypan blue exclusion test Induction of free radicals, measured by the thiobarbituric acid test, showed cell-type specific differences
Kligerman et al. (2010)	Chromosome aberration assay	Freshly prepared splenic lymphocyte cultures	MMA(III), 0.3 and 0.5 μM (12–17 h)	**Positive:** significant increase of CA at both concentrations. MMA(III) (0.5 μM) positive when cells were treated in late G1- or S-phase; negative when treatment was confined to the G_0- or G_1-phase of the cell cycle	Replication index indicates that both concentrations are cytotoxic DNA lesions produced by MMA(III)^I that can lead to cytogenetic damage are short-lived

(Continues)

TABLE 8 (Continued)

Reference	Test system	Cells	Concentration/treatment time	Results	Additional information
Bartel et al. (2011)	MN assay Alkaline unwinding	Human A549 lung cells	Arsenite, MMA(III), DMA(III), MMA(V), DMA(V), thio-DMA(V) (1, 24 h)	**Positive:** significant increase of MN frequency at non- cytotoxic/slightly cytotoxic concentrations for 24 h (< IC70): MMA(III) (0.5, 1 μM), thio-DMA(V) (5 μM), MMA(V) (250 μM) and DMA(V) (250 μM) At cytotoxic concentrations significant increases also for arsenite (≥ 50 μM for 24 h) (≥ IC70) **Negative**: thio-DMA(V) did not induce DNA strand breaks up to high cytotoxic doses (100 μM for 1 h, 75 μM for 24 h)	Cell viability: cell number and colony forming ability. Based on the effective cellular arsenic concentrations, the cytotoxic order was: thio-DMA(V) ~ arsenite ~ MMA(III) > DMA(III) MMA(V) ~ DMA(V) Thio-DMA(V) and especially DMA(III) increased the formation of multinucleated cells (significant effects at cytotoxic concentrations, 15 μM, IC70 = 7.2 μM)
Ebert et al. (2011)	DNA repair enzymes cleavage assay, gene expression and western blotting of cell extracts	A549 human epithelial lung adenocarcinoma cells	Arsenite: up to 100 μM DMA(III): up to 7.5 μM MMA(III): up to 7.5 μM MMA(V): up to 500 μM DMA(V): up to 500 μM 24 h exposure followed by preparation of cell extracts	Specific inhibitory effects on OGG1 activity by DMA(V), on LigIII by arsenite, on XRCC1 by MMA(V) (starting at ≥ 3.2 μM cellular arsenic; cytotoxicity < 30%); the trivalent methylated metabolites effective only at cytotoxic concentrations	Cytotoxicity, cell number and colony forming ability Cytotoxic effects correlate with cellular uptake in the decreasing order DMA(III), MMA(III), arsenite, MMA(V), DMA(V)
Lai et al. (2011)	Alkaline comet assay Micronucleus assay	Mouse embryonic fibroblasts (MEF) Pol $\beta^{+/+}$ and Pol $\beta^{-/-}$	Sodium arsenite: 2.5, 5, 10, μM (24 h)	**Positive:** accumulation of DNA breaks (comet rate%) at 2.5, 5 and 10 μM in both cell lines, more pronounced in Pol $\beta^{-/-}$cells **Positive:** significantly increased number of micronuclei at 2,5, 5 and 10 μM in both cell lines, more pronounced in Pol $\beta^{-/-}$ cells Viability > 80% Pol $\beta^{+/+}$ IC_{50} = 58.3 μM Pol $\beta^{-/-}$ IC_{50} = 46.6 μM	Cell viability: MTT assay Comet rate (%) = (total number of cells with tails/ total number of counted cells) x 100. Slower DNA repair kinetics in Pol $\beta^{-/-}$ cells
Naranmandura, Xu, et al. (2011)	Intracellular ROS generation measured by oxidation-sensitive fluorescent probe (DCFH-DA)	At liver RLC-16 cells	MMA(III) (IC50 = 1 μM), DMA(III) (IC50 = 2 μM), iAsIII (IC_{50} = 18 μM) (24 h)	MMA(III), ROS generated primarily in mitochondria; DMA(III), ROS generation in other organelles; iAS(III), no ROS generation	Cytotoxicity: MMA(III) (IC50 = 1μM) > DMA(III) (IC50 = 2μM) > iAs(III) (IC50 = 18 μM) Mitochondria are the primary target for MMA(III)-induced cytotoxicity
Naranmandura, Carew, et al. (2011)	Alkaline comet assay	Human bladder cancer cells (EJ-1)	iAsIII (75 μM), DMA(III) (12 μM), Thio-DMA(V) (here named DMMTA(V)) (17 μM) (3–6-24 h). All tested at IC50	**Positive**: iAs(III), significant increase of DNA breaks (tail length) after 6 and 24 h exposure; DMA(III) and thio-DMA(V) after 3,6 and 24 h exposure; all tested at IC_{50} (MTS assay)	Concomitant measurement of ROS levels: iAs(III), increase only after 24 h exposure; DMA(III) and thio-DMA(V) after 3, 6, 24 h exposure iAs(III), increased GSH levels; DMA(III) and thio-DMA(V), reduction of GSH(5μM for 24 h). iAs(III) increased expression of p21 and p53; DMA(III) and thio-DMA(V) decreased expression of p21 and p53 (dose dependent)

TABLE 8 (Continued)

Reference	Test system	Cells	Concentration/treatment time	Results	Additional information
Singh et al. (2011)	Alkaline comet assay Mitochondrial DNA mutation assay by multiplex PCR	Immortalised normal prostate epithelial cells (RWPE-1)	Sodium arsenite: 100 pg/mL (90 days)	**Positive:** increased DNA breaks (tail length) as compared to control cells (no tails) No major deletions or insertions in the sequence of mitochondrial DNA; insertion mutation (a 'G') in the mitochondrial ATPase gene	Cell viability: cell count Chronic exposure to 100 pg/mL: Increase in cell proliferation (cells become resistant to As)
Jiang et al. (2013)	Alkaline comet assay Micronucleus assay	Human lung adenocarcinoma cells (A549)	Sodium arsenite: 5, 10, 15, 20, 25 μM (24 h)	**Positive:** significant increase of DNA breaks (tail moment) in the full concentration range. (cell viability > 70% up to 15μM) **Positive:** significant ($p < 0.05$) increase of MN frequency from 10 μM (cell viability > 70%)	Cell viability measured by the MTT assay and Trypan blue exclusion. Induction of cell cycle arrest at G2/M phase and apoptosis.
Leffers et al. (2013)	Micronucleus assay	Immortalised human urothelial cells (UROtsa)	Sodium arsenite: 0.1, 0.5, 1, 2, 3.5 μM (48 h) DMA(V): 50, 100, 170, 200 μM (48 h) Thio-DMA(V): 0.1, 0.5, 1, 2 μM (48 h)	**Positive:** Arsenite: significant increase ($p < 0.001$) of induced MN from 0.5 to 3.5 μM (including a subtoxic concentration range) DMA(V) and thio-DMA(V): significant increase ($p < 0.001$) of bi- and multi-nucleated cells from 100 to 200 μM (DMA(V)) and at 2 μM (thio-DMA(V)), at incipient cytotoxic concentrations. 30% reduction of CFA: Arsenite 2 μM; DMA(V) 150 μM; thio-DMA(V) 1.5 μM	Cell viability: cell number and colony forming ability. Arsenite: No increase in the number of bi- or multinucleated cells.
Tokar et al. (2013)	Cell transformation (agar assay and invasion assay) ROS generation by the immuno-spin trapping analysis of protein radicals (immunochemical quantification)	Arsenic methylation-proficient TRL1215 liver cell line and methylation-deficient RWPE1 prostate cell line	MMA(III): 0.25–1.0 μM (20 weeks or more)	**Positive:** increased matrix metalloproteinase secretion, colony formation and invasion at 18–22 weeks in both cell lines	Similar alterations in arsenic and oxidative stress adaptation factors in both cell lines MMA(III) and iAs cause an acquired malignant phenotype in methylation-deficient cells, yet iAs does not induce oxidative DNA damage
Bach et al. (2014)	FPG-modified comet assay	Mouse embryo fibroblasts (MEF) *Ogg1*$^{+/+}$ and *Ogg1*$^{-/-}$	Sodium arsenite: Short-term studies: up to 20 μM for 24 or 48 h; Long-term studies: 0.5, 1 and 2 μM for up to 17 weeks	**Positive**: significant levels of oxidative DNA lesions (%DNA in tail) in *Ogg1*$^{-/-}$ cells at subtoxic concentrations (> 80% survival) in both short-term (5 μM for 1.5, 3, 24 h) and long-term (0.5 μM for 4, 10, 17 weeks) studies; in *Ogg1* wt at 20 μM for 24 h and 1 and 2 μM for 17 weeks	Cell viability: Beckman counter method (up to 80 μM for 24 or 48 h) Analysis of arsenic metabolism in the cells; similar in MEF wt and *Ogg1*$^{-/-}$

(Continues)

TABLE 8 (Continued)

Reference	Test system	Cells	Concentration/treatment time	Results	Additional information
Ebert et al. (2014)	Alkaline unwinding with FPG	Immortalised human urothelial cells (UROtsa)	Sodium arsenite and thio-DMA(V): up to 5 μM (1, 24 and 48 h)	**Negative:** arsenite and thio-DMA(V) significant increase of DNA breaks only at cytotoxic concentration (5 μM) Arsenite and thio-DMA(V): CFA, IC70 = 5.2 μM	Cell viability: cell number and colony forming ability Inhibition of damage-induced poly (ADP)-ribosylation: arsenite at high concentration (3.5 μM), thio-DMA(V): at 35,000-fold lower concentration Thio-DMAV or arsenite induced significant S phase and G2/M phase arrest; higher induction of apoptosis by thio-DMA(V)
Li et al. (2014)	Alkaline comet assay	Rat pheochromocytoma cell line (PC12)	Sodium arsenite: 5, 20 μM for 24 h	**Positive:** increase of DNA breaks (%tail DNA) at both doses, dose-related (cell viability 5 μM, 97%; 20 μM, 81%)	Cell viability: MTT assay Increased ROS levels
Rehman et al. (2014)	Intracellular ROS generation measured by oxidation-sensitive fluorescent probe (DCFH-DA)	Human myeloid leukaemia HL-60 cells	MMA(III), DMA(III) and iAs(III): (1 μM for 12 h) MMA(III): (IC50 3 μM) DMA(III): (IC50 2 μM) iAs(III): (IC50 10 μM)	MMA(III) and DMA(III) but not iAs(III) increased oxidative stress, loss of mitochondrial membrane potential and apoptosis	
Unterberg et al. (2014)	Micronucleus assay	Non-tumorigenic urothelial cell line (UROtsa)	Arsenite and thio-DMA(V): 0.005, 0.01, 0.1, 1, 10, 100, 250, 500 nM (7, 14 and 21 days)	**Positive:** Arsenite, 100 nM, 14 days and 250 and 500 nM all exposure times (100 nM subtoxic dose, > 80% CFA). Thio-DMA(V): negative in the full concentration range. No cytotoxicity up to 500 μM	Cell viability: cell number and colony forming ability. Induction of global DNA methylation
Xie et al. (2014)	Chromosomal aberration assay Neutral comet assay and gH2AX foci forming assay	Human primary bronchial fibroblast (NHBF) and epithelial (NHBE) cells.	Sodium arsenite: 0.5, 1, 5, 10 μM (24 and 120 h)	**Positive:** increase in chromosome damage in fibroblasts but not in epithelial cells, significant at 5, 10 μM with both exposure times High cytotoxicity at both concentrations (≤ 50% CFA) Induction of aneuploidy and mitotic abnormalities in fibroblasts only. **Positive:** induction of DNA double strand breaks in both fibroblast and epithelial cells Range 1–10 μM, 24 h, 120 h) including sub-toxic doses in the case of epithelial cells	Cell viability: colony forming ability
Meyer et al. (2015)	Micronucleus assay	Human liver HepG2 cells	DMA(V): 0, 1, 10, 100, 500 μM (48 h)	**Positive:** significant increase of MN at 100 and 500 μM, IC70 155 μM	
Benhusein et al. (2016)	Alkaline comet assay	HepG2 Liver Cells	Arsenate, sodium arsenite and DMA(V): 10 μM for 24 h	**Positive**: increase of DNA breaks (tail moment) with arsenate and arsenite **Negative**: with DMA(V) Cell viability: 85%–90%	Cell viability: trypan blue exclusion test Increase of cellular levels of glutathione with arsenate and arsenite

TABLE 8 (Continued)

Reference	Test system	Cells	Concentration/treatment time	Results	Additional information
Okamura and Nohara et al. (2016)	γ-H2AX by western blotting	Mouse B lymphoma cells (A20)	Sodium arsenite: 10 μM (up to 14 days)	**Positive**: γ-H2AX was increased following exposure for 8 and 14 days	Activation of the p53-p21 pathway. Decreased expression of DNA repair genes. Increased expression of cytidine deaminases. Increased Bcl6 mutations (point mutations, deletions and insertions). Induction of senescence
Xu et al. (2016)	Alkaline and hOGG1-modified (FLARE) comet assay	Isolated mouse bone marrow, spleen, thymus cells	Sodium arsenite or MMA(III): 5, 50 and 500 nM (4 h)	**Positive**: Arsenite: bone marrow cells significant increase of DNA breaks (% DNA in tail) from 5 to 500 nM, spleen and thymus cells only at 500 nM. MMA(III): cells from all the three organs showed significant increase of DNA breaks starting at 5 μM	No data on cytotoxicity MMA(III) is more genotoxic than iAs(III) *in vitro*
Holcomb et al. (2017)	NER capacity by slot-blot assay	Human lung fibroblasts (IMR-90 cells) and primary mouse keratinocytes	Sodium arsenite: 10–20-40 μM (24 h)	Concentration-dependent inhibition of the removal of 6–4 PPs and CPDs in both cell types Significant reduction of XPC protein levels. Significant effects at 20 and 40 μM Viability: 10 μM ~ 80%; 20 μM ~ 70%; 40 μM ~ 50% (from the graph)	Cell viability: trypan blue exclusion test
Jiang et al. (2017)	*In vitro* binding assay, streptavidin agarose affinity assay, western blotting, fluorescence microscopy, mass spectrometry, clonogenic survival	HEK293T human embryonic kidney epithelial cells and HeLa cell	Sodium arsenite: 5 μM (cell exposure for 24 h)	Arsenite binding to FANCL *in vitro* and in cells. Reduction of FANCD2 recruitment to chromatin and DNA damage sites in cells upon ICL induction. Increased cell sensitivity toward ICL-inducing agents	No data on arsenite cytotoxicity are presented
Xu et al. (2017)	Alkaline comet assay and γ-H2AX foci forming assay ROS detection by flow cytometry	Isolated mouse thymus cells. DN, double negative, do not express CD4 or CD8; DP, double positive, express both cell markers (obtained by cell sorting)	MMA(III): 5, 50 and 500 nM (18 h)	**Positive**: MMA(III) significant increase of DNA breaks (%DNA in tail) in DN cells in the whole concentration range; DP cells at 50 and 500 nM. Significant increase of gH2AX fluorescence and reactive oxygen species level (DN cells, 50 and 500 nM; DP cells, 500 nM)	Cell viability: MTS assay. No quantitative data provided. Low (5 nM, ~ 80% survival) to moderate (500 nM ~ 50% srv)) cytotoxicity (from the graph)

(Continues)

TABLE 8 (Continued)

Reference	Test system	Cells	Concentration/treatment time	Results	Additional information
Kopp et al. (2018)	γ-H2AX by western blotting	Human hepatoblastoma cells (HepG2) Human epithelial colorectal adenocarcinoma cells (LS-174T)	Sodium arsenite: 1, 10, 25, 50, 75, 100 μM (24 h) Arsenic pentoxide: 10, 50, 100, 250, 500 μM (24 h)	**Positive:** significant increase ($p < 0.01$) of gH2AX levels at subtoxic doses for both arsenicals Arsenite: in HepG2 cells, LOAEC 25 μM, %RCC = 92; LS-174T, LOAEC 10 μM, %RCC = 100. Arsenic pentoxide: in HepG2 cells, LOAEC 250 μM, %RCC = 88; LS-174T: LOAEC 100 uM, %RCC = 96	Cell viability: comparison of DNA content (related to the number of cells) in treated versus control cells and expressed as relative cell count, %RCC
Ganapathy et al. (2019)	Aneuploidy test	Human lung epithelial BEAS-2B cells and keratinocytes	Sodium arsenite: 0.5 μM (2 months)	**Positive:** significant increase of cells with aneuploidy (~2% in untreated cells versus ~14% in arsenite-treated cells)	No data on cytotoxicity are presented. 100 cells scored for each treatment, 5 experiments per point Perturbation of mitosis via activation of Akt and upregulation of Plk1. Suppression of Akt or Plk1 inhibited aneuploidy

Abbreviations: 8-OHdG, 8-hydroxy-2′-deoxyguanosine; 8-oxodG, 8-hydroxydeoxyguanosine; ADP, adenosine diphosphate; Akt, protein kinase B or PKB; As(III), arsenite; BEAS-2B, bronchial epithelial airway sensitive-2B (normal human bronchial epithelial cell line); CA, chromosomal aberration; CD4 / CD8, cluster of differentiation 4 and 8; CFA, colony-forming ability; CM-H_2DCFDA, chloromethyl derivative of H_2DCFDA; CPD, cyclobutane pyrimidine dimer; DCFH-DA, 2′,7′ dichloro-dihydrofluorescein diacetate; DMA(III), dimethylarsinous acid; DMA(V), dimethylarsinic acid; DN, double negative; DNA, deoxyribonucleic acid; DP, double positive; DSB, double-strand break; FANCD2, fanconi anaemia complementation group D2; FANCL, fanconi anaemia complementation group L; FLARE, fragment length analysis using repair enzymes; FPG, formamidopyrimidine DNA glycosylase; gH2AX, serine139-phosphorylated histone H2AX; GSH, glutathione; Gy, Grey; HaCaT, human epidermal keratinocyte line; HeLa cells, human cell line named after Henrietta Lacks; HEK293T, human embryonic kidney epithelial cells; HepG2, human hepatoblastoma cells; hOGG1, human 8-oxoguanine DNA glycosylase 1; HPLC-ED, high-performance liquid chromatography with electrochemical detection; HR, homologous recombination; iAs, inorganic arsenic; iAs(V), arsenate; IC_{50}, inhibitory concentration 50%; ICL, inter-strand DNA cross-link; IMR-90 cells, human lung fibroblasts; LC50, lethal dose killing 50% of the animals; LigIII, DNA ligase III; LOAEC, lowest-observed-adverse-effect-concentration; LS-174T, human epithelial colorectal adenocarcinoma cell; MEF, mouse embryo fibroblast; MMA(III), monomethylarsonous acid; MMA(V), monomethylarsonic acid; MN, micronucleus; MTS, 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide; NER, nucleotide excision repair; NHBE, normal human bronchial epithelial cells; NHBF, normal human bronchial fibroblast cells; OGG1, 8-oxoguanine DNA glycosylase 1; PARPzf, the first zinc finger of PARP-1; PARP-1, poly (adenosine diphosphate-ribose) polymerase 1; PCR, polymerase chain reaction; PFGE, pulse field gel electrophoresis; pg, picogram(s); PLK1, polo-like kinase 1; Pol β, DNA polymerase beta; PP, photoproduct; RCC, reactive cell count; ROS, reactive oxygen species; RWPE-1, immortalised normal prostate epithelial cells; SSB, single-strand break; UROtsa, immortalised human urothelial cells; VH10hTert, tert-immortalised human diploid skin fibroblasts; thio-DMA(V), thio-dimethylarsinic acid; u-tiAs, total urinary inorganic arsenic (sum of inorganic arsenic and its methylated metabolites MMA and DMA); UVC, ultraviolet C light; UVR, ultraviolet radiation; wt, wild-type; XPC, Xeroderma pigmentosum complementation group C; XPE, Xeroderma pigmentosum complementation group E; XRCC1, X-ray repair cross-complementing protein 1.

3.1.3.2 | *In vivo genotoxicity*

In 2014, Takumi et al. (2014) published the first study addressing the mutational activity and mutational spectrum of iAs in animal models. By using the *gpt* mutation assay in *gpt* delta mice they showed that oral administration of arsenite induces a significant increase in mutation frequency in the liver and sequence analysis revealed a predominance of GC to TA transversions which is a hallmark of 8-oxoguanine mutagenesis (Moriya & Grollman, 1993). To support the suggestion that DNA base oxidation might underly the mutagenic activity of arsenic they showed that under the same experimental conditions increased levels of 8-oxoguanine are induced in the livers of arsenite-exposed mice. A successive study (Fujioka et al., 2016) was unable to confirm the mutational activity of arsenic *in vivo* by analysing *gpt* mutations in urinary bladder epithelium and liver of rats exposed orally to similar arsenite doses for longer exposure times. This discrepancy might be explained by differences in iAs toxicokinetics between rats and mice (see Section 3.1.1.1 Metabolism). In addition, the exposure regimen was poorly tolerated by the test animals as shown by the significant reduction in water intake and food consumption from week 2 and the significant reduction in body weight. No effects on the *gpt* mutant frequencies or mutation spectrum were reported. In this study, in addition to the *gp*t mutational assay, the *Spi*$^-$ assay was used. This assay efficiently detects intra-chromosomal deletions but not inter- chromosomal translocations or intrachromosomal megabase deletions. No long DNA fragment deletions were detected in the bladder or livers of treated rats. Negative results were also obtained following administration of DMA(V).

A few studies published since 2009 were identified regarding the genotoxic effects of iAs in animal cell/tissues. Mehta and Hundal (2014) addressed the question of whether iAs induces chromosomal aberrations in bone marrow cells of female rats after chronic exposure to low doses of arsenite (10–50 μg/L) for 30–60 days. The results show a statistically significant dose-related increase of chromosomal aberrations, but the conclusions are weakened by the lack of important experimental information (e.g. number of metaphases scored, mitotic index).

DNA damage, as detected by alkaline comet assay, was shown to occur in tissues, in particular ovary and uterus, of mice and rats orally exposed to arsenite (Dash et al., 2018; Nath Barbhuiya et al., 2020). Arsenite-induced oxidative stress was suggested to be involved (Dash et al., 2018). Inhibition of DNA repair by arsenic is well documented in cells in culture. Osmond et al. (2010) demonstrated the same effect in mice upon consumption of arsenic in lactational milk or drinking water. In particular, the reduction of BER gene transcript levels was detected in lung tissue harvested from treated adults and altered transcript levels were also reported in neonates feeding from exposed lactating mothers.

Arsenic trioxide is a well-known toxic metalloid mostly used as an anti-cancer drug. In cells in culture, it induces more severe genotoxic effects, apoptosis and oxidative stress than sodium arsenite (Jiang et al., 2013). Differences in toxicokinetics between the two arsenical compounds might account for the stronger toxic effects induced by arsenic trioxide (Liu et al., 2021). Three studies of genotoxicity in rodents upon oral administration of arsenic trioxide have been identified and they are reported below. Mice orally exposed to arsenic trioxide for 15 days showed significant increases of chromosomal aberrations in bone marrow cells (Kesari et al., 2012) and of micronuclei in erythrocytes (Khan et al., 2013) when exposed to a range of doses of arsenic (from 0.3 to 30 μg/kg per day). Notwithstanding some experimental limitations (e.g. low number of metaphases scored, lack of cytotoxicity data) the effects are statistically significant and dose-related. A recent study (Nava-Rivera et al., 2021) addressed the transgenerational (F1, F2, F3) genotoxic potential of arsenic in a rat model. Rats chronically exposed to arsenic in drinking water (As_2O_3, 1 mg/L) were mated to produce the arsenic lineage (F1, F2, F3). The induction of DNA breaks was measured by the comet assay in WBC. A significant increase in the level of DNA breaks (measured as percentage of DNA in the tail) in the arsenic-exposed lineage compared to the control lineage was found in all generations (F0–F3) in both females and males. The genotoxic effects decreased across generations but without loss of statistical significance compared to the control group. Upon chronic exposure to arsenic, transgenerational effects on global DNA methylation and reproductive phenotype were also reported, suggesting that early life exposure to arsenic may affect the health of later generations. An overview of the *in vivo* genotoxicity studies is provided in Table 9.

TABLE 9 *In vivo* genotoxicity of inorganic arsenic.

Reference	Test system	Animals	Concentration/treatment time	Results	Comments/additional information
Inorganic arsenic species other than arsenic trioxide					
Osmond et al. (2010)	Quantitative PCR transcript amplification Lung	Mice (1, 8, 24 weeks old) (three to five animals/group)	Sodium arsenite 2 or 50 mg/kg bw/day in drinking water (24 h or 2 weeks), oral route	Adult animals (24-week-old): decrease of all BER gene transcript levels (APE1, LIG1, LIG3, OGG1, PARP1 and POLB) in lung tissue upon 2 weeks treatment Neonates whose mothers were exposed to 50 mg/kg. for 24 h or 2 weeks: increased levels of the APE1, LIG1, OGG1 and PARP1 transcripts in lung tissue	Number of animals not specified
Mehta & Hundal (2014)	Chromosomal aberrations Bone marrow	Mature female rats ($n = 48$; 12 animals/group)	Sodium arsenite 10, 30, 50 mg/kg (30 and 60 days), oral route	**Positive:** significant increase of CA in bone marrow cells after 30 days of exposure to 30 and 50 mg/kg; after 60 days exposure to all three doses (10, 30 and 50 mg/kg), dose-dependent increase	Significant loss of bw Lack of data on cytotoxicity (mitotic index is not reported) Poor experimental details and data quality (unknown number of metaphases scored)
Takumi et al. (2014)	*gpt* mutation assay Liver Electrochemical detection (EC)-HPLC, measurement of 8-oxodG	Male gpt delta mice (5 weeks old), $n = 12$; 6 animals/group	Sodium arsenite 85 mg/kg (85 mg/L) in drinking water ad libitum (3 weeks); estimated: 4.3 mg/kg per day per mouse	**Positive:** increased gpt mutation frequency in the liver by 1.5-fold. Mutational spectra: predominance of G:C to T:A transversion and higher frequency of deletion mutations Significantly higher levels of 8-oxodG in the livers of arsenite-exposed group	No changes in the average body weight, average relative liver weight significantly lower than in the control group
Fujioka et al. (2016)	*gpt* and *Spi* – mutation assay. Urinary epithelium liver	Old male gpt delta F344 rats, $n = 36$, 12 animals/group)	Sodium arsenite 87 mg/L; DMA(V) 92 mg/L in drinking water (13 weeks)	**Negative:** no effects on the mutant frequencies or mutation spectrum in urinary bladder epithelium or liver for both arsenicals	In the arsenite treatment group: the final body weights and absolute liver weights were significantly decreased; water intake and food consumption were significantly decreased from week 2. In the DMA(V) group: no effects on body and liver weights; increased water intake, no effects on food consumption A:T to T:A transversions in the gpt gene, being spontaneous mutations, excluded from mutation frequency and spectra.
Dash et al. (2018)	Alkaline comet assay in uterine cells	Female virgin albino Wistar strain rats ($n = 24$; six animals/group)	Sodium arsenite 10 mg/kg bw/day (2 or 8 days) without and with *N*-acetyl-L-cysteine (NAC), oral route	**Positive:** Arsenite: significant increase of DNA breaks (number of comets, tail length); decreased DNA damage by co-treatment with NAC	No changes in bw Significant weight loss for ovaries and uterus; ovarian and uterine tissue damage, disruption in steroidogenesis in the arsenic-treated group
Nath Barbhuiya et al. (2020)	Alkaline comet assay in ovary and uterus	Swiss albino mice (6–8 week old; $n = 30$; six animals/group; five experimental points)	Sodium arsenite 2 mg/kg bw per day (30 days) Exposure also to smokeless tobacco alone and in combination with sodium arsenite, oral route	**Positive:** significant increase of DNA breaks (head/tail DNA, tail moment, tail length)	Significant loss of bw Data on target tissue toxicity: 50% decrease of relative organ weight and extensive histological abnormalities for both ovary and uterus

TABLE 9 (Continued)

Reference	Test system	Animals	Concentration/treatment time	Results	Comments/additional information
Arsenic trioxide					
Kesari et al. (2012)	CA in bone marrow cells	Swiss albino mice (6–8 week old, *n* = 30, six animals/group)	Daily oral gavaging of aqueous solution of arsenic trioxide: arsenic content 3.0 mg/L, 1.5 mg/L, 150 µg/L and 30 µg/L (15 consecutive days) Doses tested: 0.0 0.3, 1.5, 15, 30 µg/kg bw per day	**Positive:** significant increase of structural chromosomal abnormalities upon exposure to the full range of doses tested; dose-dependent increase Numerical abnormalities were induced by doses higher than 0.3 µg/kg bw per day	Lack of data on cytotoxicity (mitotic index is not reported) Too few metaphases scored per animal (50 instead of 200)
Khan et al. (2013)	MN assay in erythrocytes from bone marrow cells	Swiss albino mice (6–8-week-old, four groups, number of animals/group is not specified)	Daily oral gavaging of aqueous solution of arsenic trioxide: arsenic content 1.5 mg/L, 150 µg/L and 30 µg/L (15 consecutive days) Doses tested: 0.0–0.3-1.5–15 µg/kg bw per day	**Positive:** significant increase in micronucleated cells al all doses tested, dose-dependent	1000 erythrocytes scored (OECD protocol 2000) About six-fold increase in micronucleated cells at the human reference dose of arsenic (0.3 µg/kg per day)
Nava-Rivera et al. (2021)	Alkaline comet assay	Rats about 3 weeks old; males (*n* = 12) and females (*n* = 12)	Arsenic trioxide in drinking water 1 mg/L of arsenic equivalent to 1 mg/kg bw, for an interrupted period of 16 weeks	**Positive**: significant intra-generational increase in the level of DNA breaks (% DNA in tail) in the arsenic lineage compared to the control lineage in all generations in both females and males. The inter-genotoxic effect following the arsenic lineage, was in decrement across generations but with statistical significance in the F3 generation compared to the control group	The F0 parental was directly exposed to As; the F1 offspring experienced indirect exposure in utero and trough being breastfed until weaning in 21st day, F2 had a multigenerational indirect exposure as F1 germinal line, F3 transgenerational lineage neither direct nor indirect exposure to arsenic

Abbreviations: 8-oxodG, 8-hydroxydeoxyguanosine; A, adenine; APE1, apurinic/apyrimidinic endonuclease 1; BER, base excision repair; bw, body weight; C, cytosine; CA, chromosomal aberration; DMA(V), dimethylarsinic acid; DNA, deoxyribonucleic acid; EC-HPLC, high-performance liquid chromatography with electrochemical detection; F0, F1, F2, F3, filial generation 0, 1, 2, 3; G, guanine; LIG1, DNA ligase 1; LIG3, DNA ligase 3; MN, micronucleus; *n*, number; NAC, *N*-acetyl-L-cysteine; NAC, *N*-acetyl-L-cysteine; OECD, Organisation for Economic Co-operation and Development; OGG1, 8-oxoguanine DNA glycosylase 1; PARP1, poly (adenosine diphosphate-ribose) polymerase 1; PCR, polymerase chain reaction; POLB, DNA polymerase beta; T, thymine.

In conclusion, iAs does not interact directly with DNA but induces DNA base oxidation and both DNA SSB and DSB. The mutational spectrum of oxidised guanine bases, characterised by G > T transversions, has been detected in animal models. DSB are one of the most deleterious types of DNA lesions. Arsenic induces clastogenic and aneugenic effects both *in vitro* and *in vivo* as measured by chromosomal aberrations, micronuclei and aneuploidy with evidence of dose–response effects. In addition, iAs effectively inhibits DNA repair both *in vitro* and *in vivo* thus enhancing its own genotoxic potential and acting as a co-mutagen (EFSA CONTAM Panel, 2009). All these effects occur *in vitro* at subtoxic concentrations. The methylation of iAs, particularly to trivalent methylated species, should be regarded as an activation process that forms more reactive species, which exert stronger cyto- and genotoxic effects (induction of DNA breaks and clastogenic effects), inhibit DNA repair, promote ROS generation and induce cell transformation. Thio-DMA(V) is emerging as the most cytotoxic arsenic metabolite. The transgenerational genotoxic potential of arsenic has been shown in a rat model upon parental chronic exposure to As_2O_3 (Nava-Rivera et al., 2021).

3.1.3.3 | *Mode of action for genotoxicity*

Arsenic species exposure causes oxidative stress which is likely involved in multiple effects by altering signalling pathways and epigenetic modifications or causing direct oxidative damage to molecules.

Arsenic species induce oxidative stress

The mechanisms that have been proposed for arsenic species induced oxidative stress include: (i) As-induced mitochondrial toxicity, (ii) generation of RONS (reactive oxygen and nitrogen species) during formation of intermediate arsine species (e.g. metabolic processing of DMA), (iii) oxidation of arsenite to arsenate and (iv) interference with cellular antioxidative enzymes such as SOD, CAT and GSH which indirectly result in an increase of RONS levels (reviewed in Hu et al., 2020). Induction of RONS by iAs itself at low doses is questionable, more efficient inducers are the iAs metabolites (see Section on Genotoxicity). Arsenic species induced DNA damage is a mirror of the genotoxic potential of RONS.

Oxidation of DNA guanines occurs and *in vivo* mutational spectra indicate the typical fingerprint of oxidative DNA damage, i.e. G > T transversions. iAs is an efficient inducer of both single and double DNA strand breaks. Of the many different classes of damage, DNA DSB are the most dangerous since their processing may lead to mutations, loss of heterozygosity and chromosome rearrangements that results in cell death and cancer (Cannan & Pederson, 2016).

Based on the current literature, we can envisage different mechanisms for DSB generation by iAs: (i) during the processing of SSB left unrepaired in the S-phase (Ying et al., 2009); (ii) during attempted repair of oxidised DNA bases when they occur simultaneously on opposing strands (Cannan & Pederson, 2016); or, (iii) during all cell cycle phases due to in situ production of free radicals which may generate breaks on opposing strands (Litwin et al., 2013). In this case the short-lived, but highly reactive hydroxyl radicals may react with nearby DNA, producing SSBs. Closely opposed SSBs, created by either route, may spontaneously convert into a DSB. In the simplest version of the SSB to DSB conversion hypothesis, each SSB forms independently (reviewed in da Silva, 2021). In all three scenarios, the inhibition of DNA repair by iAs is the promoting event since the probability of DSB generation increases if SSB persist for a large fraction of the cell cycle.

Arsenic species interfere with the DNA damage response (DDR)

Interference with DDR occurs at two levels: by inhibition of DNA repair and by interference with cell cycle control and the apoptotic pathways. The disturbance of DNA repair systems has been observed at very low concentrations of iAs and its metabolites. Many DNA repair proteins contain redox-sensitive cysteine residues within zinc finger domains and therefore arsenite-induced oxidative stress can result in inactivation of their enzymatic function (see Section 3.1.3.1). This has been demonstrated for adenosine diphosphate poly-ribose polymerase-1 (PARP1), which could be inhibited by peroxynitrite-mediated S-nitrosation of its zinc finger cysteine(s) (Zhou et al., 2019). In the low nanomolar range, arsenite and some of its metabolites -MMA(III and DMA(III)-, are sufficient to interfere with the activity of PARP-1, thereby increasing SSB and DSB formation in cells in culture. Furthermore, all three trivalent arsenicals inhibited isolated PARP1, indicating a direct interaction with this enzyme (reviewed in Hartwig et al., 2020). Interestingly, one of the three zinc fingers of PARP-1 (ZnF1) exerts a quite low affinity toward zinc (Bossak et al., 2015) and zinc release due to oxidative stress has been recently shown to regulate PARP1 activity (Wedler et al., 2021). If the first zinc finger of PARP-1 is not occupied by zinc under normal cellular conditions, this may also explain the particularly high sensitivity of PARP-1 toward toxic metal ions such as arsenite.

In addition, iAs has been shown to inhibit the main DNA repair mechanisms for both SSB and DSB (i.e. BER, HR, NHEJ) (reviewed in Tam et al., 2020). Arsenite can disrupt DSB repair by multiple mechanisms such as by inhibiting histone epigenetic modifications, which leads to compact chromatin structures unfavourable for DNA DSB repair, or by inactivating the myriad of zinc finger proteins involved in post-translational modifications of proteins that control DDR and transcription of DNA repair genes (reviewed in Tam et al., 2020). Epigenetic alterations appear also to be relevant at very low concentrations (see Section 3.1.2.3). It is of note that some iAs metabolites have been shown to disturb similar but also different DDR targets (see Section 3.1.3.1). Thus, under mixed exposure conditions, which occur when iAs is metabolised, genomic stability is affected by different pathways.

Arsenic species modulate cellular signalling pathways that affect diverse processes such as cell proliferation, differentiation and apoptosis. Arsenic may influence cell cycle regulators at either the transcriptional or post-translational levels or affect specific protein–protein interactions. Arsenic has been shown to interfere with protein ubiquitination of cell

regulatory proteins (e.g. cyclins, p53), thus playing a key role in cell cycle control. In addition, arsenic may activate the intrinsic and extrinsic caspase pathways, and induce cell apoptosis (reviewed in Tam et al., 2020).

Induction of clastogenic and aneugenic events

iAs is a powerful inducer of CA and MN in both *in vitro* and *in vivo* models as well as in humans. In a comparative analysis of occupational and environmental studies reporting MN frequency in lymphocytes of individuals exposed to different genotoxic agents (including pesticides, herbicides, PAHs, formaldehyde, etc.), metals showed the most pronounced fold increase of MN frequency over background with exposure to arsenic (seven studies) being the most effective (6.5-fold increase) (Nersesyan et al., 2016).

MN are extra-nuclear bodies originating from acentric chromatid/chromosome fragments or whole chromatids/chromosomes that were not incorporated into the nucleus after cell division. The multiple effects of iAs are compatible with both mechanisms of MN formation. iAs may induce MN containing acentric chromatids/chromosomes fragments by causing DNA breaks and inhibiting their repair. On the other side, disruption of mitotic progression by arsenic species (e.g. through interaction with the mitotic spindle or affecting the methylation pattern of centromere satellite sequences) may generate MN with whole chromatids/chromosomes.

MN as markers of exposure are not very sensitive due to the high baseline level in the healthy population and to the confounding factors (age, sex, diet and lifestyle) that can significantly affect their frequency (Fenech & Bonassi, 2011). In the As-exposed populations an approximately three-fold increase of MN frequency is observed when the concentrations of As in drinking water are above 50 µg/L. Conversely, other markers of genotoxicity such as induction of DNA breaks reveal genetic damage at lower As concentrations (positive in a range of concentrations from 10 to 40 µg/L) (see Section 3.1.2.2). This is expected considering that the induction of DNA breaks precedes the formation of MN. Several studies consistently report increased MN frequency in As-exposed populations revealing the induction of genetic damage that may generate genetic instability. New knowledge obtained over past few years indicates that MN are not only markers of DNA damage and aneuploidy but also inducers of chromosomal hypermutation and sources of pro-inflammatory DNA leaking from disrupted MN (reviewed in Fenech et al., 2021). The inflammatory consequences of MN formation and their disruption provide a further important explanation why MN are linked prospectively not only with cancer but also with other inflammation-driven diseases.

Induction of gene mutations

Inorganic arsenic alone is a weak inducer of gene mutations. If diminished DNA repair and elevated oxidative DNA damage constitute the major mechanisms of iAs carcinogenesis, one would expect to observe elevated rates of mutations in iAs-exposed cell and animal models. Clear evidence indicates that arsenite increases the mutagenicity of other DNA damaging agents such as UV radiation, but it shows a low, if any, mutagenic activity in bacterial as well as in mammalian test systems. However, limitations of the mutation assay systems used, mostly designed to detect point mutations, might be responsible for this failure. Indeed, Hei et al. (1998), by employing a human–hamster hybrid cell assay in which both intragenic and multilocus mutations are detectable, demonstrated that arsenite could induce, in a dose-dependent manner, mutations (mostly large deletions). They also observed that the mutagenicity of arsenite could be diminished markedly by cotreating cells with a radical scavenger, dimethyl sulfoxide, thus suggesting that RONS species are involved. More recently, by using high-resolution genomic profiling, Martinez et al. (2010) analysed copy number variations (CNVs) in lung squamous cell carcinomas (SCC) from patients chronically exposed to arsenic with or without smoking history. The results of these specimens were compared with those derived from a panel of lung SCC from an unrelated population without known exposure to As. Multiple CNVs were identified in association with arsenic exposure and were not attributable to smoking status or germline CNVs. Recent advances in next-generation sequencing, should be applied to unveil how arsenic exposure leads to mutagenesis in animal models or human subjects.

Summary on genotoxicity

Inorganic arsenic and its metabolites, via generation of oxidative stress, induce DNA base oxidation, DNA single and double strand breaks and clastogenic and aneugenic events both *in vitro* and *in vivo*. The same events are reported in humans upon chronic iAs exposure.

The Genetic Toxicology Technical Committee (GTCC) of the Health and Environmental Sciences Institute (HESI) has developed an adverse outcome pathway (AOP) that links oxidative DNA damage to two adverse outcomes (AO): mutations and chromosomal aberrations (Cho et al., 2022). Both events have been shown to occur upon exposure to iAs. Because of the lack of direct interaction with DNA, iAs is classified as an indirect genotoxin. However, iAs presents a unique feature, that is its extraordinary ability to inhibit DNA repair at very low concentrations *in vitro* and at low exposure levels in human studies as inferred from the elevated levels of DNA damage. The inhibition of DNA repair can potentially exacerbate the genotoxic effects not only of exogeneous DNA damage but also of endogenously induced DNA damage that is an important source of genomic instability in cancer (reviewed in Tubbs & Nussenzweig, 2017). This is a detrimental combination that makes of iAs a 'special' indirect genotoxin. Even though the interactions with the DNA repair/DDR system are based on protein interactions, and may, therefore, follow non-linear dose–response relationships, it should be considered that the

response of cells under chronic exposure to iAs is similar to that of DNA repair/DDR-defective cells that present increased genomic instability and increased risk of disease.

3.1.4 | Carcinogenicity studies in animals

EFSA CONTAM Panel (2009) noted that most oral carcinogenicity studies on various iAs species gave negative results in mice, rats and dogs, and that an important exception was the studies in which pregnant mice were treated with sodium arsenite in drinking water, and tumours were observed in the adult offspring, demonstrating transplacental carcinogenesis (Liu & Waalkes, 2008; Waalkes et al., 2007). In addition, several studies indicated that iAs is co-carcinogenic (EFSA CONTAM Panel, 2009). As noted in Section 1.2.3, more recent IARC evaluations have concluded that 'in view of the overall findings in animals, there is sufficient evidence in experimental animals for the carcinogenicity of iAs compounds' (IARC, 2012). This conclusion is based on evaluation of studies on a range of arsenic compounds (e.g. dimethylarsenic acid, calcium and sodium arsenate, calcium and sodium arsenite, gallium arsenide, arsenic trioxide and trimethylarsine oxide) performed using different routes of administration (oral, intratracheal and intravenous).

In the early studies of Waalkes and colleagues, noted in the EFSA CONTAM Panel (2009), pregnant CH3 and CD1 mice were treated with drinking water containing sodium arsenite at concentrations of 42,500 or 85,000 μg/L from GD 8 to 18, and the offspring were observed for up to 2 years. The male offspring of C3H mice developed tumours of the liver and adrenal cortex in a dose-related fashion during adulthood. Female C3H offspring showed dose-related increases in ovarian and lung tumours. Male CD1 offspring developed tumours of the liver and adrenals while females developed tumours of the urogenital system, ovary, uterus and adrenal.

Since the previous EFSA Opinion, Waalkes and colleagues have published new studies involving 'whole-life' exposure, in which mice were exposed via drinking water prior to breeding, during pregnancy and lactation and the offspring were similarly exposed after weaning. Exposure to sodium arsenite at 0, 6000, 12,000 or 24,000 μg/L in the drinking water resulted in dose-related increases in lung adenocarcinoma (both sexes), hepatocellular carcinoma (both sexes), gallbladder tumours (males) and uterine carcinomas. Dose-related increases in ovarian tumours (including carcinomas), and adrenal tumours (both sexes) were increased at all doses (Tokar et al., 2011). In a subsequent study, designed to encompass concentrations of iAs more relevant for human exposure, CD1 mice were exposed to 0, 50, 500 or 5000 μg/L sodium arsenite in drinking water for 3 weeks prior to breeding, during pregnancy and lactation and the offspring were exposed after weaning for up to 2 years (Waalkes et al., 2014). In males, a statistically significant increase in lung adenomas was reported in males at 500 μg/L, and in lung carcinomas at 50 μg/L. In females there was a statistically significant increase in lung adenomas at 50 μg/L. Survival was decreased in this female dose group but not in other groups of females or males. No increase in lung tumours was reported for the other dose groups, and tumours at sites other than the lung are not described. The authors described the dose–response relationship as 'unusual' and could not explain it. Cohen et al. (2014) commented on the lack of consistency between the results reported in Waalkes et al. (2014) and Tokar et al. (2011) and suggested that the conflicting results could be due to the high variability in incidence of lung tumours in CD-1 mice, noting that the incidences were within the range of historical controls reported by Charles River.

Studies of gestational arsenic exposure have been reported by one other research group (Nohara et al., 2012, 2016). In Nohara et al. (2012), pregnant C3H/HeN mice were given drinking water containing 0 or 85,000 μg/L sodium arsenite from day 8 to 18 of gestation. The authors reported that arsenic exposure resulted in a 'tendency' toward a higher number of mice with hepatic tumours and a greater multiplicity and size of the tumours compared to the control group. However, statistical analysis was not reported and no tissues other than the liver were examined. In Nohara et al. (2016), pregnant C3H/HeN mice were also given drinking water containing 0 or 85,000 μg/L sodium arsenite from day 8 to 18 of gestation, followed by a reciprocal crossing experiment among the control F1 males and females and arsenite F1 males and females. Male and female F1 mice were mated at 10 weeks of age and the liver tumours were examined in the F2 males at 75–82 weeks. There was a significantly higher incidence of liver tumours in the F2 male offspring of arsenite F1 males than in those of the control F1 males. In contrast, the tumour incidence of the F2 male offspring of arsenite F1 females and the control F1 females were not significantly different. The authors concluded that the tumour-augmenting effect of gestational arsenite exposure is transmitted to the F2 males via the F1 male offspring, but not via the F1 female offspring.

Garry et al. (2015) reported a detailed analysis of the toxicology literature evaluating the role of in utero arsenic exposure in carcinogenesis. They concluded that the available data did not 'provide evidence of a causal link between *in utero* arsenic exposure and cancer or indicated early life-stage susceptibility to arsenic-induced cancer, particularly at environmentally relevant doses'.

The CONTAM Panel concluded that although some studies have shown increased tumour incidences following oral (drinking water) administration of iAs, the results of different studies with respect to tumour sites and doses are inconsistent and do not provide a robust basis for use in the risk assessment of iAs.

3.2 | Observations in humans

3.2.1 | Short-term effects

In its previous Opinion (EFSA CONTAM Panel, 2009) the CONTAM Panel reported that the acute oral lethal dose of arsenic ranges between 1 and 5 mg arsenic/kg bw and that acute and subacute arsenic poisoning can affect almost all physiological systems of the body including the gastrointestinal, cardiovascular, renal and nervous systems, and to a lesser degree the respiratory, hepatic, haematological and dermal systems. They concluded that while human case reports concerning iAs can provide important information for the clinical course of the poisoning such reports generally do not provide information on dose response which is necessary for risk assessment.

3.2.2 | Chronic effects

In its previous Opinion (EFSA CONTAM Panel, 2009) the CONTAM Panel concluded that data from experimental animals cannot be used for risk characterisation because of important species differences in iAs toxicokinetics. The available epidemiological studies related to arsenic in drinking water, or in some instances biomarkers of exposure. Total dietary exposure to iAs was not specifically measured in these studies. The main adverse effects reported to be associated with chronic oral exposure to iAs in humans were skin lesions, cancer, developmental toxicity, neurotoxicity, cardiovascular diseases, abnormal glucose metabolism and diabetes. Neurotoxicity was predominantly reported from acute exposure upon poisoning or suicide, or at high concentrations in drinking water. The evidence of associations of arsenic exposure with cardiovascular diseases (i.e. Blackfoot disease, peripheral vascular disease, coronary heart disease, myocardial infarction and stroke) and diabetes in areas with relatively low levels of iAs exposure was inconclusive. There was also emerging evidence of negative impacts on fetal and infant development, particularly reduced birth weight. The CONTAM Panel concluded that there was sufficient evidence to assume a causal relationship of arsenic exposure with skin lesions and cancers of the urinary bladder, lung and skin.

3.2.2.1 | *Selection of studies*

Although reviews and meta-analyses were also reviewed, only original cross-sectional, case–control and cohort studies characterised by estimates on the individual or group level of exposure to iAs were considered. Exposure metrics accepted were estimates of iAs ingestion (usually principally from water), or arsenic drinking water concentrations (assuming 100% iAs), or biomarkers of iAs (which required speciated arsenic metabolites). Only studies that include study subjects with long-term low to moderate levels of arsenic defined as concentrations of arsenic in water of less than ~150 μg/L or biomarker concentrations estimated to results in equivalent doses, were considered. One reason for this was that studies used in previous risk assessments based on arsenic in drinking water showed dose–response relationships with skin lesions and cancer outcomes at arsenic concentrations in water well below 150 μg/L. In addition, studies with only high exposures are much less informative for deriving dose response relationships at low levels. Studies on occupational arsenic exposure were excluded, as well as studies based on total As, unless knowledge of the arsenic sources allowed a reliable estimate of inorganic As. This required reliable information that the relative contribution from recent seafood intake was negligible.

The reliability of all epidemiological studies was assessed in terms of design, exposure assessment, assessment of outcomes, confounding and risk of other sources of bias. For four outcomes, studies exclusion criteria were applied from the start: Studies of lung or urinary bladder cancer were excluded if smoking data were not available. Studies of type 2 diabetes were excluded if data were not available on smoking and BMI. Studies on skin cancer were included only if sun exposure or skin sensitivity to UV light was considered or could be assumed not to affect results. Information on possible use of tanning bed/solarium was not available. Studies on neurodevelopment were excluded if data were not available for key covariates that are important for neurodevelopment. The covariates were (based on Lanphear et al. (2005) that evaluated low-level exposure to lead and neurodevelopment): (1) sex and age, anthropometry or nutrition, (2) socioeconomic status (SES) or HOME (Home Observation Measurement of the Environment) score and (3) parental education/intelligence quotient (IQ). Because of some overlap of these factors (e.g. between SES and parental education, and between nutrition and SES), the selected studies were required to have adjusted for at least two of these groups of covariates. The CONTAM Panel notes that study populations may have been exposed also to other contaminants than iAs but found no clear indications that there was residual confounding from such exposure.

For multiple studies from the same cohort, we included only the publication with the longest follow-up time provided that it included appropriate data on exposure, outcomes and covariates. The inclusion and exclusion criteria for epidemiological studies are presented in Table 10 below.

TABLE 10 Criteria for epidemiological studies of long-term effects in humans.

Study design	In	Cross-sectional studies Cohort studies Case–control studies
Study characteristics	In	Duration of exposure > 6 months. For continuous outcomes > 100 subjects and for discrete outcomes > 5, Exposures to arsenic concentrations < 150 µg/L in drinking water or corresponding exposure level for arsenic biomarkers
Population	In	Any country. Any age groups
Exposure estimate	In	iAs intake per day As in drinking water iAs in urine and its metabolites Total urinary iAs (u-tiAs), i.e. sum of iAs and metabolites MMA and DMA Other iAs biomarkers that can be transformed into iAs intake
	Out	Intake of total As Total As in urine or blood, unless arsenobetaine could be excluded Studies on inhalation of arsenic Studies with occupational exposure
Outcomes	In	Any long-term adverse outcomes
Covariates	Out	Lack of age or sex Lack of smoking data for lung and bladder cancer outcome Lack of data on sun exposure or skin sensitivity to UV light for skin cancer Lack of smoking or BMI for T2D outcome Lack of covariates (child characteristics/parents' education or maternal intelligence/ socioeconomic status) for neurodevelopment
Language	In	English
	Out	Non-English
Time period	In	From 1/1/2009 to 18/7/2022 and papers described reviewed by EFSA in 2009
Publication type	In	Peer-reviewed original research, systematic reviews, meta-analyses[a]
	Out	Expert opinions. Editorials. Letters. PhD theses. Conference proceedings. Conference abstracts.

Abbreviations: As, arsenic; BMI, body mass index; DMA, sum of dimethylarsinous acid and dimethylarsinic acid; EFSA, European Food Safety Authority; iAs, inorganic arsenic; MMA, sum of monomethylarsonous acid and monomethylarsonic acid; PhD, Doctor of Philosophy; T2D, type 2 diabetes; u-tiAs, total urinary iAs (sum of iAs and its methylated metabolites MMA and DMA); UV, ultraviolet.

[a]Such publications have not been used for risk assessment.

3.2.2.2 | *Cancers*

Skin cancer

In 1973, IARC concluded that there was sufficient evidence that arsenic and arsenic compounds caused cancers of the skin (and liver) (IARC, 1973) and assigned it to Group 1 (IARC, 1979). The causal association of arsenic exposure with skin cancer has been confirmed in a number of subsequent re-evaluations, most recently in 2009 (IARC, 2012; Straif et al., 2009). The CONTAM Opinion of 2009 (EFSA CONTAM Panel, 2009) noted that earlier risk assessments were based on ecological studies from Taiwan (primarily in the southwest endemic arsenic region) that showed strong dose-related effects of village drinking water arsenic concentrations on skin cancer incidence, prevalence and mortality with extrapolation to lower levels of exposure (Tseng et al., 1968). In 2009, the CONTAM Panel focussed on epidemiological studies on skin cancer with lower levels of exposure (e.g. including drinking water concentrations below 100 µg/L) and derived a Reference Point equivalent to 1–2 µg/L As in drinking water from the study of Karagas et al. (2002).

For the present Opinion, the CONTAM Panel identified 15 studies from a literature search (see Section 2 on Methodology). Out of these, 10 studies did not meet the inclusion criteria (Alshana et al., 2022; Bedaiwi et al., 2022; Choudhury et al., 2018; Engström et al., 2015; Gossai et al., 2017; Kim et al., 2017; Knobeloch et al., 2006; Langston et al., 2022; Wheeler et al., 2013; Zhang et al., 2016). Five studies that fulfilled the inclusion criteria were considered further (see Table 11 below).

Three of these studies were already reviewed in the 2009 Opinion. In a population-based case–control study of skin cancers (both basal cell and squamous cell carcinoma) from the U.S., an increased risk of squamous cell carcinomas in the highest exposure category was reported in relation to arsenic measured in toenail clippings (Karagas et al., 2001). In a geographic information system (GIS) analysis of water arsenic and nonmelanoma skin cancer and melanoma in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort in Denmark, no association was observed after adjustment for region (Baastrup et al., 2008). The CONTAM Panel noted that exposure in this study was based on relatively crude aggregated estimates of water arsenic at low levels (median 0.7 µg/L), with low contrast (only 1% above 5 µg/L). A population-based case–control study from the U.S. investigated the risk of melanoma skin cancer in relation to toenail arsenic concentration and found a dose-related increase in risk (Beane Freeman et al., 2004).

Two studies that fulfilled the inclusion criteria were published after the 2009 Opinion. In the Arsenic Health Risk Assessment and Molecular Epidemiology (ASHRAM) study in Hungary, Romania and Slovakia, the relative risk of basal cell carcinoma (BCC) cases showed a dose–response in relation to all three indices of long-term iAs exposure (lifetime average concentration, cumulative and peak dose), with and without controlling for potential confounders, including indices of

UV exposure (Leonardi et al., 2012). An odds ratio of 1.18 (95% CI = 1.08, 1.28) was associated with each 10 µg/L increase in average lifetime drinking water concentration of arsenic (Leonardi et al., 2012). A population-based case–control study in the U.S. found increased risk of squamous cell carcinomas of the skin with increasing u-tiAs (OR = 1.37, 95% CI = 1.04, 1.80 per unit increase of ln-transformed concentrations of arsenic). There was an increasing trend in the odds ratios for squamous cell carcinomas with each urinary arsenic metabolite, with the strongest association for MMA (Gilbert-Diamond et al., 2013). Exposure to UV radiation is a confounding factor for skin lesions. All studies assessed data on sun exposure or skin sensitivity to UV light in one way or another. However, the studies did not evaluate whether the skin cancer occurred in a UV-exposed or UV-unexposed area.

In summary, the epidemiological studies provide sufficient evidence for an association between low to moderate exposure to iAs and both basal cell carcinoma and squamous cell carcinomas of the skin. The data on possible associations with melanoma are not sufficient to reach conclusions.

The results for the key studies are summarised in Table 11.

TABLE 11 Key epidemiological studies on skin cancer in humans in relation to ingested inorganic arsenic exposure.

Reference study population design	Outcome definition	Population size (*n*) case/control	Arsenic concentration/exposure	Results	Additional information/confounders
Karagas et al. (2001) USA (New Hampshire) Case–control study	Histologically confirmed, incident BCC and SCC	**BCC/SCC/controls** 281/155/263 156/64/136 92/33/73 22/14/26 10/5/11 26/13/15	**Concentration in toenail (μg/g)** 0.009–0.089 0.090–0.133 0.134–0.211 0.212–0.280 0.281–0.344 0.345–0.81	**OR (95% CI) BCC** 1.00 (reference) 1.01 (0.76, 1.35) 1.06 (0.74, 1.51) 0.72 (0.40, 1.31) 0.75 (0.31, 1.81) 1.44 (0.74, 2.81) **OR (95% CI) SCC** 1.00 (reference) 0.93 (0.64, 1.34) 0.98 (0.61, 1.58) 1.10 (0.55, 2.21) 1.00 (0.33, 3.01) 2.07 (0.92, 4.66)	Adjusted for age and sex. Other covariates, such as smoking and UV light, evaluated but no appreciable effect
Beane Freeman et al. (2004) USA Case–control study	Cutaneous melanoma	326/329 52/82 58/83 95/82 121/82	**Concentration in toenail (μg/g)** ≤ 0.020 0.021–0.039 0.040–0.083 ≥ 0.084	**OR (95% CI)** 1.0 1.0 (0.6, 1.6) 1.7 (1.1, 2.7) 2.1 (1.4, 3.3)	Patients with colorectal cancer as controls. Adjusted for age, gender and education. Effect of history of sunburn considered
Baastrup et al. (2008) Denmark Cohort study	Nonmelanoma and melanoma of the skin	1010 nonmelanoma/147 melanoma/56,378	**Time-weighted average water concentration (μg/L) median CI (95% CI)** 0.7 (0.3–2.1)	**IRR (95% CI) Nonmelanoma** 0.99 0.94–1.06 **IRR (95% CI) Melanoma** 0.80 0.59–1.08	Adjusted for many factors including UV exposure and smoking
Leonardi et al. (2012) Hungary, Romania, Slovakia Case–control study	Histologically confirmed, incident BCC	529/540	**Lifetime average water As concentration (μg/L)** 0.00–0.68 0.68–0.98 0.98–7.00 7.10–19.43 19.54–167.29 **Peak daily As dose rate (μg/day)** 0.00–0.73 0.73–1.48 1.48–9.09 9.09–32.23 32.23–242.14 **Cumulative As dose (g)** 0.00–0.01 0.01–0.03 0.03–0.13 0.13–0.55 0.55–4.46	**OR (95% CI) BCC** 1.00 (reference) 1.39 (0.89, 2.19) 1.20 (0.77, 1.88) 1.73 (0.97, 3.11) 3.03 (1.70, 5.41) **OR (95% CI) BCC** 1.00 0.91 (0.59, 1.39) 1.55 (1.00, 2.41) 1.76 (1.01, 3.07) 2.50 (1.39, 4.49) **OR (95% CI) BCC** 1.00 1.09 (0.72, 1.67) 1.46 (0.93, 2.27) 1.76 (1.02, 3.04) 2.63 (1.45, 4.78)	Controls were general surgery, orthopaedic and trauma patients. The controls were frequency matched to all potential cancer cases by sex, 5-year age band and residence in the same county/region of the study area Adjusted for county, age and sex, education, skin response to 1-h midday sun and skin complexion Smoking and BMI data available but did not influence the results and not included in the final models

TABLE 11 (Continued)

Reference study population design	Outcome definition	Population size (*n*) case/control	Arsenic concentration/exposure	Results	Additional information/confounders
Gilbert-Diamond et al. (2013) USA (New Hampshire) Case–control study	Histologically confirmed, incident SCC	470/447, Included in the analysis: 323 cases and 319 controls with no seafood intake	**u-tiAs (µg/L)** < 3.36 3.36 to < 5.31 ≥ 5.31 Continuous (per ln-transformed ΣAs µg/L increase)	**OR (95% CI) SCC** 1 (reference) 0.94 (0.60, 1.45) 1.43 (0.91, 2.27) 1.37 (1.04,1.80)	Population-based: controls frequency matched to cases on sex and age. Adjusted for sex, age, BMI, education, smoking status, skin reaction to chronic sun exposure and urinary creatinine concentration

Abbreviations: As, arsenic; BCC, basal cell carcinoma; BMI, body mass index; CI, confidence interval; iAs, inorganic arsenic; IRR, incidence rate ratio; *n*, number; OR, odds ratio; SCC, squamous cell carcinoma; USA, Unites States of America; u-tiAs, total urinary iAs (sum of iAs and its methylated metabolites MMA and DMA); UV, ultraviolet.

Bladder cancer

In 2002, the IARC concluded that there was sufficient evidence in humans that arsenic in drinking-water causes cancer of the urinary bladder (as well as of the lung and skin) and assigned it to Group 1 (IARC, 2004). The assessment was based on ecological studies from Taiwan, Chile and Argentina that were supported by evidence from cohort and case–control studies in Taiwan. The 2009 Opinion (EFSA CONTAM Panel, 2009) focussed on epidemiological studies on bladder cancer in humans informing on dose–response at exposure levels below 100 µg/L in drinking water. The CONTAM Panel noted that some of the studies published since the IARC report supported an excess risk of bladder cancer whereas others did not.

For the present Opinion, the CONTAM Panel identified 26 studies from a literature search. Sixteen of these studies were not considered further as they did either not fulfil the inclusion criteria or were not relevant for this risk assessment (Amin, Stafford, & Guttmann, 2019; Andrew et al., 2009; Chen, Grollman, et al., 2021; Chung et al., 2019; Ferreccio, Smith, et al., 2013; Koutros et al., 2018; Krajewski et al., 2021; Lamm et al., 2013; Liao et al., 2009; Melak et al., 2014; Mendez Jr et al., 2017; Moazed et al., 2021; Saint-Jacques et al., 2018; Signes-Pastor, Scot Zens, et al., 2019; Steinmaus et al., 2014b; Tsai, Kuo, et al., 2021). Ten studies met the inclusion criteria (see Section 3.2.2.1).

Three of these studies were already reviewed in the 2009 Opinion: studies in North East Taiwan (Chiou et al., 2001), New Hampshire, USA (Karagas et al., 2004), which were used to calculate reference points in the 2009 Opinion (see Table 12) and in Denmark (Baastrup et al., 2008). The case–control study from Taiwan showed a dose–response in bladder cancer risk, but the number of cases with low-to-moderate As concentrations was very low (Chiou et al., 2001). The case–control study from New Hampshire found about a two-fold risk of bladder cancer in the highest exposure category, but with wide CIs, and the increased risk was found only among smokers (Karagas et al., 2004). In the EPIC cohort in Denmark, no positive association was observed (Baastrup et al., 2008), but as mentioned for skin cancer, exposure in this study was based on relatively crude aggregated estimates of water arsenic at low levels (median 0.7 µg/L), and with low contrast (only 1% above 5 µg/L).

There were seven new studies considered by the CONTAM Panel. In a cohort study in Taiwan (Chen et al., 2010b), an increasing risk of urothelial carcinoma, the main cancer form in the bladder, was found with increasing arsenic concentrations in well water. Two further case–control studies from Taiwan found increased risk of bladder cancer with increased u-tiAs (Huang et al., 2018; Wu et al., 2013). In Wu et al. (2013) a significantly increased bladder cancer OR of 3.20 was also found for never smokers with a high u-tiAs (> 15.40 mg/g creatinine). In the study by Huang et al. (2018) the validity might be influenced by the presence of high amounts of DMA in the urine. It should be noted that occupational exposure to bladder carcinogens may be a confounding factor and it was taken into account in most studies.

Two case–control studies with information about life-time exposure to arsenic were performed in the US. In a population-based case–control study in South-eastern Michigan, with low levels of arsenic in drinking water (among cases the median concentration in private wells was 5.3 µg/L and in public supply 0.3 µg/L) no increased risk of bladder cancer was found (Meliker et al., 2010). The effect estimates were similar in never-smokers and ever smokers. In a larger population-based case–control study from Northern New England (average arsenic in drinking water between < 0.5 to more than 10 µg/L) (Baris et al., 2016). Koutros et al. (2018) found in the same study population as in Baris et al. (2016), that former smokers and current smokers with the highest cumulative arsenic intake had elevated risks of bladder cancer: OR = 1.4, 95% CI: 0.96–2.0 and OR = 1.6, 0.91–3.0, respectively), whereas the OR among never smokers was 1.1, 0.6–1.9, *p*-interaction = 0.49). In a case–control study from Chile, an increased risk of bladder cancer was found in the group with lifetime average water arsenic 80–197 µg/L (Steinmaus et al., 2013). When comparing an average lifetime exposure to arsenic of 11–91 µg/L versus < 11 µg/L, smokers that smoked > 10 cigarettes per day showed increased risk (OR 4.72, 95% CI 1.54–14.49) whereas never smokers showed a weaker increased risk (OR 2.66, 95% CI 0.91–7.83) (Ferreccio, Yuan, et al., 2013).

In a study in Bangladesh no consistent trend was seen for urothelial carcinoma[17] with increasing arsenic concentration (Mostafa & Cherry, 2015). The authors suggested that this lack of association may be due to the fact that the controls were patients with benign lesions in the urinary tract. Arsenic exposure was positively associated with chronic cystitis, the major benign lesion in the controls, meaning that the control group carried a condition that may itself be caused by the exposure.

In summary, the epidemiological studies provide sufficient evidence for an association between low to moderate exposure to iAs and bladder cancer. The results for the key studies are summarised in Table 12.

[17]Formerly termed transitional cell carcinoma.

TABLE 12 Key epidemiological studies on bladder cancer and As exposure.

Reference study population design	Outcome definition	Population size (*n*) case/control	Arsenic exposure	Results	Additional information/confounders
Chiou et al. (2001) North-east Taiwan Cohort study	Area endemic for arseniasis	Cases/person-years of observation 3/7978 3/6694 2/3013 7/5220 1/7978 1/6694 2/3013 6/5220	**As in well water (μg/L)** < 10.0 10.1–50.0 50.1–100.0 > 100.0 < 10.0 10.1–50.0 50.1–100.0 > 100.0	**OR (95% CI)** Urinary tract 1.0 1.5 (0.3–8.0) 2.2 (0.4–13.7) 4.8 (1.2–19.4) Transitional cell carcinoma 1.0 1.9 (0.1–32.5) 8.2 (0.7–99.1) 15.3 (1.7–139.2)	Adjusted for age, sex, smoking and duration of drinking well water Duration of the study ~4 years
Karagas et al. (2004) USA Case–control study	Incident transitional cell carcinoma	Cases = 383, controls = 641 Never smoker 15/41 20/56 22/48 11/29 3/14 0/3 0/8 Ever smoker 75/121 99/105 66/109 37/67 18/18 3/10 14/11	**Toenail As (μg/g)** 0.009–0.059 0.060–0.086 0.087–0.126 0.127–0.193 0.194–0.277 0.278–0.330 0.331–2.484 0.009–0.059 0.060–0.086 0.087–0.126 0.127–0.193 0.194–0.277 0.278–0.330 0.331–2.484	**OR (95% CI)** Never smoker 1.00 0.85 (0.38–1.91) 1.18 (0.53–2.66) 1.10 (0.42–2.90) 0.49 (0.12–2.05) – – Ever smoker 1.00 1.53 (1.02–2.29) 1.02 (0.66–1.56) 1.00 (0.60–1.67) 1.78 (0.86–3.67) 0.50 (0.1–1.88) 2.17 (0.92–5.11)	ORs are age and sex adjusted Maximum likelihood estimate change-point of 0.326 μg/g (95% CI 0.121–0.446), which equates to approximately 50 μg/L, with a 1.1% increase in ORs for 1% increase in toenail As concentration above change-point ($p = 0.10$)
Baastrup et al. (2008) Denmark Cohort study	First bladder cancer	56,378 214 Bladder cancer cases	**Time-weighted average exposure (μg/L) median CI (95% CI)** 0.7 (0.3–2.1) **Cumulative exposure** (5 mg)	**IRR (95% CI)** 1.01 (0.93–1.11) 1.0 (0.98–1.04)	Adjusted for smoking status, smoking duration, smoking intensity, education, occupation
Chen et al., 2010b Taiwan Cohort study	Incident urothelial carcinoma	36/8086 3/2288 6/2093 3/907 7/909 10/691	**As concentration in well water at enrolment (μg/L)** < 10 10–49.9 50–99.9 100–299.9 ≥ 300	**RR (95% CI) Urothelial carcinoma** 1.00 (reference) 1.85 (0.45–7.61) 2.19 (0.43–11.1) 5.50 (1.39–21.8) 10.8 (2.60–40.3)	Relative to the As concentration < 10 μg/L, those who drank well water with higher (≥ 10 μg/L) concentrations from birth (RR, 4.39; 95% CI, 1.18–16.3), and still drank at enrolment (RR, 4.55; 95% CI, 1.34–15.5), had a significantly increased risk of urinary cancer. Adjusted for age, gender, education, whether started drinking well water from birth, cigarettes smoking status and alcohol consumption status at enrolment

(Continues)

TABLE 12 (Continued)

Reference study population design	Outcome definition	Population size (*n*) case/control	Arsenic exposure	Results	Additional information/confounders
Meliker et al. (2010) USA Case–control	Bladder cancer	411/566 188/264 185/263 38/39	**Time-weighted average water As (μg/L)** < 1 1–10 > 10 Continuous (per 5 μg/L increase)	**OR (95% CI)** 1.00 0.84 (0.63, 1.12) 1.10 (0.65, 1.86) Ever smoker 0.95 (0.81, 1.11) Never-smoker 1.29 (1.03, 1.63)	Controls from the general population. Adjusted for cigarette smoking history, education, history of employment in high-risk occupation, family history of bladder cancer, age, race and sex Very similar OR for arsenic intake from water
Steinmaus et al. (2013) Chile Case–control	Incidence bladder cancer	232/640 33/202 33/189 71/142 95/107	**Lifetime average water As (μg/L)** < 26 26–79 80–197 > 197	**OR (95% CI)** 1.0 (reference) 0.92 (0.52–1.61) 2.62 (1.53–4.50) 6.00 (3.38–10.64)	Hospital-based controls. Adjusted for age, sex, smoking, mining work, race, BMI and SES
Wu et al. (2013) Taiwan Case–control study	Urothelial carcinoma	261/672 36/224 55/224 170/224	**u-tiAs (μg/L)** < 11.50 11–50-20.40 ≥ 20.40	**OR (95% CI)** 1.0 1.50 (0.95–2.39) 4.68 (3.06–7.14)	Controls from the hospital having a health examination Adjusted for age, sex, educational level and alcohol consumption. Evaluation of arsenic-smoking in interaction analyses
Mostafa and Cherry (2015) Bangladesh Case–control study	Urothelial carcinoma (formerly termed transitional cell carcinoma) (histologically confirmed)	1446/1078 238/206 319/190 204/145 278/244 251/143 156/150	**Water As μg/L** < 10 10 < 50 50 < 100 100 < 200 200 < 300 300 or more	**OR (95% CI)** 1.0 1.52 (1.08–2.14) 1.07 (0.73–1.57) 0.99 (0.69–1.41) 1.63 (1.08–2.46) 0.89 (0.55–1.43)	Controls having benign lesions in the ureter, bladder or urethra Adjusted for sex and smoking
Baris et al. (2016) USA, New Hampshire Case–control study	Newly diagnosed histologically confirmed carcinoma of the urinary bladder (including carcinoma in situ)	1213/1418 280/314 260/309 233/304 220/248 26/33 37/29 233/313 269/308 260/311 213/247 34/29 47/29	**Average water As concentration, μg/L, average over 40 years** ≤ 0.4 > 0.4–0.7 > 0.7–1.6 > 1.6–5.7 > 5.7–8.7 > 8.7 **Cumulative As intake, mg, lagged 40 years** ≤ 3.5 > 3.5–8.8 > 8.8–22.4 > 22.4–83.5 > 83.5–124.8 > 124.8	**OR (95% CI) Bladder Cancer** 1.0 (reference) 0.91 (0.71–1.17) 0.93 (0.72–1.20) 1.06 (0.81–1.40) 0.92 (0.51–1.66) 1.49 (0.85–2.61) **OR (95% CI) Bladder Cancer** 1.00 (reference) 1.13 (0.87–1.47) 1.21 (0.92–1.58) 1.28 (0.95–1.72) 1.72 (0.96–3.10) 2.24 (1.29–3.89)	Control subjects selected randomly, and frequency matched to cases by state, sex and five-year age group at diagnosis. Adjusted for age, sex, Hispanic ethnicity, state of residence, smoking status, high-risk occupation and exposure to disinfection by-products Adjusted for age, sex, Hispanic ethnicity, state of residence, smoking status, high-risk occupation and exposure to disinfection by-products

TABLE 12 (Continued)

Reference study population design	Outcome definition	Population size (*n*) case/control	Arsenic exposure	Results	Additional information/confounders
Huang et al. (2018) Taiwan Case–control study	Bladder cancer	216/813 72/204 64/203 46/203 34/203	**u-tiAs (μg/L)** ≤ 9.78 9.78–17.91 17.91–30.28 > 30.28	**OR (95% CI)** 1.00 (reference) 1.94 (1.18–3.20) 2.09 (1.18–3.69) 3.52 (1.77–6.96)	Hospital-based study. Non-cancer controls were recruited from those receiving health examinations. Adjusted for age, gender, schools, father's educational level, cigarette smoking, alcohol, tea and coffee drinking, pesticide contact, urinary tract calculus, hypertension and diabetes history, and urinary creatinine

Abbreviations: As, arsenic; BMI, body mass index; CI, confidence interval; IRR, incidence rate ratio; *n*, number; OR, odds ratio; RR, relative risk; SES, socioeconomic status; USA, United States of America; u-tiAs, total urinary iAs (sum of iAs and its methylated metabolites MMA and DMA).

Lung cancer

Based on studies from Taiwan, Japan, Chile, Argentina and the US, IARC concluded that there was sufficient evidence in humans that arsenic in drinking-water causes cancer of the lung and assigned it to Group 1 (IARC, 2004). The 2009 Opinion (EFSA CONTAM Panel, 2009) focussed on epidemiological studies on lung cancer in humans informing on dose–response at exposure levels below 100 µg/L in drinking water. The CONTAM Panel noted that some of the studies published since the IARC report supported an excess risk of lung cancer whereas others did not.

The CONTAM Panel identified 19 recent research articles on arsenic exposure and risk for lung cancer. Ten out of these 19 did not meet the inclusion criteria (D'Ippoliti et al., 2015; Fan et al., 2016; Ferdosi et al., 2016; Gamboa-Loira et al., 2017; Huang et al., 2013; Mannetje et al., 2011; Melak et al., 2014; Mendez Jr et al., 2017; Putila & Guo, 2011; Steinmaus et al., 2014b) and were therefore not considered further.

Nine studies that fulfilled the inclusion criteria were considered further (see Table 13) plus the one study that was used in 2009 for deriving the reference point (Ferreccio et al., 2000). This case–control study from Chile found evidence of an arsenic drinking water exposure-related increase in lung cancer incidence (Ferreccio et al., 2000). Also, among cases that never smoked, there was an increased risk of lung cancer in the exposure group with 50–199 µg/L arsenic in drinking water (OR = 5.9, 95% CI 1.2–40.2) versus arsenic ≤ 49 µg/L. A re-analysis of this study performed by Smith and colleagues, which also estimated u-tiAs, found a similar trend in risk, associated with urinary arsenic and with water As levels (Smith et al., 2009). A more recent case–control study in Chile has shown increased lung cancer risk in relation to As exposure dating back to 40 years ago (Steinmaus et al., 2013; 2014a), of which Steinmaus et al. (2014a) focused on exposure levels below 100 µg/L. This more recent case–control study is larger than the first one presented by Ferreccio et al. (2000) and Smith et al. (2009), and the choice of controls is superior. Results from this study in Chile (Steinmaus et al., 2014a) also indicates that the risk of lung cancer in adult age is affected by exposure during childhood or adolescence, and suggest that early-life exposures carry a higher risk than exposures during adulthood. A cohort study from Taiwan reported an increased risk of lung cancer with drinking water concentrations of 100 µg/L arsenic, while no excess risk was found in the 10–99 µg/L As concentration range (Chen et al., 2010). In never-smokers, a tendency toward increasing risk was found with higher arsenic in drinking water (OR = 1.22, 95% CI 0.64–2.32 among cases with 10–99.9 µg/L, OR = 1.32, 0.64–2.74 among cases with ≥ 100 µg/L, compared with arsenic < 10 µg/L). In a follow-up study, a higher risk of lung cancer was found among those individuals that had a low methylation capacity. However, the study was based on only 39 cases of lung cancer in total (Hsu, Tsui, et al., 2017).

In a cohort study from Bangladesh with arsenic-contaminated water, lung cancer mortality was not associated with either concentrations of arsenic in drinking water or urinary As levels (Argos et al., 2014).

A population-based study from the U.S. found evidence of an increased risk of small cell and squamous cell carcinomas of the lung in the highest tertile of toenail As, but no overall association with lung cancers or interaction effect between arsenic exposure and cigarette smoking in relation to lung cancer risk (Heck et al., 2009). No increased lung cancer risk was found in a case–control study from the U.S. (Dauphiné et al., 2013). However, in a large U.S. cohort study, an association with lung cancer mortality was found in the highest tertile of u-tiAs (García-Esquinas et al., 2013).

In summary, the epidemiological studies provide sufficient evidence for an association between low to moderate exposure to iAs and lung cancer.

The results for the key studies are summarised in Table 13.

TABLE 13 Key epidemiological studies on lung cancer and As exposure.

Reference study population design	Outcome definition	Population size (*n*) cases/controls	Arsenic exposure	Results	Additional information/confounders
Ferreccio et al. (2000) Chile Case–control	Incidence lung cancer	151/419 9/104 5/39 8/23 50/124 79/129	**Average water As conc. (μg/L)** 0–10 10–29 30–49 50–199 200–400	**OR (95% CI)** 1.0 (reference) 1.60 (0.50–5.30) 3.90 (1.20–12.30) 5.20 (2.30–11.70) 8.90 (4.00–19.60)	Hospital-based controls. Adjusted for age, sex, cumulative lifetime cigarette smoking, years of work in copper smelting and socioeconomic status
Heck et al. (2009) USA, New Hampshire and Vermont Population-based case–control	Primary incident lung cancer	223/238 69/65 66/58 44/58 44/57 75/238 17/65 24/58 13/58 21/57	**Average toenail As conc. (μg/g)** < 0.05 0.05 – < 0.0768 0.0768 – < 0.1137 ≥ 0.114 **Average toenail As conc. (μg/g)** < 0.05 0.05 – < 0.0768 0.0768 – < 0.1137 ≥ 0.114	**OR (95% CI)** **Lung cancer** 1.0 1.34 (0.71–2.53) 1.10 (0.55–2.20) 0.89 (0.46–1.75) **Small cell and squamous cell carcinomas** 1.0 2.99 (1.12–7.99) 1.86 (0.62–5.58) 2.75 (1.00–7.57)	Adjusted for sex, age, race/ethnicity, educational attainment, BMI, fish servings per week, smoking (pack-years) and selenium
Smith et al. (2009) Chile Case–control	Incidence lung cancer from national cancer registry	151/419 11/92 7/81 35/87 23/44 11/12 64/103	**Average water As/urinary As exposure (μg/L)** < 10/4.9 10–59/34.0 60–199/126.1 200–399/291.0 400–699/533.5 700–999/824.5	**OR (95% CI)** 1.0 (reference) 0.70 (0.30–1.70) 3.40 (1.80–6.50) 4.70 (2.00–11.00) 5.70 (1.90–16.90) 7.1 (3.4–14.8)	Re-analysis of the Ferreccio et al. (2000) study and the addition of urine derived from water levels (Smith et al., 2009). Adjusted for age, sex, cumulative lifetime cigarette smoking, years of work in copper smelting and socioeconomic status
Chen et al. (2010a) Taiwan, arseniasis-endemic area Cohort study	Incidence primary lung cancer from national cancer registry	*N* = 8086, 6888 with Water As, 178 cases 48 cases 51 cases 20 cases 28 cases 31 cases	**Water As (μg/L)** < 10 10–49.9 50–99.9 100–299.9 > 300 μg/L	**RR (95% CI)** 1.0 (reference) 1.10 (0.74–1.63) 0.99 (0.59–1.68) 1.54 (0.97–2.46) 2.25 (1.43–3.55)	Adjusted for age, sex, education, smoking status, alcohol consumption. Significant trends for squamous cell and small cell carcinomas but not for adenocarcinoma. No interaction with smoking
Dauphiné et al. (2013) Nevada and Kings County, California Case–control	Incidence primary lung cancer, histological confirmation	196/359 141/241 37/82 18/36	**Water As: Highest 5-year average: 10-years lag** ≤ 10 11–84 ≥ 85	**OR (95% CI)** 1.0 (reference) 0.75 (0.45–1.25) 0.84 (0.41–1.72)	Randoms controls from the area, frequency-matched by age group. Adjusted for age, sex, education, smoking history and possible exposure to another known lung carcinogen. Also, no association with 40-year lag or cumulative exposure

(Continues)

TABLE 13 (Continued)

Reference study population design	Outcome definition	Population size (*n*) cases/controls	Arsenic exposure	Results	Additional information/confounders
García-Esquinas et al. (2013) USA, Arizona, Oklahoma and North/South Dakota Cohort study	Mortality lung cancer from the health register of the state	*N* = 3932 78 cases /3857 referents 27/1292 20/1296 31/1269	**u-tiAs (µg/g creatinine)** < 6.91 6.91–13.32 > 13.32	**HR (95% CI)** 1.0 (reference) 0.94 (0.51–1.72) 1.82 (1.00–3.31)	Adjusted for sex, age, education, smoking status, drinking status and BMI
Steinmaus et al. (2013) Chile Case–control	Incidence lung cancer	306/640 61/202 61/189 85/142 99/107	**Lifetime average water As (µg/L)** < 26 26–79 80–197 > 197	**OR (95% CI)** 1.0 (reference) 0.98 (0.62–1.53) 1.70 (1.05–2.75) 3.18 (1.90–5.30)	Hospital-based. Adjusted for age, sex, smoking, mining work, race, BMI and SES
Steinmaus et al. (2014a) Chile Case–control	Primary lung cancer	92/288 23/103 32/98 37/87 25/102 31/99 36/87 27/103 29/95 36/90	**Mean water As 40 or more years ago (highest single year) (µg/L)** 6.5 23.0 58.6 **Mean water As 40 or more years ago (highest 5-year average) (µg/L)** < 10.0 10.0–54.0 > 54.0 **Mean water As 40 or more years ago (lifetime average) (µg/L)** < 6.0 6.0–22.1 > 22.1	**OR (90% CI)** 1.00, 1.43 (0.82, 2.52) 2.01 (1.14, 3.52) 1.00 1.27 (0.73, 2.20) 1.78 (1.02, 3.11) 1.00 1.14 (0.67, 1.95) 1.56 (0.91, 2.67)	Controls without lung, bladder or kidney cancer were randomly selected from the Chilean Electoral Registry and were frequency-matched by sex and 5-year age group. Adjusted odds ratios by tertile of the highest known exposure 40 or more years ago. Adjusted for age, sex and smoking behaviour
Argos et al. (2014) Bangladesh Cohort	Lung cancer mortality	90 lung cancer deaths/26,043 With baseline water As 12 11 19	**Water As (µg/L)** < 14 14.0–82.9 ≥ 83.0	**HR (95% CI)** 1.0 0.85 (0.38–1.93) 1.15 (0.55–2.38)	Adjusted for sex, age, body mass index, education, smoking status and study cohort. Water and urinary As concentrations correlated by 0.7

TABLE 13 (Continued)

Reference study population design	Outcome definition	Population size (*n*) cases/controls	Arsenic exposure	Results	Additional information/confounders
Hsu, Tsui, et al. (2017) Taiwan, arseniasis-endemic area Cohort	Incident lung cancer	39/1300 (numbers in each exposure category not available)	**As in water (μg/L)** Each 50 increment **Water As (μg/L)** 2–10 10.01–100 100.01–200 > 200 **Water As (μg/L)** 2–10 10.01–100 100.01–200 > 200	**HR (95% CI)** 1.03 (1.00–1.07) **Low methylation capacity: Incidence densities/year** 0.000799 0.002277 0.002646, 0.004674 **High methylation capacity: Incidence densities/year** 0 0.000410 0 0.001585	Study follow-up of Chen et al. (2010b) but unclear how the studies are linked. Adjusted for age, sex, education, occupation, marriage, cigarette smoking and alcohol drinking Low methylation capacity group defined as those whose PMI or SMI was lower than their respective median values

Abbreviations: As, arsenic; BMI, body mass index; CI, confidence interval; conc., concentration; HR, hazard ratio; *n*, number; OR, odds ratio; PMI, primary methylation index; RR, relative risk; SES, socioeconomic status; SMI, secondary methylation index, USA, United States of America; u-tiAs, total urinary iAs (sum of iAs and its methylated metabolites DMA and MMA).

Breast cancer

Garland et al. (1996) explored the relationship between As, measured in toenails and breast cancer in a nested case–control study of 892 individuals within the Nurses' Health Study cohort. After 5 years of follow-up, the authors reported no association between arsenic concentrations and breast cancer risk (OR Q5 vs. Q1 = 1.12, 95% CI 0.66–1.91, *p*-trend = 0.78). One study used a food frequency questionnaire to quantify As exposure from diet alone and found no association between level of As exposure and breast cancer risk in a Japanese population (Hazard Ratio [HR] = 1.06, 95% CI 0.8–1.41) (Sawada et al., 2013).

In a case–control study from a region in Mexico with elevated As in drinking water, lower total arsenic concentrations in urine were found in women with breast cancer compared with controls (cases median 14.33 μg/L, 90% 4.58–52.24; vs. controls 19.96 μg/L, 90% 6.40–100.04, $p < 0.001$) (López-Carrillo et al., 2014). However, a higher risk for breast cancer was found with lower arsenic methylation capacity. Lower total iAs in urine among patients with breast cancer compared with controls, as well as higher risk of breast cancer among women with lower methylation capacity were reported in another case–control study from the same area (López-Carrillo et al., 2020). The authors hypothesise that the lower concentrations of arsenic in urine among cases is due to less efficient metabolism of arsenic than among the controls. However, it is unclear why this phenomenon would occur for patients with arsenic-related breast cancer and not for other types of iAs-related cancer. In a study of young onset breast cancer in discordant sister pairs, there was no association between low-level arsenic concentrations in toenail clippings (cases sisters' median arsenic 0.049 μg/g, IQR 0.037–0.070; and control sisters 0.048 μg/g IQR 0.034–0.069) and breast cancer risk (O'Brien et al., 2019). In a U.S. cohort study, no increased risk for breast cancer mortality was found with increasing As concentrations in urine (García-Esquinas et al., 2013).

In further original research articles, arsenic exposure and breast cancer were evaluated, but the studies were not considered further, either because the exposure was based on rice intake as a proxy for arsenic intake (Zhang et al., 2016), or arsenic concentrations in whole blood or in air (Liu et al., 2015; Marciniak et al., 2020, 2021).

In summary, the epidemiological studies provide insufficient evidence for an association between low to moderate exposure to iAs and breast cancer.

Prostate cancer

The 2009 IARC assessment considered the evidence that arsenic causes cancer of the prostate 'limited' (Straif et al., 2009).

Earlier ecological studies have found excess of prostate cancer in relation to iAs exposure (Hinwood et al., 1999; Lewis et al., 1999). A report from the southwest of Taiwan, an area with high endemic As concentrations, found a decline in SMRs for prostate cancer since the introduction of tap water with lower As concentrations, suggesting the association may be causal (Yang et al., 2008). As a follow-up to this study, Hsueh et al. (2017) found in a case–control study from a non-endemic area in Taiwan that participants with u-tiAs a concentration > 29.28 μg/L had a significantly higher risk (OR 1.75, 1.06–2.89) of prostate cancer than participants with less than 29.28 μg/L. In a U.S. cohort study, arsenic exposure (median u-tiAs 9.7, IQR 5.8–15.6, μg/g creatinine), was prospectively associated with prostate cancer mortality (adjusted HRs comparing the 80th vs. 20th percentiles of arsenic 3.30, 95% CI 1.28–8.48; García-Esquinas et al., 2013). In a case–control study in Cordoba, Argentina, a synergistic effect of having As in drinking water above 10 μg/L and being a rural worker was found for prostate cancer risk. However, no effect estimates were presented for arsenic only (Román et al., 2018).

In summary, the epidemiological studies provide insufficient evidence for an association between low to moderate exposure to iAs and prostate cancer.

Kidney cancer

The 2009 IARC assessment considered the evidence 'limited' that iAs causes cancer of the kidney (Straif et al., 2009).

No association between As exposure and kidney cancer was found in a study from Australia (Hinwood et al., 1999), or a study from Utah (Lewis et al., 1999). In an ecological study on two regions in Chile with different concentrations in arsenic in drinking water, a higher mortality from kidney cancer was found in the region with high arsenic drinking water concentrations (Yuan et al., 2010), and with increased risks manifesting 40 years after exposure reduction (Smith et al., 2018). In a case–control study in Chile based on cases (renal cell carcinoma and transitional cell renal pelvis and ureter, and other kidney cancers) recruited 2007–2010, with individual data on exposure and potential confounders, an increased risk for renal pelvis and ureter cancers was found at high exposure level (Ferreccio, Smith, et al., 2013): the adjusted odds ratios by average arsenic intakes of < 400, 400–1000 and > 1000 μg/day (median water concentrations of 60, 300 and 860 μg/L) were 1.00, 5.71 (95% confidence interval: 1.65, 19.82) and 11.09 (3.60, 34.16) ($p < 0.001$), respectively. Odds ratios were not elevated for renal cell cancer. However, in an ecological study of cases and referents (benign cases) from Bangladesh with low-level exposure, the risk for renal cell carcinoma increased monotonically with arsenic concentration > 50 μg/L for renal cell carcinoma (Mostafa & Cherry, 2013). Stratification by 'ever smoked' confirmed the presence of risk in non-smokers. In areas with hand-pumped wells installed more than 15 years ago, the excess risks were observed below 50 μg/L arsenic in drinking water. In a U.S. cohort study, no association was found between increasing u-tiAs concentrations and kidney cancer mortality (García-Esquinas et al., 2013). However, an ecological study from the U.S. showed positive association between the highest quartile of exposure (aggregated cumulative county-level arsenic concentration > 12.89 ppb-year), compared to

the lowest (< 3.83 ppb-year) for kidney cancer weighted for proportion of population served by community water system adjusted risk ratio: 1.69 (1.37, 2.09) (Krajewski et al., 2021).

In summary, the epidemiological studies provide insufficient evidence for an association between low to moderate exposure to iAs and kidney cancer.

Other cancers

The 2009 IARC assessment considered the evidence 'limited' for cancers of the liver and prostate (Straif et al., 2009).

There were few studies on low-to-moderate As exposure and risk of cancers of the pancreas, liver and gallbladder and there were few with individual arsenic exposure data taking organic arsenic species into account. Here ecological studies are described where follow-up case–control studies have been performed.

Arsenic has been linked to liver and pancreatic cancers from ecological observations. Neonatal exposure to arsenic from contaminated milk was associated with increases in liver and pancreatic cancer (Yorifuji et al., 2011). An ecological study from Florida also found that pancreatic cancer patients living within 1 mile of known arsenic-contaminated wells were significantly more likely to be diagnosed within a cluster of pancreatic cancers relative to cases living more than 3 miles from known sites (OR = 2.1, 95% CI = 1.9, 2.4) (Liu-Mares et al., 2013). In a Spanish case–control study, where arsenic in toenails was measured before the cancer treatment, an increased risk of pancreatic cancer was found (OR = 2.02, 95% CI 1.08–3.78; $p = 0.009$) when comparing the highest quartile (> 0.1061 μg/g) versus the lowest quartile (< 0.0518) of concentrations of arsenic on toenails (Amaral et al., 2012). Additional adjustment for the elements found significant in the basic model attenuated the OR estimate, and association with arsenic was no longer statistically significant (highest vs. lowest quartile: OR = 1.72, 95% CI 0.77–3.86; $p = 0.201$). In a U.S. cohort study, arsenic exposure (median urine iAs metabolite concentrations 9.7, IQR 5.8–15.6, μg/g creatinine), was prospectively associated with pancreatic cancer mortality (adjusted HRs comparing the 80th vs. 20th percentiles of arsenic 2.46, 95% CI 1.09–5.58; García-Esquinas et al., 2013).

For liver, Wadhwa et al. (2011) reported increased hair and blood levels of arsenic among liver cancer cases from an exposed area in Pakistan, but no risk estimates or dose–response were reported. Further, in a U.S. cohort study, no association was found between increasing total sum of urinary iAs metabolite concentrations and liver cancer mortality (García-Esquinas et al., 2013).

Head and neck cancers have been linked to arsenic exposure. Still, the data published suffer from several drawbacks which makes it difficult to draw firm conclusions. Either the studies were confounded by high frequency of smokers and alcohol drinkers in the case group, and no analysis was performed among non-smokers or non-drinkers (Pal et al., 2017; Pal & Halder, 2019), or only total arsenic was measured in blood or in serum precluding conclusions regarding exposure to iAs (Chen, Qiu, et al., 2021; Khlifi et al., 2014). However, one case–control study on arsenic in non-smoking tobacco included only non-smoking and non-alcohol drinking study participants (Arain et al., 2015). The cases and controls differed in arsenic concentrations in hair and blood, but no risk estimates were provided.

In a large study, 259 patients with gallbladder cancer, 701 patients with gallstones and 851 population-based controls from China were analysed for total serum arsenic, however, with no speciation or adjustment of seafood intake (Lee et al., 2020). A reduced risk of gallbladder cancer was found with increasing As. For stomach and ovarian cancers, only ecological studies were found (Amin, Ross, et al., 2019; Chen et al., 2015; Núñez et al., 2016). No other cancers have been found to be consistently related to drinking water As exposure.

In summary, the epidemiological studies provide insufficient evidence for an association between low to moderate exposure to iAs and liver, pancreatic and gallbladder cancer.

3.2.2.3 | *Skin lesions*

The potential of iAs to induce skin lesions such as hypo- or hyperpigmentation and hyperkeratosis has been well known since the 1960s (Tseng et al., 1968). The 2009 Opinion concluded that As concentrations in drinking water or urine below 100 μg/L were associated with increased incidences of skin lesions (EFSA CONTAM Panel, 2009).

For the present Opinion, the CONTAM Panel identified 18 studies published since 2009 from a literature search (see Section 3.2.2.1). Out of these, three studies met the inclusion criteria which were considered further together with the studies in Bangladesh (Ahsan et al., 2006) and Mongolia (Xia et al., 2009) that were used to calculate reference points in the 2009 Opinion (see Table 14). Fifteen studies did not meet the inclusion criteria (Argos et al., 2015; Das et al., 2016; Guha Mazumder et al., 2009, 2010, 2014; Guo et al., 2006; Hashim et al., 2013; Kazi et al., 2009; Li et al., 2011; Liao et al., 2010; Sy et al., 2017; Wei et al., 2018; Wen et al., 2012; Yajima et al., 2018; Zhang et al., 2014).

The study by Ahsan et al. (2006) (statistically significant increases in men) and Xia et al. (2009) (statistically significant increases in men and women combined) showed increased risks below < 10 μg/L of As in drinking water. Furthermore, in the study from Inner Mongolia, China, 5% (632) of the 12,334 residents surveyed had skin lesions characteristics of arsenic exposure (Xia et al., 2009).

In a study in Bangladesh from Pierce et al. (2011) increased risks (men and women combined) were found at 50–100 μg/L. The study by Pierce et al. (2011) is a follow-up study of Ahsan et al. (2006) and is in addition focusing on the role of the diet.

In a new study from Inner Mongolia increasing prevalence of skin lesions were found, particularly in men, in the concentration range 10–100 μg/L (Yang et al., 2017). However, no statistical analysis was performed.

In a study from Pakistan (Fatmi et al., 2013), cases with skin lesions were identified among households with water source concentrations above 50 µg/L. The prevalence of cases with skin lesions was 4.5% in the group with water concentrations 50–99 µg/L, and 14.8 in the group with water concentrations 100–299 µg/L.

Several studies have evaluated modifying factors for the association between arsenic exposure and skin lesions. Higher risks of arsenic-related skin lesions are for males (Rahman et al., 2006), having low body weight (Guha Mazumder et al., 1998), low levels of amino acids (Wei et al., 2019), impaired one-carbon metabolism (Pilsner et al., 2009), being anaemic (Kile, Faraj, et al., 2016) and poor arsenic metabolism efficiency (Kile et al., 2011; Yang et al., 2017).

In a large genome-wide association study in Bangladesh, Pierce et al. (2012) identified the arsenic methylating gene *AS3MT* to be associated with arsenic metabolism and risk of arsenic skin lesions.

The key studies on skin lesions are presented in Table 14.

In summary, the epidemiological studies provide sufficient evidence that low to moderate arsenic concentrations in drinking water are associated with an increased risk of skin lesions.

Nevertheless, since the major studies are performed in low and medium income regions, and nutrition and health status are modifying factors, it is difficult to translate the risks to populations with more adequate nutrition such as in Europe. The CONTAM Panel is not aware of studies with Western populations showing an association of skin lesions with arsenic exposure.

TABLE 14 Key epidemiological studies on skin lesions and As exposure.

Reference study population design	Outcome definition	Population size (*n*) case/control	Arsenic exposure concentration in water (μg/L)	Results odds/risk ratio (95% CI)	Additional information/confounders
Ahsan et al. (2006) Bangladesh Cross-sectional	Dermal lesions	Cases/total 57/2259 90/2122 144/2202 162/2185 242/2183	 0.1–8.0 8.1–40.0 40.1–91 91.1–175 175.1–864.0	**POR (prevalence odds ratio)** 1.00 (reference) 1.91 (1.26, 2.89) 3.03 (2.05, 4.50) 3.71 (2.53, 5.44) 5.39 (3.69, 7.86)	Adjusted for age, BMI, education, cigarette smoking, hukka (waterpipe) smoking, sun exposure in males and land ownership
Xia et al. (2009) Inner Mongolia, China Cross-sectional	Dermal lesions	 3215 845 1277 3429 1537 1021 92	 0–5 5.1–10 10.1–20 20.1–50 50.1–100 100.1–300 >300	**OR** 1.0 2.52 (1.47–4.30) 2.83 (1.773–4.525) 3.94 (2.78–5.59) 6.03 (4.05–8.97) 8.83 (5.77–13.51) 7.94 (2.73–23.12)	At the time of interview, they collected water samples at the household's primary source of water Adjusted for drinking, smoking, education, sex, farm work, income, well type and age
Pierce et al. (2011) Bangladesh Longitudinal (cohort) study	Dermal lesions	Cases/total 131/2358 125/2118 140/1726 318/2855 100/617	 0.1–10 10.1–50 50.1–100 100.1–200 ≥200.1	**HR** 1.00 1.17 [0.92, 1.50] 1.70 [1.34, 2.16] 2.22 [1.81, 2.73] 3.76 [2.85, 4.95]	Follow-up of Ahsan et al. (2006). Age- and sex-adjusted effect estimates. Skin lesion incidence was defined as a new occurrence of skin lesions of any type (as determined at one of the follow-up interviews) among individuals who previously had no manifestation of any lesion (as determined at baseline and previous follow-up interviews)
Fatmi et al. (2013) Pakistan Nested case-referent study	Dermal lesions	72/462 44 315 78 97	 50–99 100–299 300–399 >400	**Prevalence (%)** 4.5 (2.74–6.26) 14.8 (10.88–18.72) 11.7 (13.85–20.23) 12.8 (9.24–14.76)	Nested study was based on household with water arsenic concentrations >50 μg/L. No adjustments but stratified analysis was performed for age, sex and smoking
Yang et al. (2017) Inner Mongolia Cross-sectional	Dermal lesions	168/380	 <10 10–100 100–200 200–300 300–400 >400	**Prevalence (%)** F M 19.2 19.4 22.6 25 24.6 37.5 38.8 21.9 47.5 52.9 38.5 61.9	No information about number of case/controls in each arsenic in water concentration group. No adjustments

Abbreviations: As, arsenic; BMI, body mass index; CI, confidence interval; f, female; HR, hazard ratio; m, male; *n*, number; OR, odds ratio; POR, prevalence odds ratio.

3.2.2.4 | *Developmental toxicity*

The previous EFSA assessment on arsenic (EFSA CONTAM Panel, 2009) considered the following developmental outcomes in humans: birth weight (BW), preterm birth (PTB), fetal loss/infant death, birth defects and cognitive performance.

Many additional studies on arsenic exposure and developmental effects in humans has been published since the previous EFSA Opinion. In addition to the outcomes previously considered, the CONTAM Panel also reviewed associations between prenatal exposure to iAs and additional outcomes related to fetal growth, namely GA, fetal growth and anthropometric outcomes in childhood.

Birth weight

In the previous EFSA Opinion (EFSA CONTAM Panel, 2009) it was noted that *'there is emerging evidence of negative impacts on fetal and infant development, particularly reduced birth weight, and there is a need for further evidence regarding the dose-response relationships and critical exposure times for these outcomes'*. Regarding birth weight, only five studies were available at that time (Hopenhayn et al., 2003; Huyck et al., 2007; Myers et al., 2010; Rahman et al., 2009; Yang et al., 2003 [see Table 15]). One of these studies was very small (Huyck et al., 2007), and for two studies exposure assessment was based on aggregated water arsenic.

The CONTAM Panel identified 40 additional papers that were not included in the EFSA 2009 Opinion. In 25 of these papers, As exposure and birth weight were reported, but the studies were not considered further either because exposure was assessed by total As in blood, serum or urine and it was not possible to evaluate the contributions of organic vs. inorganic As (Bermúdez et al., 2015; Bloom et al., 2015; Deyssenroth et al., 2018; Govarts et al., 2016; Guan et al., 2012; Hameed et al., 2019; Henn et al., 2016; Lee et al., 2021; Liao et al., 2018; Liu et al., 2018; Mullin et al., 2019; Nyanza et al., 2020, Rahman, Oken, et al., 2021; Remy et al., 2014; Röllin et al., 2017; Wang, Li, Zhang, et al., 2018; Wang, Wang, Wang, et al., 2022; Xu et al., 2011; Xu, Hansen, et al., 2022), and/or the papers did not explicitly report associations between As exposure and birth weight (Fei et al., 2013; Mullin et al., 2019; Muse et al., 2020; Remy et al., 2014; Saha et al., 2012; Thomas et al., 2015; Wai et al., 2020; Wei, Shi, et al., 2017).

In 15 of the studies not previously evaluated exposure assessment was based on water arsenic, urinary inorganic arsenic (iAs species, MMA, or DMA or u-tiAs), toenail As or hair-As, and results on associations with birth weight (BW) were reported. These 15 studies, and the five reviewed in the 2009 Opinion are summarised in Table 15.

Three of the five studies reviewed in the 2009 Opinion indicated that infants born to women who drink water with elevated arsenic concentrations during pregnancy have a lower birthweight (Hopenhayn et al., 2003; Rahman et al., 2009; Yang et al., 2003). However, the longitudinal study, carried out in Bangladesh, showed a significant negative association between birthweight or head and chest circumferences and urinary As in the low concentration range (< 100 µg/L in urine), but no further negative effects were shown above about 100 µg/L (Rahman et al., 2009). A study performed in Mongolia did not show adverse birth outcomes (Myers et al., 2010).

In a publication not reported in the 2009 Opinion, Kwok et al. (2006) studied low birth weight (LBW) in 2006 live births in 261 rural Bangladesh villages. No significant association was found between water As and the risk of LBW.

Gelmann et al. (2013) reported 'a pilot study' with 19 live births selected from Romanian villages with elevated As in drinking water and 19 from villages with low As in water. Among 19 infants from the As-exposed villages, u-tiAs was significantly higher in infants with LBW compared to infants with normal BW.

Chou et al. (2014) studied associations between maternal u-tiAs and BW in 299 infants in Taiwan and found a significant association between u-MMA (but not the other species) and BW.

Laine et al. (2015) found no significant association between water As, u-tiAs, or u-DMA and BW in 199 Mexican infants. For u-MMA there was a significant inverse association. It was attenuated when GA (which was inversely associated with u-MMA) was added to the model.

Bloom et al. (2016) found no overall significant association between maternal As in drinking water (mean 4.1 µg/L) and BW in 122 infants in Romania.

Gilbert-Diamond et al. (2016) found no significant associations between maternal u-tiAs, MMA or DMA and BW in infants in New Hampshire, US. However, the median concentration of As in water was only 0.5 µg/L (P75 2.7 µg/L) Therefore, in contrast to the above-mentioned studies these women had a low As intake from drinking water, and other dietary sources would be important. Results were unchanged if women with recent seafood or rice consumption were excluded.

Kile, Cardenas, et al. (2016) found a statistically significant inverse association between household water As and BW, and between maternal nail-As and BW in 1153 infants in rural Bangladesh. Structural equation modelling suggested that almost all the association was mediated by GA (which was inversely associated with water As and toenail-As).

Rahman et al. (2017) used the same study base as in Kile, Cardenas, et al. (2016) and found similar overall associations in 1180 infants but used mediation analysis instead of structural equations. Again, most of the association with BW was mediated by GA ('indirect effect'), while among the smallest (< p20) infants there was also a direct effect.

Lin et al. (2019) also used this Bangladesh study base (now 1057 infants) but used only toenail As and focused on the possible interaction between As and macronutrients (total energy, fat, carbohydrate and fibre intakes). Maternal intakes of macronutrients were associated with BW, but toenail As did not mediate these associations. Interestingly, in regression models adjusted for energy intake and a number of additional potential confounders compared with the study by Kile, Cardenas, et al. (2016), the inverse relation between toenail As and BW was no longer statistically significant (in contrast to the finding in Kile, Cardenas, et al., 2016).

A fourth paper based on the same Bangladesh study base as in Kile, Cardenas, et al. (2016) was published by Bozack et al. (2020). It included 413 infants with data on the percentage of DNA methylation of CpG sites in cord blood. A significant inverse association was found between toenail As and BW, mediated by GA and DNA methylation, indicating an involvement of epigenetic programming. Analyses were not adjusted for intake of macronutrients.

Almberg et al. (2017) found no statistically significant association between water-As and LBW in > 400,000 live singleton births in Ohio, US. The median water-As in community water systems by county was 1.5 µg/L (range 0.5–12 µg/L). There was no overall association between water As and LBW (OR 0.99 (0.98–1.10)) or VLBW, but when the analyses were restricted to counties where use of private wells were uncommon (< 10% of households) 20 counties with about 216,000 births remained. Then the adjusted OR for LBW was 1.06 (95% CI 0.98–1.15) and for VLBW it was 1.14 (1.04–1.24). The presence of private wells is assumed to cause misclassification, since exposure categorisation was only based on water As in community water systems.

Shih et al. (2020) found no significant association between u-DMA and BW in a mother–child cohort from seven areas in the US. The LODs were high, so only total u-As and u-DMA could be quantified.

Howe, Farzan, et al. (2020) found no significant associations between maternal u-tiAs and BW in 167 infants from Los Angeles US. There was an inverse association between hair-As and BW, but the levels of hair As were very low (median 0.01 µg/g).

In another population from Los Angeles, Howe, Claus Henn, et al. (2020) found no statistically significant associations between maternal ui-As and BW in relation to GA in 262 mother-infant pairs.

Bulka et al. (2022) estimated the probability that As in private well water exceeded certain cut-offs in the whole of US and compared aggregated estimates on county level with BW in about 3.3 million births in 2016. Estimates were based on machine learning methods taking into account As measurements and a large number of other factors. Associations between the estimated probabilities for As in water and BW were examined, assuming that also As in public water sources was correlated with As in private wells. Significant associations were found as shown in Table 15, though the methods and units make it difficult to evaluate the magnitude of association.

Among the 19 studies using water As, u-tiAs or toenail As as exposure metrics, the studies by Huyck et al. (2007) and Gelmann et al. (2013) examined very few births. The study by Shih et al. (2020) had high As detection limits. These three studies are therefore less informative in risk assessment.

Overall summary on As and birth weight (BW)

Overall, several studies on exposure to iAs, mainly from As in drinking water show an inverse association with BW. Exposure misclassification (both in Bangladesh and elsewhere), and questionable adjustment for GA may have attenuated some exposure-outcome estimates. The studies from Bangladesh (Kile, Cardenas, et al., 2016; Rahman et al., 2009) provide strong evidence for reduced BW at low to moderate exposure to iAs. The studies from Chile (Hopenhayn et al., 2003) and Taiwan (Yang et al., 2003) provide moderate evidence for such an association, but there was no association in studies from Mongolia (Myers et al., 2010) and Mexico (Laine et al., 2015). The US studies have low exposure to iAs, low exposure contrast, and there may be an impact of organic As on the As biomarkers, e.g. DMA. This makes these studies less informative. The US study by Bulka et al. (2022) found a significant association despite crude estimates on the individual level, which causes misclassification and therefore may have attenuated a true association. In Bangladesh maternal and fetal undernutrition is common, and low BW and PTB is much more common than in Europe. Therefore, it is uncertain if the findings from Bangladesh are relevant for European populations.

In summary, the epidemiological studies provide sufficient evidence for an association between low to moderate exposure to iAs and BW in Bangladesh. Studies from other countries are not consistent. The relevance for Europe of the results from Bangladesh is unclear.

TABLE 15 Key epidemiological studies relating As exposure with birth weight.

Reference study population design	Outcome definition	Population size (*n*)	Arsenic exposure[a]	Results	Additional information/confounders
Included in 2009 EFSA Opinion					
Hopenhayn et al. (2003) Chile Cohort	BW	844 (442 from Antofagasta and 444 from Valparaiso)	Water: Antofagasta: 30–40 µg/L Valparaiso: < 1 µg/L	–57 g in Antofagasta (95% CI -123, +9)	Aggregated w-As data Adjusted for many potential confounders, **including GA**
Yang et al. (2003) Taiwan Cohort	BW	18,259 (3872 from As-exposed townships, and 14,387 from similar reference townships)	Water: In As-exposed townships 30% > 50 µg/L	–29 g (95% CI –44, –14) in As-exposed townships	Aggregated w-As data. Adjusted for some potential confounders
Huyck et al. (2007) Rural Dacca, Bangladesh CS/cohort (samplings early pregnancy and around birth)	BW, LBW	49 live births	Water: max Q1: 0.5, Q2: 1.3, Q3: 9.0, Q4: 734 µg/L. Maternal hair 0.14–3.3, toenail 0.2–6.2 (both t-As µg/g)	–194 g per µg/g As in hair No association between BW and water-As or nail-As OR for LBW versus hair As around 2 but CI included 1	LBW = < 2750 (=median in these newborns). Poor correlations between w-As and most biomarkers Adjusted for a number of potential confounders including GA
Rahman et al. (2009) Matlab Bangladesh Cohort	BW	1578 singleton live births	Maternal u-tiAs: median 95 µg/L	No overall association, but –1.7 g per µg/L in u-tiAs at 0–100 µg/L. Mean BW 2.6 kg	Adjusted for many potential confounders. Exposure from water (70% > 10 µg/L, see Rahman et al., 2006)
Myers et al. (2010) Inner Mongolia, China CS	BW in term births	9890 singleton births 1996–1999 with As measured in the wells of the sub village	Water: 66% < 20, 20% 21–50, 7% 50–100, 7% > 100 µg/L. Data from 1991 to 1997 in well-water registry	No association between BW and water-As categories	w-As data were averaged by sub village. No potential confounders were detected for BW. Women were generally health and well-nourished
Not included in the 2009 Opinion					
Kwok et al. (2006) Rural Bangladesh, 261 villages in 3 districts CS	LBW in term (≥ 37 week) births	2006 live singleton births with As measured in the wells of the villages	Water: 2003 samples, mean about 70 µg/L, six categories < 10 µg/L to > 300 µg/L	Adjusted OR 1.00 for LBW (< 2500 g) in full term births BW not analysed as continuous variable	Water samples (for each household), birth data for 2002, and covariates were collected in 2003 from Community Centres' registers + maternal interviews (2003). Most births at home
Gelmann et al. (2013) Romania CS	LBW	38 singleton live births with LBW and normal BW from As-in-water exposed (19) and unexposed (19) villages	Water: means in exposed 54 µg/L and in unexposed 1 µg/L. u-iAs 2–90 µg/L in exp and 0–1 µg/L in unexposed	Among exposed those with LBW had higher u-tiAs than those with normal BW	Pilot study with too few cases
Chou et al. (2014) Taiwan Cohort	BW, LBW	299 live births, 21 (7%) LBW (< 2500 g)	Maternal u-tiAs. Median 22 µg/g Cr (90% DMA)	Significant adjusted association (multiple linear regression) between u-MMA and BW. No association with LBW	The association btw u-MMA and BW disappeared after further adjustment for DNA damage (N7-MeG)
Laine et al. (2015) Mexico CS	BW	199 singleton live births, only 4 with LBW	Water: < 0.5–236, median 13 µg/L. Maternal u-tiAs median 23 µg/L	w-As, u-tiAs, u-DMA: null U-MMA and U-%MMA had a significant adjusted negative slope	Mean u-DMA 43 µg/L in women reporting seafood and 31 µg/L in the others. The association with BW seemed to be at least partly caused by an association with GA
Bloom et al. (2016) Romania CS	BW	122 live singleton births	Water: mean 4.1 µg/L	No overall association between As and BW	Adjusted for potential confounders. An inverse association was found in the 29 smoking mothers

TABLE 15 (Continued)

Reference study population design	Outcome definition	Population size (*n*)	Arsenic exposure[a]	Results	Additional information/confounders
Gilbert-Diamond et al. (2016) USA, New Hampshire Cohort	BW	706 live singleton births	Maternal u-tiAs. Median 3.4 µg/L	No association between u-tiAs, MMA or DMA and BW	General additive models adjusted for some potential confounders ***including gestational age***
Kile, Cardenas, et al. (2016) Rural Bangladesh Cohort	BW	1153 live singleton births	Water: < 0.5–1400, median 2.3 µg/L Maternal toenail t-As 0.2–35 µg/g, median 1.5 µg/g	Significant adjusted inverse association (multiple linear regression) between water As and BW, and between nail-As and BW	Structural equation modelling suggested that almost all the association was mediated by an association with GA
Almberg et al. (2017) USA, Ohio CS	LBW and VLBW (< 1500 g) in term infants	428,804 live singleton births from records 2006–2008. In term births 2.9% LBW and 1.2% VLBW	W-As aggregated by 88 counties and year: 0.5–12 µg/L, median 1.5 µg/L. Based on 2968 measurements in 975 water systems	Adjusted ORs for LBW (1.00) and VLBW (0.99) were normal	ORs adjusted for many potential confounders from the records ORs were increased in some sub analyses excluding counties with many private wells
Rahman et al. (2017) Rural Bangladesh Cohort	BW	1180 live singleton births, same study base as Kile, Cardenas, et al. (2016)	See Kile, Cardenas, et al. (2016), but median w-As here 2.2 µg/L and nail-As 1.2 µg/g	Associations: See Kile, Cardenas, et al. (2016)	Mediation analyses suggested that most of the association was mediated by GA, but among the smallest infants there was also a direct effect
Lin et al. (2019) Rural Bangladesh Cohort	BW	1057 live singleton births, Same study bas as Kile, Cardenas, et al. (2016) and Rahman et al. (2017)	Toenail As 0.04–47, median 1.2	BW inversely associated with protein, fat and fibre intake, but positively associated with carbohydrate intake. Nail-As not significantly associated with BW, when adjusted for macronutrients, and nail-As was not a significant mediator for BW	Seems to weaken the conclusions from Kile, Cardenas, et al. (2016) regarding BW versus nail-As, where macronutrients were not adjusted for. But still association between nail-As and GA; the latter was a mediator to BW in Kile, Cardenas, et al. (2016)
Bozack et al. (2020) Rural Bangladesh Cohort	BW	Subset of Kile, Cardenas, et al. (2016): 413 births with % methylation of DNA cord blood at 3 CpG sites in the gene body of DNA methyltransferase 3 alpha	See Kile, Cardenas, et al. (2016)	Significant inverse association between nail-As and BW.	See Kile, Cardenas, et al. (2016), Rahman et al. (2017) and Lin et al. (2019). Here structural equation modelling also includes DNA methylation in cord blood.
Howe, Farzan, et al. (2020) USA, Los Angeles Cohort	BW	Births with maternal: 116 (hair-As) 100 (blood As) 167 (u-iAs)	Medians: Hair: 0.01 µg/g Blood: 0.67 µg/g u-tiAs: 5.7 µg/L	No association with u-tiAs	In urine additionally 0.5 µg/L AsB
Howe, Claus Henn, et al. (2020)	BW	262	Median u-tiAs 5.8 µg/L	No significant association with BW in relation to GA	Note that then a possible impact of As on BW via GA is not taken into account
Shih et al. (2020) USA, seven areas Cohort (NCS)	BW	212	Total As (median 7.8 and DMA median 3.4 µg/L) in maternal urine	No association btw u-DMA and BW	High LODs: u-tiAs 1.25, DMA 1.7, MMA 0.9. All had u-tiAs >LOD and 77% had DMA > LOD, but for other species > 60% < LOD

(Continues)

TABLE 15 (Continued)

Reference study population design	Outcome definition	Population size (*n*)	Arsenic exposure[a]	Results	Additional information/confounders
Bulka et al. (2022) USA nationwide Cross-sectional	BW	3,305,090 term births in 3105 counties	The probability of As in water in four categories (≤ 1, > 1, ≤ 5, > 5, ≤ 10, > 10) was estimated in 1 × 1 km grids, based on about 20,000 As measurements in private wells. Estimates were then aggregated on county level	Adjusted beta (grams) per 10% increase in probability of exceeding the following thresholds: ≤ 1, > 1 −3.1 (−4.0, −2.2) ≤ 5, > 5 −2.8 (−4.2, −1.3) ≤ 10, > 10 −3.9 (−6.1, −1.7)	Adjusted for proportion of private wells, maternal age, race/ethnicity, marital status, education, smoking during pregnancy, pre-pregnancy BMI, rurality/urbanicity, annual concentration of PM < 2.5 μm in the county

Abbreviations: As, arsenic; AsB, arsenobetaine; BMI, body mass index; BW, birth weight; CI, confidence interval; Cr, creatinine; CpG, cytosine-phosphate-guanine; CS, cross-sectional study; DMA, sum of dimethylarsinous acid and dimethylarsinic acid; DNA, deoxyribonucleic acid; EFSA, European Food Safety Authority; GA, gestational age; iAs, inorganic arsenic; km, kilometre(s); LBW, low birth weight; LOD, limit of detection; MMA, sum of monomethylarsonous acid and monomethylarsonic acid; *n*, number; N7-MeG, N7-methylguanine; NCS, National Children's Study; OR, odds ratio; PM, particulate matter; t-As, total arsenic; u-DMA, urinary DMA; u-iAs, urinary inorganic arsenic; u-MMA, urinary MMA; USA, United States of America; u-tiAs, total urinary iAs (sum of iAs and methylated its metabolites MMA and DMA); VLBW, very low birth weight; w-As, water arsenic.

[a]iAs in urine includes MMA and DMA, but not AsB.

Preterm birth and gestational age

Many of the studies of birth weight reviewed above also examined associations with preterm birth (PTB) and gestational age (GA). They are summarised in Table 16. Of the studies reviewed in the 2009 Opinion, only one (Yang et al., 2003) met the inclusion criteria for the current evaluation. This study found no statistically significant association between arsenic in water and PTB in Taiwan.

The CONTAM Panel identified 11 additional papers, meeting the inclusion criteria, that were not included in the EFSA 2009 Opinion.

Some of the studies on GA or PTB that did not fulfil the inclusion criteria are found among those mentioned in the previous Section on BW. Another study not fulfilling the inclusion criteria was a study on PTB by Huang et al. (2021).

Two of the additional studies (Myers et al., 2010 in Mongolia and Almberg et al., 2017 in the US) evaluated the association between iAs exposure and PTB. Myers et al. (2010) found no significant association with PTB, while the study by Almberg et al. (2017) found an association with PTB in a subset of births when the analyses were restricted to counties where use of private wells were uncommon (< 10% of households) and where therefore the exposure assessment is likely to be more valid.

Seven studies that had become available since the 2009 Opinion evaluated the association with GA (see Table 16). The studies from Mexico (Laine et al., 2015), and the US (Gilbert-Diamond et al., 2016; Howe, Farzan, et al., 2020; Shih et al., 2020) showed no significant associations between u-tiAs and GA. u-tiAs levels in the US studies were low. The studies based on a Bangladesh cohort (Bozack et al., 2020; Kile, Cardenas, et al., 2016; Lin et al., 2019) showed inverse associations between u-tiAs and toenail As and GA. As mentioned in the Section on BW, the inverse association between iAs exposure and BW seemed to be mediated by the inverse association between iAs exposure and GA.

Overall, there is some evidence from the study by Kile, Cardenas, et al. (2016) in Bangladesh that iAs exposure reduces GA (mean 38 weeks in the study). For populations in other countries the evidence of an association is insufficient.

In summary, the epidemiological studies provide insufficient evidence for an association between low to moderate exposure to iAs and gestational age.

TABLE 16 Key epidemiological studies on associations between As exposure and preterm birth (PTB GA < 37 weeks) or gestational age (GA).

Reference study population design	Outcome definition	Population size (*n*)	Arsenic exposure[a]	Results	Additional information/confounders
Yang et al. (2003) Taiwan Cohort	PTB	18,259 (3872 from As-exposed townships, and 14,387 from similar reference townships)	Water: In As-exposed townships 30% > 50 µg/L	639 cases (3.5%) of PTB. OR 1.10 (0.91–1.33) for As-exposed women	Aggregated water As data. Adjusted for some potential confounders
Myers et al. (2010) Inner Mongolia, China CS	PTB	9890 singleton births 1996–1999 with As measured in the wells of the subvillage	Water: 66% < 20, 20% 21–50, 7% 50–100, 7% > 100 µg/L. Data from 1991 to 1997 in well-water registry	289 cases (2.9%) of PTB. OR 1.02 (0.72–1.44) for water-As > 50 versus < 50 µg/L	Water-As data were averaged by subvillage. Adjusted only for antenatal care. No other potential confounders were detected. Women were generally health and well-nourished
Laine et al. (2015) Mexico CS	GA	199 singleton live births, only 3 with PTB	Water: < 0.5–236, median 13 µg/L. Maternal u-tiAs median 23 µg/L	Median GA 39 weeks No association btw w-As, u-DMA and GA u-tiAs, u-MMA and u-%MMA had significant adjusted negative slopes	Mean u-DMA 43 µg/L in women reporting seafood and 31 µg/L in the others
Gilbert-Diamond et al. (2016) USA, New Hampshire Cohort	GA	706 live singleton births	Maternal u-tiAs. Median 3.4 µg/L	Median GA 39.5. No association btw u-tiAs, MMA or DMA and GA	General additive models adjusted for some potential confounders
Kile, Cardenas, et al. (2016) Rural Bangladesh Cohort	GA	1153 live singleton births	Water: < 0.5–1400, median 2.3 µg/L Maternal toenail t-As 0.2–35 µg/g, median 1.5 µg/g	254 (22%) with PTB. Significant adjusted inverse association (multiple linear regression) btw water As and GA, and btw nail-As and GA	Structural equation modelling suggested that the impact of As on GA mediated almost all the association btw As and birth weight
Almberg et al. (2017) USA, Ohio CS	PTB	428,804 live singleton births from records 2006–2008. In term births 2.9% LBW and 1.2% VLBW	w-As aggregated by 88 counties and year: 0.5–12 µg/L, median 1.5 µg/L. Based on 2968 measurements in 975 water systems (only regulated water systems, As in private wells unknown)	11% were PTB. Overall adjusted OR (per mean As in µg/L) for PTB 0.99 (0.98–1.01). Adjusted OR for women from counties with < 20% private wells: 1.08 (1.02–1.14)	ORs adjusted for many potential confounders from the records. ORs were increased in subanalyses excluding counties with many private wells
Lin et al. (2019) Rural Bangladesh Cohort	GA	1057 live singleton births, Same study bas as Kile, Cardenas, et al. (2016) and Rahman et al. (2017)	Toenail As 0.04–47, median 1.2 µg/g	GA inversely associated with protein, fat and fibre intake, but positively associated with carbohydrate intake. Nail As inversely associated with GA, when adjusted for macronutrients	As Kile, Cardenas, et al. (2016), but points out the impact of macronutrients, some of which are also associated with As
Bozack et al. (2020) Rural Bangladesh Cohort	GA	Subset of Kile, Cardenas, et al. (2016): 413 births with % methylation of DNA cord blood at 3 CpG sites in the DNA sequence of the gene DNA methyltransferase 3 alpha	See Kile, Cardenas, et al. (2016)	Significant inverse association between nail As and GA	See Kile, Cardenas, et al. (2016), Rahman et al. (2017) and Lin et al. (2019). Here structural equation modelling also includes DNA methylation in cord blood
Howe, Farzan, et al. (2020) USA, Los Angeles Cohort	GA	Births with maternal: 116 (hair-As) 100 (blood As) 167 (u-iAs)	Medians: Hair: 0.01 µg/g Blood: 0.67 µg/g u-tiAs: 5.7 µg/L	No association with u-iAs	In urine additionally 0.5 µg/L AsB

TABLE 16 (Continued)

Reference study population design	Outcome definition	Population size (*n*)	Arsenic exposure[a]	Results	Additional information/confounders
Shih et al. (2020) USA, seven areas Cohort (NCS)	GA	212	Total As (median 7.8 and DMA median 3.4 μg/L) in maternal urine	Mean GA 38.8 weeks. No association btw u-DMA and GA	High LODs: t-As 1.25, DMA 1.7, MMA 0.9. All had t-As > LOD and 77% had DMA > LOD, but for other species > 60% < LOD
Bulka et al. (2022) USA nationwide Cross-sectional	GA, PTB	3,580,755 births in 3105 counties	The probability of As in water in four categories (≤ 1, > 1, ≤ 5, > 5, ≤ 10, > 10) was estimated in 1 × 1 km grids, based on about 20,000 As measurements in private wells. Estimates were then aggregated on county level	Adjusted beta (grams) per 10% increase in probability of exceeding the following thresholds: ≤ 1, > 1 −0.01 (−0.01, −0.01) ≤ 5, > 5 −0.01 (−0.01, −0.00) ≤ 10, > 10 −0.00 (−0.02, −0.00) Risk differences for PTB zero in all comparisons	Adjusted for proportion of private wells, maternal age, race/ethnicity, marital status, education, smoking during pregnancy, pre-pregnancy BMI, rurality/urbanicity, annual concentration of PM < 2.5 μm in the county

Abbreviations: As, arsenic; AsB, arsenobetaine; BMI, body mass index; CpG, cytosine-phosphate-guanine; CS, cross-sectional study; DMA, sum of dimethylarsinous acid and dimethylarsinic acid; DNA, deoxyribonucleic acid; GA, gestational age; km, kilometre(s); LOD, limit of detection; LBW, low birth weight; MMA, sum of monomethylarsonous acid and monomethylarsonic acid; *n*, number; NCS, National Children's Study; OR, odds ratio; PM, particulate matter; PTB, pre-term birth; t-As, total arsenic; u-DMA, urinary DMA; u-MMA, urinary MMA. u-tiAs, total urinary inorganic arsenic (sum of inorganic arsenic and its methylated metabolites MMA and DMA); USA, United States of America; VLBW, very low birth weight; w-As, water-arsenic.

[a]iAs in urine includes MMA and DMA, but not AsB.

Other anthropometric birth outcomes and in utero growth before birth

Among the studies mentioned in the Section on birth weight, five also examined other anthropometric data (Bloom et al., 2016; Gilbert-Diamond et al., 2016; Laine et al., 2015; Rahman et al., 2009; Shih et al., 2020). For characteristics of the studies, see Table 15 on BW.

Thus, for birth length, head circumference, chest circumference and ponderal index, relatively few studies examined associations with iAs. The results were not consistent.

In addition, there are two studies which assessed fetal growth in utero by ultrasound. Kippler et al. (2012) studied u-tiAs in pregnant women in rural Bangladesh, 1885 in gestational week (GW) 8 and 1929 at GW 30. Head size, abdominal circumference and femur length were measured by ultrasound at GW 14 and 30. Median maternal u-tiAs was 79 µg/L at GW 8 and 85 µg/L at GW 30. The authors concluded that u-tiAs was weakly associated with decreased fetal size in boys.

Another study using ultrasound for assessment of fetal growth was published by Davis et al. (2015) based on 223 pregnant women from New Hampshire, US with a median u-tiAs of 3.1 µg/L at GW 24–28. In adjusted analyses there was no significant association between maternal u-tiAs and birth size.

In summary, there is some evidence from studies in Bangladesh that iAs exposure reduces birth size (in addition to birth weight as reviewed above). The relevance for Europe of the results from Bangladesh is unclear. For populations in other countries the evidence of an association is insufficient.

Spontaneous abortion, stillbirth, neonatal mortality

The CONTAM Opinion of 2009 noted that increased risk of spontaneous abortion, stillbirth, preterm birth and/or neonatal death at elevated water arsenic concentrations were indicated in some but not all of the reviewed studies (Ahmad et al., 2001; Cherry et al., 2008; Hopenhayn-Rich et al., 2000; Kwok et al., 2006; Milton et al., 2005; Rahman et al., 2007; Sen & Chaudhuri, 2008; von Ehrenstein et al., 2006). At that time, the Panel concluded that further evidence was required regarding the dose–response relationships and critical exposure times for these outcomes.

The CONTAM Panel identified 20 publications related to spontaneous abortion, stillbirth and neonatal mortality, of which 8 met the inclusion criteria. Five of these (Cherry et al., 2008; Hopenhayn-Rich et al., 2000; Kwok et al., 2006; Milton et al., 2005; Rahman et al., 2007) were previously described in EFSA CONTAM Opinion (2009), see Table 17.

Hopenhayn-Rich et al. (2000) performed an ecological study in Chile, comparing the rates of stillbirths and infant mortality in the population of Antofagasta, where public water had high As levels with the population of Valparaiso where water As was low (< 2 µg/L). Average water As in Antofagasta was 860 µg/L in 1958–1970, 110 µg/L 1971–1979, 70 µg/L in 1980–1987and 40 µg/L in 1988–1996. Stillbirths declined markedly in Chile over this period, see Table 17. The risk differences in 1958–1969 and 1970–1973 are highly statistically significant. The average socioeconomic status was slightly lower in Valparaiso than in Antofagasta (based on education and % poverty). From 1974 to 1996, the rates were the same in the two cities. The rates of neonatal mortality were also higher in Antofagasta, and the rate difference was significantly higher also in the 1980s when water As was 70 µg/L.

Milton et al. (2005) examined the association between As in drinking water and spontaneous abortion, stillbirth or neonatal death (within 28 days in live births) in 533 first pregnancies in rural Bangladesh and found significant associations with As in water (Table 17).

The study by Kwok et al. (2006) found no association between As in water and stillbirth, based on 53 cases (2.6%) in rural Bangladesh. The study only presents associations with As in water as a continuous variable. The CI is remarkably narrow, considering the low number of cases, so the result is difficult to assess.

Rahman et al. (2007) performed a large register-based cohort study in Matlab, Bangladesh on associations between As in water and stillbirth, neonatal (within 28 days) death and infant death (within 12 months). Associations with stillbirth were not reported separately from other fetal loss (including induced abortion). For infant mortality there was a significant positive association with increasing water As with similar estimates if divided into death within 28 days or later.

Cherry et al. (2008) performed a large study of water As vs. stillbirth in rural Bangladesh. Based on health registers, 971 stillbirths (3.4%) were found among 30,500 pregnancies in 600 villages. The water As concentrations in 13 subareas were averaged (7–14 tested wells per area) but outcomes and potential confounders were available on the individual level. The authors consider the ORs likely to be underestimated due to (1) the fact that low birth weight and short gestation (which are associated with As exposure and likely mediators) were adjusted for and (2) the averaged exposure estimates of water As, which will cause non-differential misclassification and attenuation of a true risk. This interpretation is reasonable.

Three studies not included in the EFSA CONTAM Opinion 2009 are shown in Table 17, Rahman et al. (2010) studied the risk of spontaneous abortion, stillbirth and infant mortality versus As exposure (u-As in pregnancy weeks 8 and 30) in rural Bangladesh (Matlab area). There were significant dose–response associations with stillbirth ($p = 0.02$ for linear trend) and infant mortality ($p = 0.005$).

Myers et al. (2010) examined associations between water As and stillbirth and neonatal death in Mongolia. The OR for water As > 50 µg/L versus < 50 µg/L was 1.18 (95% CI 0.55–2.51) for stillbirth (eight cases in the higher category) and 2.01 (1.12–3.59) for neonatal death (15 cases in the higher category).

Bloom et al. (2014) performed a case–control study of As in maternal drinking water and spontaneous abortion before GW 20 and found no association in Romania. The median water As concentrations were, however, low both in cases and controls.

Several studies not fulfilling the inclusion criteria in the present assessment were identified (Ahamed et al., 2006; Ahmad et al., 2001; Aschengrau et al., 1989; Börzsönyi et al., 1992; Buck Louis et al., 2017; Chakraborti et al., 2003, 2004; Guo et al., 2003; Mukherjee et al., 2005; Sen & Chaudhuri, 2008; Shih et al., 2017; von Ehrenstein et al., 2006).

In summary, eight studies fulfilled the inclusion criteria, one from Chile, one from Romania, one from Mongolia and five from Bangladesh.

For spontaneous abortion the studies by Milton et al. (2005), and Rahman et al. (2010) provide sufficient evidence for an association with exposure to iAs in Bangladesh, but the relevance for Europe is unclear.

Regarding stillbirth, there is sufficient evidence for an association with exposure to inorganic As in Bangladesh based on the studies by Milton et al. (2005), Cherry et al. (2008) and Rahman et al. (2010), but the relevance for a Europe is unclear. The study from Chile (Hopenhayn-Rich et al., 2000) suggested an increased risk at water As of about 100 µg/L, but the risk was not increased in the study from Mongolia at similar water As levels.

For infant mortality (in the neonatal period or later) associations with exposure to inorganic As have been shown in several studies from Bangladesh, as well as in the Chilean study at water As levels of 70 µg/L and in the study from Mongolia at a water As level of about 100 µg/L. Thus, there is sufficient evidence for an association between iAs exposure and infant mortality.

TABLE 17 Key epidemiological studies on associations between As exposure and spontaneous abortion, stillbirth, neonatal (1–28 days) and infant (1–365 days) mortality.

Reference study population design	Outcome definition	Population size and number of cases	Arsenic exposure	Results	Additional information/ confounders
Included in 2009 EFSA Opinion					
Hopenhayn-Rich et al. (2000) Chile Ecological longitudinal study	Stillbirth Infant mortality	Populations of Antofagasta and Valparaiso	w-As in Antofagasta (μg/L): 1958–70: 860 1971–79: 110 1980–87: 70 1988–96: 40 Water As in Valparaiso < 2 μg/L	Rates of stillbirth/1000 1958–69: Ant 28, Val 11 1970–73: Ant 19, Val 8 1974–77: Ant 9, Val 11 1978–96: Ant 5, Val 6 Rates of neonatal mort. 1958–61: Ant 46, Val 22* 1962–65: Ant 43, Val 25* 1966–69: Ant 34, Val 23* 1970–73: Ant 24, Val 23* 1974–77: Ant 21, Val 21 1978–81: Ant 17, Val 14* 1982–85: Ant 13, Val 10* 1986–89: Ant 11, Val 9.3* 1990–93: Ant 8.5, Val 8.0* 1994–96: Ant 7.3, Val 8	Slightly more poverty and low education in Valparaiso at time of the study. Stillbirth was more common in Antofagasta only 1958–1973. The asterisks in the Results column indicate time periods when stillbirth or neonatal mortality were higher in Antofagasta with a statistically significant difference. For neonatal mortality, rates were significantly higher in Valparaiso 1974–77 and 1994–96
Milton et al. (2005) Rural Bangladesh Cross-sectional study	Spontaneous abortion Stillbirth Neonatal mortality	533 first pregnancies Spontaneous abortion: 90 Stillbirth: 60 Neonatal death: 86	w-As (μg/L) Median 116 < 50 (33%) 51–100 (10%) > 100 (57%) < 50 (33%) 51–100 (10%) > 100 (57%) < 50 (33%) 51–100 (10%) > 100 (57%)	OR spontaneous abortion (cases) 1.0 (19) 2.4 (1.2–5.1) (12) 2.5 (1.5–4.4) (59) Stillbirth (cases) 1.0 (13) 1.1 (0.3–3.1) (4) 2.5 (1.5–5.9) (45) Neonatal death (cases) 1.0 (16) 2.7 (1.1–6.7) (12) 1.7 (0.8–3.3) (58)	First model was adjusted for education, age at marriage, age at first pregnancy, history of antenatal care, weight, height, age at first menstruation, duration of menstrual period, history of hypertension, diabetes and vaccination during pregnancy Final model included only covariates altering the OR by > 10%: participant's height, history of hypertension and diabetes, age at first pregnancy

TABLE 17 (Continued)

Reference study population design	Outcome definition	Population size and number of cases	Arsenic exposure	Results	Additional information/ confounders
Kwok et al. (2006) Rural Bangladesh, 261 villages Cross-sectional study	Stillbirth	2006 singleton births with As measured in the wells of the villages Stillbirth: 53 (2.6%)	w-As: 2003 samples, median about 150 µg/L, 36% > 200 µg/L. ORs only presented versus As as continuous variable	Adjusted OR 1.00 (1.00–1.00) per µg/L of water-As	Water samples (for each household), birth data for 2002, and covariates were collected in 2003 from Community Centres' registers + maternal interviews (2003). Most births at home. Adjusted for maternal age, household assets, smoking in the household, parity, baseline BMI and duration of tubewell-use. Strange CI for the OR
Rahman et al. (2007) Matlab Bangladesh Cohort study	Neonatal mortality Infant mortality	29,134 pregnancies Stillbirth: 829 Neonatal death: 850 Infant death: 1373	w-As (µg/L), quintiles: < 10 (median < 1) 10–166 (median 77) 167–276 (median 225) 277–408 (median 340) ≥ 409 (median 515) < 10 (median < 1) 10–166 (median 77) 167–276 (median 225) 277–408 (median 340) ≥ 409 (median 515)	HR Neonatal death 1.0 1.11 (0.89–1.38) 1.18 (0.95–1.47) 1.17 (0.94–1.46) 1.21 (0.98–1.50) HR Infant death 1.0 1.13 (0.95–1.35) 1.19 (1.00–1.42) 1.29 (1.08–1.53) 1.19 (1.00–1.41)	Age at pregnancy, order of pregnancy, education, socioeconomic status by asset score, six seasons, calendar year of outcome, location according to service area) were tested, but only calendar was a confounder and adjusted for *p* for trend for infant death 0.02 HR for stillbirth not reported
Cherry et al. (2008) Rural Bangladesh Semi-ecological longitudinal study	Stillbirth	30,486 pregnancies in 16 areas with As measured in 7–14 wells in each area Stillbirth: 971 (3.4%)	w-As (µg/L) < 10 10–49 ≥ 50	OR 1.0 1.23 (0.87–1.74) 1.80 (1.14–2.86)	As in water averaged per area. Adjusted for individual factors: sex, age, multiple birth, previous pregnancies, previous stillbirth, low SES, maternal and paternal education, maternal high blood pressure and oedema, short gestation, low birth weight, prolonged labour, excess bleeding
Other studies on iAs exposure					
Myers et al. (2010) Inner Mongolia, China Cohort study	Stillbirth Neonatal mortality	9890 singleton births 1996–1999 with As measured in the wells of the sub village. Stillbirth: 51 Neonatal death: 64	Water: 66% < 20, 20% 21–50, 7% 50–100, 7% > 100 µg/L. Data from 1991 to 1997 ≤ 50 (median < 20) > 50 (median about 100) ≤ 50 (median < 20) > 50 (median about 100)	OR (number of cases) Stillbirth: 1.0 (43) 1.18 (0.55–2.51) (8) Neonatal death: 1.0 (49) 2.01 (1.12–3.59) (15)	Maternal age, child sex, previous pregnancies and adequacy of prenatal care utilisation were evaluated, but the only confounder was prenatal care, which was adjusted for

(Continues)

TABLE 17 (Continued)

Reference study population design	Outcome definition	Population size and number of cases	Arsenic exposure	Results	Additional information/ confounders
Rahman et al. (2010) Matlab Bangladesh Cohort study	Spontaneous abortion Stillbirth Infant mortality	2924 pregnancies with data on u-As in GW8. Spontaneous abortion 275 (9.4%). For stillbirth and 1725 pregnancies with data on u-As in GW8 and GW30. Stillbirth: 32 (1.9%) Infant mortality: 36 (2.1%)	u-tiAs (µg/L), quintiles in GW8, adjusted for SG (median) <33 (23) 33–57 (42) 58–121 (80) 122–248 (177) >248 (382) u-tiAs (mean of GW8 and GW30) (median) <38 (30) 39–67 (50) 68–133 (94) 134–267 (189) >267 (390) <38 (30) 39–67 (50) 68–133 (94) 134–267 (189) >267 (390)	OR Spontaneous abortion: 1.00 (45) 1.28 (0.85–1.93) (57) 1.41 (0.94–2.11) (63) 1.06 (0.69–1.62) (47) 1.44 (0.96–2.15) (63) Stillbirth: 1.0 (3) 2.06 (0.51–8.38) (6) 2.35 (0.60–9.23) (7) 3.41 (0.92–12.63) (10) 2.02 (0.50–8.24) (6) Infant mortality: 1.0 (3) 1.78 (0.44–7.16) (6) 1.83 (0.45–7.35) (6) 2.29 (0.58–9.05) (7) 5.01 (1.41–17.84) (14)	Maternal age, previous pregnancies and births, education, economic status, location of residence, season, BMI and GA were evaluated, but none was a confounder for spontaneous abortion. OR for stillbirth adjusted for economic status and GA OR for infant mortality adjusted for economic status, location of residence, season and GA
Bloom et al. (2014) Romania Case–control study	Spontaneous abortion	150 cases and 150 controls	Water As (µg/L), median 0.4, p90 9.4. Median (range) Cases: 0.17 (0–175) Controls: 1.28 (0–130)	OR 0.98 (0.96–1.01)	Adjusted for GA, maternal age smoking in pregnancy, education, vitamin use

Abbreviations: Ant, Antofagasta; As, arsenic; BMI, body mass index; CI, confidence interval; EFSA, European Food Safety Authority; GA, gestational age; GW, gestational week; HR, hazard ratio; OR, odds ratio; SES, socioeconomic status; SG, specific gravity; u-As, urinary arsenic; u-tiAs, total urinary iAs (sum of iAs and its methylated metabolites MMA and DMA); Val, Valparaiso; w-As, water arsenic.

*statistically significant difference.

Birth Defects/Congenital malformations

Teratogenicity of arsenic has been shown in animals (see EFSA CONTAM Panel, 2009), especially neural tube defects (NTD), such as anencephaly, meningocele and myelomeningocele (spina bifida). Other relatively common birth defects in humans include congenital heart disease, such as septal defects and orofacial defects (cleft lip and/or palate), which are reviewed separately below.

The previous EFSA Opinion reviewed one study on birth defects in relation to water As (Kwok et al., 2006). Further details on that study are found in the birth weight Section. There was possibly a weak association between water-As and risk of birth defects, but there were only 11 cases (in 2189 births) and of very different character.

The CONTAM Panel identified 28 additional studies on associations between As exposure and birth defects, 14 of which met the inclusion criteria. The other 14 studies did not fulfil the inclusion criteria because it was either not possible to evaluate the contributions of organic vs. inorganic As (Demir et al., 2019; Jin et al., 2014; Nyanza et al., 2020; Ovayolu et al., 2020; Özel et al., 2019; van Brusselen et al., 2020; Wang, Pi, Yin, et al., 2022), or because of the use of soil As concentrations (Huang et al., 2011; Wu et al., 2011, 2014) or As in placenta (Jin et al., 2013; Pi et al., 2023) as surrogate for As exposure, or because the studies were purely ecological (Engel & Smith, 1994; Sanders et al., 2014; Yu & Zhang, 2011).

Among the 13 additional studies that fulfilled the inclusion criteria, five examined NTD (Brender et al., 2006; Mazumdar et al., 2015; Tauheed et al., 2017; Tindula et al., 2021; Wang, Zhu, et al., 2019), four examined congenital heart disease (Jin et al., 2016; Richter et al., 2022; Rudnai et al., 2014; Zierler et al., 1988) and two (Marie et al., 2018; Suhl et al., 2022) examined many types of birth defects, including NTD and congenital heart disease). One study (Suhl et al., 2018), was focused on OFC.

Neural tube defects

Brender et al. (2006) performed a case–control study of pregnancies with NTD and normal pregnancies from the same area in Texas, US. Total As in urine was analysed in 56 cases and 74 controls 1 year after conception, and participants instructed to refrain from seafood for 2 days. No association was found between u-As and NTD. However, the levels of total As in urine (median 9 μg/L) were comparable with those found in populations without elevated iAs exposure.

Mazumdar et al. (2015) performed a case–control study in Bangladesh including 57 cases of myelomeningocele and 55 controls. As in drinking water was lower in cases than in controls (75-percentile 13 μg/L in the cases and 55 μg/L in the controls). Data for a number of potential confounders, including folate supplementation, was collected. No association was found between water As and risk of myelomeningocele, but the interaction between water As and folate supplementation was significant with respect to risk of myelomeningocele, high water As decreasing the protective impact of folate. In a subsequent subgroup study (Tauheed et al., 2017) also investigated epigenetic markers, but the study provides no further data on associations between As exposure and myelomeningocele. The same group performed a new case–control study in Bangladesh with 192 cases of spina bifida (meningocele or myelomeningocele) and 171 hospital-based controls (Tindula et al., 2021). As was analysed in toenail clippings from mothers and fathers for 155 cases and 123 controls. The GMs of maternal nail As in cases and controls were 0.55 and 0.53 μg/g, and for paternal nail As the GMs were 0.72 and 0.52 μg/g. There was no association between maternal nail-As and adjusted risk of spina bifida, nor any interaction with maternal serum folate. The OR for paternal toenail As was increased (1.7, 95% CI 1.3–2.4).

Marie et al. (2018) studied the association between several congenital anomalies (including NTD) and water As in a region of France with elevated As in ground water. They included 5263 children with various anomalies and collected data on As in tap water aggregated by commune for each mother/child in the 12 months before birth. Children were categorised in those with water As < 10 μg/L (92.6%, $N = 4871$) and ≥ 10 (7.4%, $N = 392$, median 15.5) μg/L. Among cases with water As ≥ 10, only 18 cases (0.03% of 5263) had water As > 30 μg/L. In an adjusted model, also including an interaction term for gender, the OR for any anomaly was 2.2 (95% CI 1.3–3.6). The interaction with gender was significant, with an increased OR only found for girls (OR 2.4, 95% CI 1.4–4.1). In boys the OR was 0.8 (95% CI 0.4–1.5). For girls, overall ORs for anomalies could be separated into ≥ 10–30 μg/L (OR 2.2, 95% CI 1.2–2.8) and ≥ 30 μg/L (OR 10, 95% CI 2.0–41). There was no association between water As and risk of NTD.

In a case–control study from China (511 controls and 263 cases with neural tube defects) with maternal hair arsenic measurements 3 months before and 3 months after conception, a higher hair arsenic concentration in the cases than in the controls was found, median (inter-quartile range) of 0.093 (0.025–0.387) μg/g hair, and 0.082 (0.030–0.414) μg/g in the controls (Wang, Zhu, et al., 2019). However, in the adjusted logistic regression analysis, maternal hair arsenic concentration above its median of the controls was not associated with a risk of total neural tube defects (OR = 1.32, 95% CI 0.91–1.92), and there was no dose–response relationship.

Suhl et al. (2022) examined non-cardiac birth defects in a large case–control study in the US. Cases were retrieved from 10 US States in 1997–2011, and controls were selected from hospital logs and birth certificates matched by State and year of the cases. The exposure to iAs was estimated from a food frequency questionnaire, and potential confounders from telephone interviews. The mean iAs intake was estimated at 0.08 μg/kg body weight and day in cases and controls. There were 2130 cases of CNS malformations, about 1600 of which were NTD. There were no significant associations between estimated iAs intake and risk of NTD (aOR for anencephaly 0.8 (0.6–1.0), and for spina bifida 0.8 (0.7–1.0).

In summary, the epidemiological studies provide insufficient evidence for an association between low to moderate exposure to iAs and neural tube defects.

Congenital heart disease

An early study, not described in EFSA CONTAM Panel (2009) was a case–control study of congenital heart disease in Massachusetts, US by Zierler et al. (1988), Table 18. As levels were mostly below the detection limit (LOD 0.8 µg/L), and the 90-percentile was 0.8 µg/L. It should be noted that at As < 1 µg/L, the contribution of As from drinking water is low compared to intake of iAs from other dietary components. For example, the median lower bound estimated intake for European adults at the time the previous EFSA Opinion (EFSA CONTAM Panel, 2009) was about 0.3 µg/kg corresponding to 20 µg/day for a 70 kg person.

Rudnai et al. (2014) performed a very large case–control study, in Hungary, of congenital heart disease. Cases and controls were selected from the same registry, and controls were births with the diagnoses Down syndrome, Club foot and multiple congenital malformations. Data on As in drinking water in 2412 settlements all over Hungary (urban and rural) were collected for each year of the observation period. It should be noted that births with multiple malformations as controls might result in an underestimation of a possible true risk. The exposure response relation was not linear. The OR increased up to water As of 10–20 µg/L, then did not increase further. No increased risk was seen at water As > 50 µg/L (see Table 18).

Jin et al. (2016) studied associations between As in hair and risk of congenital heart disease in a case–control study in China. Increased adjusted ORs were found for quartiles 2–4 of hair-As compared to the first quartiles, with a dose–response pattern. The median hair-As was 0.074 µg/g in controls and 0.089 µg/g in the cases. These hair-As are compatible with other reports in general populations without known increased exposure to iAs (Fowler et al., 2022).

The study by Marie et al. (2018) found an association between As in water and risk of congenital heart defects, but only in girls. The interaction with gender was significant.

Richter et al. (2022) studied the association between As in drinking water (98% from public water works) and congenital heart disease in a national cohort study including all live births in Denmark 1997–2014. Water As in early pregnancy based on residential address and As in water supply areas. There were 3700 cases of congenital heart disease with water-As > 1 µg/L, and 228 cases with water-As ≥ 5 µg/L. The adjusted OR increased in all categories of water As above the reference category, which was < 0.5 µg/L with a supralinear exposure-response relation. Most of the increase in risk was found from the reference category up to a few µg/L. There was no interaction with sex. Results were essentially the same in a large number of sensitivity analyses. As mentioned above, the contribution of As from drinking water at levels < 1 µg/L is low compared to intake of iAs from other dietary components.

In the studies by Zierler et al. (1988) in the US, and by Richter et al. (2022) in Denmark, the water-As levels (aggregate data linking residences with measurements in public water works) were very low. The size of the study by Zierler et al. (1988), which found no association with congenital heart disease, was modest with 31 cases with estimated As in water > 0.8 µg/L. The Danish cohort study by Richter et al. (2022) had a very impressive size, analysing 10,600 cases of congenital heart disease in all Denmark over an 18-year period. This study found a very clear association between estimated water As and congenital heart disease. Imprecision in the estimates from the aggregated data, and the varying contribution of iAs in other dietary items might have caused misclassification of iAs exposure, which can be assumed to be non-differential, and therefore the true association between iAs exposure and the outcome may be even stronger. A caveat is that the exposure-response found is strange, since the increase in relative risk per increase of water-As is highest at the very low water-As levels. This may be less biologically plausible.

In the studies by Rudnai et al. (2014) in Hungary, and Marie et al. (2018) in France there were larger proportions of the populations with high water As as compared to the studies by Zierler et al. (1988) and Richter et al. (2022). The results in these two studies support an association with congenital heart disease at water-As > 10 µg/L, although Marie et al. (2018) found an increased risk only in girls.

All studies reviewed above find associations between iAs exposure and congenital heart disease. In summary, the epidemiological studies provide sufficient evidence for an association between low to moderate exposure to iAs and congenital heart disease. However, the exposure-response relations in key studies were atypical.

Table 18 depicts the studies on As and congenital heart defects.

TABLE 18 Key epidemiological studies relating arsenic and congenital heart disease.

Reference study population design	Outcome definition	Population size (*n*) case/control	Arsenic exposure	Results	Additional information/confounders
Zierler et al. (1988) Massachusetts, USA Case–control study	Congenital heart disease in live births, retrieved from birth registry (excluding persistent ductus art. and Downs syndrome)	270 cases and 665 controls (random from the same registry)	w-As in public water supplies, P90 was 0.8 µg/L, which was also the LOD	aOR for detectable vs. no-detectable w-As was 0.98 (0.59–1.64) based on 31 cases with As > LOD	Adjusted for type of water source (ground or surface), other water contaminants and maternal education. OR for coarctation of aorta was 3.4 (1.3–8.9)
Rudnai et al. (2014) Hungary Case–control study	Congenital heart disease in live births, retrieved from registry of congenital malformations over 1987–2003	4889 cases and 4007 controls from the same registry. Controls were children with club foot, Downs syndrome and multiple malformations	w-As (µg/L) 0–10 (80%) 10–20 (12%) 20–30 (3.5%) 30–40 (2%) 40–50 (1.1%) > 50 (1.4%)	OR 1.0 1.5 (1.3–1.7) 1.3 (1.0–1.6) 1.4 (1.1–1.9) 1.4 (0.9–2.1) 1.0 (0.7–1.4)	Adjusted for child sex and age of mother OR for w-As > 10 µg/L was increased both in urban and rural areas
Jin et al. (2016) China Case–control study	Congenital heart disease from hospital records	339 cases and 333 controls	Hair As ng/g Medians 74 (controls and 89 (cases) < 62 62–86 87–118 > 118	OR 1.0 2.34 (1.46–3.76) 3.43 (2.23–5.83) 5.62 (3.43–9.24)	Adjusted for maternal age, gestational age, previous pregnancy, folic acid suppl., BMI, paternal smoking These levels are relatively normal also for humans without known exposure to elevated iAs
Marie et al. (2018) Auvergne, France Cross-sectional study	Congenital heart disease from national registry	4891 pregnancies 99 cases	w-As (µg/L) 12 months before birth 7.4% had ≥ 10 µg/L < 10 ≥ 10 (median 15.5) < 10 ≥ 10	OR Males (2416) 1 0.73 (0.17–2.13) Females (2475) 1 3.66 (1.62–7.64)	w-As aggregated on commune level ORs adjusted for maternal age, parity, paid employment, size of municipality, year of birth. Interaction with sex was significant
Richter et al. (2022) Denmark Cohort study	Congenital heart disease From national registry	1,042,413 births in 1997–2014 10,600 cases	w-As (µg/L) (number) < 0.5 (495970) 0.5–0.9 (235630) 1.0–4.9 (292222) ≥ 5 (18591)	OR (cases) 1.0 (4583) 1.13 (1.08–1.19) (2339) 1.33 (1.27–1.49) (3477) 1.42 (1.24–1.62) (228)	w-As aggregated by water supplies Adjusted for year of birth, mother's education and ethnicity. No interaction with sex. Excluding private wells did not change results

Abbreviations: As, arsenic; aOR, adjusted odds ratio; BMI, body mass index; iAs, inorganic arsenic; LOD, limit of detection; *n*, number; OR, odds ratio; USA, United States of America; w-As, water arsenic.

Water As and orofacial cleft

Suhl et al. (2018) performed a case–control study of OFC and As exposure in Iowa, US. 370 cases 1067 controls. There was no association between drinking water As and risk of OFC, but only about 4% had water As > 5 μg/L. Therefore, the impact of water As on total exposure to iAs should be modest. This single study with modest water-As levels and no increased risk does not permit any conclusion on evidence regarding this birth defect.

In summary there is insufficient evidence of an association between exposure to iAs and OFC.

Water As and any birth defect

The study by Kwok et al. (2006) is too small to permit any conclusions. The study by Marie et al. (2018) found an association between water-As and 'any birth defect' but only in girls.

In summary there is insufficient evidence of an association between exposure to iAs and 'any' birth defect.

Growth after birth

Four cohort studies including mother–child pairs investigated the associations between iAs and children's growth, two of which were from Bangladesh and one from the US (Gardner et al., 2013; Igra et al., 2021; Muse et al., 2020; Saha et al., 2012). One of the studies measured concentrations of iAs in urine only in mothers during pregnancy, whereas the other two measured it also in the children. A study from Bangladesh who followed the children until the age of 2 years, found no associations when the quintiles with the highest concentrations of iAs in urine were compared with the quintiles with the lowest concentrations (Saha et al., 2012). Another study from Bangladesh found an association between concentration of iAs in urine and the children's weight at 5 years of age, most apparent among girls (Gardner et al., 2013). However, no association was observed between prenatal exposure (maternal urine at early gestation) and children's weight at 5 years of age. A third study from Bangladesh which followed the children until the age of 10 years did not observe associations between iAs and growth (Igra et al., 2021). A study from the US observed an association between concentrations of iAs in urine and increased length during the first year of life (Muse et al., 2020). However, although the association was statistically significant the magnitude of the effect was very small, each doubling of tAs increased the length among males with 0.12 cm and among females with 0.13 cm. In addition, no associations were observed in the study between concentrations of iAs in urine and weight gain, change in weight-for-length or head circumference.

Table 19 depicts the studies on children's growth.

In summary, there is insufficient evidence that iAs is associated with children's growth.

TABLE 19 Key epidemiological studies on children's growth in humans in relation to iAs exposure.

Reference study population design	Outcome definition	Population size (*n*) case/control	Arsenic exposure	Results	Additional information/confounders
Saha et al. (2012) Bangladesh Cohort study	Weight and length from birth to 2 years of age	2372 mother–child pairs	**Urinary exposure of iAs, μg/L (median)** Mothers at 8 weeks gestation: 80.9 Mothers at 30 weeks gestation: 84.0 Children at 18 months: 34.2	No significant associations at 2 years of age when comparing highest versus lowest quintiles in the adjusted analyses	Adjusted for age, sex, maternal BMI and SES
Gardner et al. (2013) Bangladesh Cohort study	Children's weight and height at 5 years of age	1505 mother–child pairs	**Urinary exposure of u-tiAs μg/L (median)** Mothers at 8 weeks gestation: 82 Children at 5 years: 51	Adjusted differences when comparing the highest (≥ 95th percentile) with the lowest (≤ 5th percentile): Weight: −0.33 kg (95% CI; −0.60, −0.06) Height: −0.50 cm (95% CI; −1.20, 0.21) The associations were apparent primarily among girls	Adjusted for child's sex, family SES, season of birth, gestational age, maternal education, maternal height or BMI, maternal tobacco chewing, indoor cooking without ventilation and birth order The study did also include Cd and Pb
Muse et al. (2020) New Hampshire, USA Cohort study	Growth parameters from medical records at different timepoints during the first year	760 mother–child pairs	**Urinary exposure, μg/L (median)** Maternal in second trimester iAs 0.36 MMA 0.34 DMA 2.84 u-tiAs 3.96	Each doubling of urinary u-tiAs increased the length over the first year of life with ~0.12 cm in males and 0.13 cm in females No associations with weight gain, change in weight-for-length and head circumferences	Adjusted for gestational age, sex, maternal BMI, IOM gestational weight gain, education, parity, duration of breast feeding and smoking
Igra et al. (2021) Bangladesh Cohort study	Growth until the age of 10 years	1530 mother–child pairs	**Maternal erythrocytes during pregnancy, μg/kg (median):** 4.3 **Total urinary in children's urine at age 10 years, μg/L (median):** 57	No associations with growth up to 10 years	Adjusted for gender, age at 10 years, maternal parity, education, socioeconomic status, maternal height and weight

Abbreviations: BMI, body mass index; Cd, cadmium; CI, confidence interval; DMA, sum of dimethylarsinous acid and dimethylarsinic acid; iAs, inorganic arsenic; IOM, Institute of Medicine; MMA, sum of monomethylarsonous acid and monomethylarsonic acid; *n*, number; Pb, lead; SES, socioeconomic status; u-tiAs, total urinary iAs (sum of iAs and its methylated metabolites MMA and DMA), USA, United States of America.

Neurodevelopmental effects

The previous EFSA CONTAM Opinion (EFSA CONTAM Panel, 2009), described eight studies investigating associations between iAs exposure and developmental effects (cognitive performance) (Calderon et al., 2001; Rosado et al., 2007; Tofail et al., 2009; Tseng et al., 2006; von Ehrenstein et al., 2007; Wang, Wang, et al., 2007; Wasserman et al., 2004, 2007). Based on those studies, the CONTAM Panel concluded '*Taken together, these studies provide some evidence for neurobehavioural effects of arsenic during childhood, also at exposure levels occurring in areas with elevated arsenic exposure via drinking water. More longitudinal studies are warranted to evaluate the most critical windows of exposure, the type of effects and dose-response relationships*'.

Since then, many studies have been published but most are cross-sectional and relatively small. Different tests for cognitive, behavioural or motor/sensory function in children have been applied and at different ages, but the majority of studies have evaluated arsenic exposure vs. cognitive function and in the age span 5–11 years. Further studies have evaluated arsenic exposure and the neurodevelopmental outcomes autism, attention deficit hyperactivity disorder (ADHD).

For the current evaluation, the CONTAM Panel identified 59 studies, of which 20 met the criteria, including five (Rosado et al., 2007; Tofail et al., 2009; von Ehrenstein et al., 2007; Wasserman et al., 2004, 2007) that were already reviewed in the 2009 Opinion.

Of the selected studies, 12 were cross-sectional, one was case–control and seven were cohort studies (i.e. prospective mother–child cohorts). Thirty-nine further studies were not selected as they did not meet the inclusion criteria (Calderon et al., 2001; Cusick et al., 2018; de Assis Araujo et al., 2022; de Water et al., 2022; do Nascimento et al., 2015; Forns et al., 2014; Freire et al., 2018; Hsueh et al., 2020; Huang et al., 2011; Jiang et al., 2018, 2022; Khan et al., 2012, 2019; Langley et al., 2015; Levin-Schwartz et al., 2019; Lin et al., 2013; Lucchini et al., 2019; McDermott et al., 2012; Merced-Nieves et al., 2022; Nahar, Inaoka, & Fujimura, 2014; Nahar, Inaoka, Fujimura, Watanabe, et al., 2014; Nozadi et al., 2021; Nyanza et al., 2021; Parajuli et al., 2013, 2014, 2015; Rahman et al., 2015; Renzetti et al., 2021; Rocha-Amador et al., 2007; Rodríguez-Barranco et al., 2016; Saxena et al., 2022; Valeri et al., 2017; Vibol et al., 2015; Wang, Wang, et al., 2007; Wang, Liu, et al., 2018; Wang, Wang, & Yan, 2022; Wasserman et al., 2011; Wright et al., 2006). Table 20 summarises the selected studies from both the 2009 Opinion and the current evaluation.

Prenatal arsenic exposure and cognition

In a study from India on iAs and intellectual function in 5–15 year-old children assessed both arsenic exposure during pregnancy (mean water arsenic concentrations 110 µg/L) and childhood (mean 147 µg/L) (von Ehrenstein et al., 2007). There were no significant associations with either exposure time window when using arsenic in water as the exposure matrix. Associations were found with child urinary As, but it was not speciated for arsenic metabolites.

Rodrigues et al. (2016) evaluated water As concentrations from pregnancy up to 20–40 months in two regions (Sirajdikhan and Pabna) in Bangladesh and neurodevelopment. No associations were found between concurrent water arsenic (median Sirajdikhan 1.5 µg/L and Pabna 25.7 µg/L) and children's scores for receptive and expressive language, or gross motor domains (not in table). Increasing concurrent water arsenic concentrations were associated with decreasing cognitive scores in Pabna but not in Sirajdikhan. Similar and slightly stronger associations were observed between first trimester water arsenic concentrations and cognitive scores in Pabna.

In a large and well-characterised mother–child cohort in Matlab in rural Bangladesh, arsenic concentrations were evaluated vs. neurodevelopment at different ages: at 7 months (Tofail et al., 2009), 18 months (Hamadani et al., 2010), 5 years of age (Hamadani et al., 2011), and 10 years of age (Vahter et al., 2020, in table). In Vahter et al. (2020) cognitive abilities of children were assessed in relation to arsenic in maternal urine in early pregnancy (gestational week 8), and in child urine at 5 and 10 years, and in hair at 10 years. Both early maternal urine (82 µg/L) and child arsenic exposure (57 µg/L) at 10 years, were at low levels (around 50 µg/L) inversely associated with cognitive abilities measured as full developmental score at 10 years. Associations were found in the 2nd and 3rd quintiles. Models with children's hair arsenic concentrations showed similar results (not in Table 20).

Soler-Blasco et al. (2022) evaluated maternal urinary arsenic (geometric mean 7.78, 95% CI 7.41, 8.17 µg/g creatinine), in the first trimester and neurodevelopment (McCarthy Scales of Children's Abilities) in Spanish 4–5 years-old children. They found inverse associations between MMA concentrations and the scores for the general, verbal, quantitative, memory and working memory scales. However, no associations were found between total iAs and developmental scales in multivariate models.

Postnatal exposure and cognition

In studies from Araihazar in Bangladesh, exposure to arsenic from drinking water (mean appr. 120 µg/L across the studies) was evaluated in relation to intellectual function at different ages. In 9–10-year-old children, increasing water arsenic was associated with reduced intellectual function (full scale score), in a dose-dependent manner (Figure 1 in article, though the effect estimate for the second quartile was not provided; Wasserman et al., 2004). In 6-year-old children, increasing water arsenic was negatively associated with full scale scores, and the associations were less strong than in the previously studied 9–10-year-olds (Wasserman et al., 2007). In 14–16-year-old children, urinary arsenic showed negative associations

with all Wechsler test scores, but it is unclear whether the urinary arsenic was corrected for organic arsenic and there are no effect estimates for the dose response analysis (Wasserman et al., 2018).

Rosado et al. (2007) found in 6–7-year-old Mexican children inverse associations between urinary arsenic (mean 58.1 μg/L) and cognition measured as visual–spatial abilities with Figure Design, the Peabody Picture Vocabulary Test, the WISC-RM Digit Span subscale, visual search and letter sequencing tests.

In a study of Taiwanese children with and without developmental delay increased risk (with very wide confidence interval) for developmental delay was found in the highest tertile (> 24.71 μg/creatinine) of child urinary arsenic (Hsieh et al., 2014).

In a study on 3–5 grade school children (Wasserman et al., 2014) in the USA, associations between drinking water As (mean 9.88 μg/L) and IQ were examined. Water arsenic was negatively associated with Full Scale IQ. This association was strongest in the exposure category 5–10 μg/L arsenic in water, but no dose–response was found.

Three studies from Uruguay (Desai et al., 2018; Desai, Barg, Vahter, Queirolo, Peregalli, Mañay, Millen, Yu, Browne, & Kordas, 2020; Desai, Barg, Vahter, Queirolo, Peregalli, Mañay, Millen, Yu, & Kordas, 2020) were based on the same study population of 5–8-year-old children (median appr. 10 μg/L). Two of the studies did not find associations between arsenic and cognitive functions (Desai et al., 2018; Desai, Barg, Vahter, Queirolo, Peregalli, Mañay, Millen, Yu, Browne, & Kordas, 2020), whereas one found adverse associations with different measures of executive function (Desai, Barg, Vahter, Queirolo, Peregalli, Mañay, Millen, Yu, & Kordas, 2020).

Postnatal exposure motor/ sensory functions and behaviour

Parvez et al. (2011) investigated the relation between arsenic in water (mean 43.3 μg/L) and motor function in 8–11-year-old children and found lower total motor composite scores with increasing arsenic concentrations.

Signes-Pastor, Vioque, et al. (2019) evaluated arsenic exposure measured in urine and neuropsychological development among Spanish children of 4–5 years of age. Urinary As concentrations (median < 10 μg/L) were negatively associated with the scores of global, gross and fine motor function. They found no associations between iAs and cognitive function.

Emotional and behavioural symptoms at the subclinical level raise the risk of subsequent development of mental disorders and can be assessed during pre-adolescence through internalising and externalising problems indicators. Roy et al. (2011) found in a study of Mexican 6–7-year-old children an association between urinary arsenic (median 55.2 μg/L) in the 2nd quartile (range 36–55.2 μg/L) and teachers' ratings of oppositional behaviour, but there was no dose–response.

Khan et al. (2011) evaluated water arsenic concentrations and classroom behaviour via teacher's report of internalising and externalising problems in 8–11-year-old children in Bangladesh, and found no association with As and these outcomes.

In summary, epidemiological studies published since the EFSA Opinion 2009 provide sufficient evidence for a causal association between low to moderate exposure to iAs and impaired cognition. The study by Vahter et al. (2020) is the largest and longitudinal study which reports results both for prenatal exposure and postnatal exposure and there may be different BMD depending on the timing of exposure.

There is insufficient evidence for associations between low to moderate exposure to iAs and motor function and behaviour.

TABLE 20 Key epidemiological studies on As exposure and neurodevelopment.[a]

Reference study population design	Outcome definition	Population size (*n*), age	Arsenic exposure	Results	Additional information/confounders
Prenatal					
von Ehrenstein et al. (2007) India Prospective mother–child cohort study	Wechsler Intelligence Scale for Children (no edition provided), Raven Coloured, Progressive Matrices test, Total Sentence Recall test, Purdue pegboard test	351 5–15 years	w-As (μg/L) Mean (SD) *Peak lifetime* 147 (322) *During pregnancy* 110 (243) Tertiles < 10 10–49 50–99 > 100 < 10 10–49 50–99 > 100	B (95% CI) Full scale IQ *Peak lifetime* Ref 0.006 (−0.031, 0.33) −0.16 (−0.56, 0.23) −0.06 (−0.30, 0.18) *During pregnancy* Ref −0.047 (−0.38, 0.28) −0.007 (−0.36, 0.34) −0.002 (−0.24, 0.24)	Adjusted for age, sex, BMI, maternal and paternal education, father's occupation, number of rooms in the house, type of house building material, BMI and mother's age
Rodrigues et al. (2016) Bangladesh Prospective mother–child cohort study	Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III)	525 20–40 months Sirajdikhan (*n* = 239) Pabna (*n* = 286)	w-As (μg/L) at 20–40 months Median (IQR) Sirajdikhan 1.5 (< 0.75, 21.6) Pabna 25.7 (4.4, 130) w-As at 1st trimester pregnancy Sirajdikhan 1.3 (< LOD, 1.9) Pabna 26.5 (5.3, 81)	β (SE, *p*-value) As 20–40 months *Cognitive* Sirajdikhan −0.002 (0.02, 0.93) Pabna −0.06 (0.03, 0.05) *Fine motor* Sirajdikhan −0.05 (0.03, 0.09) Pabna 0.02 (0.03, 0.48) As during pregnancy *Cognitive* Sirajdikhan 0.009 (0.03, 0.78) Pabna −0.09 (0.03, 0.006) *Fine motor* Sirajdikhan 0.07 (0.04, 0.10) Pabna 0.007 (0.03, 0.81)	Different exposure, scores and covariates between clinics and thus were results stratified by area. Adjusted for maternal age and education, child's gender, exposure to second-hand smoke, HOME score, maternal Raven score and child haematocrit.

TABLE 20 (Continued)

Reference study population design	Outcome definition	Population size (*n*), age	Arsenic exposure	Results	Additional information/confounders
Vahter et al. (2020) Bangladesh Prospective mother–child cohort study, cross-sectional at 5 and 10 years	Wechsler Intelligence Scale for Children 4th ed. (WISC-IV)	1523 mother–child pairs 305 305 304 305 304 296 295 296 295 295 294 293 294 293 293	u-tiAs (µg/L) children 10 years, Median (range) 22.6 (7.3–29.9) 36.7 (30.0–45.5) 57.3 (45.6–73.1) 104 (73.4–162) 265 (163–940) u-tiAs children 5 years 21 (6–27) 34 (28–41) 53 (42–69) 100 (70–149) 236 (150–1020) u-tiAs mothers week 8 23.8 (3.2–32.4) 43.5 (32.5–58.8) 83.5 (58.9–122) 174 (122–246) 381 (247–1287)	B (95% CI) Full developmental score Ref −1.63 (−5.62; 2.36) −7.23 (−11.3, −3.18) −6.37 (−10.5, −2.22) −2.71 (−6.96, 1.54) Ref −1.53 (−5.63, 2.56) −3.30 (−7.41, 0.81) −2.57 (−6.78, 1.65) 0.59 (−3.67, 4.86) Ref −4.52 (−8.61, −0.43) −5.91 (−10.0, −1.77) −5.98 (−10.2, −1.77) −3.41 (−7.60, 0.77)	Adjusted for child gender, age at testing and tester, child BMI-for-age, type of school, school grade, number of children in the household, family, HOME score, father's level of education, mother's IQ, home stimulation, child, U-cadmium and W-manganese
Soler-Blasco et al. (2022) Spain Prospective mother–child cohort study	McCarthy Scales of Children's Abilities	807 4–5 y	u-tiAs mothers first trimester (µg/g creatinine) GM mean (95%CI) 7.78 (7.41–8.17)	B (95% CI) General scale *u-tiAs continuous* −0.49 (−1.53, 0.56)	Adjusted for area of study, creatinine, maternal and paternal educational level, parity, child's sex, attendance at nursery, maternal verbal intelligence quotienteason of sample collection and rice and seafood consumption during the first trimester of pregnancy.
Postnatal					
Wasserman et al. (2004) Bangladesh Cross-sectional study	Wechsler Intelligence Scale for Children, version III	201 9.5-, 0.5 years	 w-As (µg/L) Mean (SD) 117.8 (145.2) w-As (µg/L) Quartiles 0.1–5.5 5.6–50.0 50.1–176 177–790 u-As (µg/g creatinine) 296.6 (277.2)	B (*p*-value) *Full-Scale score* *w-As continuous* −1.64 (< 0.01) *w-As quartiles* Ref Not provided −7.8 (< 0.05) −11.3 (< 0.01) *u-As continuous* −2.9 (0.09)	Adjusted for maternal education, maternal intelligence, house type, television access, height, head circumference Speciated arsenic in urine but unclear if arsenobetaine and arsenocholine were subtracted from total urinary arsenic

(Continues)

TABLE 20 (Continued)

Reference study population design	Outcome definition	Population size (*n*), age	Arsenic exposure	Results	Additional information/confounders
Wasserman et al. (2007) Bangladesh Cross-sectional study	Wechsler Preschool and Primary Scale of Intelligence, version III	301 6 years	w-As (μg/L) Mean (SD) 120.1 (134.4) w-As (μg/L) Quartiles 0.1–20.9 21–77.9 78–184.9 185–864	B (SE, *p*-value) *Full-Scale IQ* *w-As continuous* −1.06 (0.57, < 0.07) *w-As quartiles* Ref Not provided Not provided −5.70 ($p = 0.09$)	Adjusted for maternal education and intelligence, home stimulation, school attendance, height, head circumference, W-manganese
Wasserman et al. (2018) Bangladesh Cross-sectional study	Wechsler Intelligence Scale for Children-Fourth Edition	694 14–16 years	u-As (μg/g creatinine) Mean (SD) 157.79 (208.87)	B (SE, *p*-value) *Full-Scale IQ, U-As continuous* −5.09 (1.38, < 0.001)	Adjusted for paternal education, maternal intelligence, house construction, head circumference, child education, w-As of the mother at baseline, B-selenium, B-cadmium, B-lead, B-manganese. Speciated arsenic in urine but unclear if arsenobetaine and arsenocholine were subtracted from total urinary arsenic
Rosado et al. (2007) Mexico Cross-sectional study	Weschsler Intelligence Scale for Children Revised Mexican Version (WISC-RM), a test of number and letter sequencing, Cognitive Abilities Test, Math Achievement Test (MAT), Visual–Spatial Abilities with Figure Design, Peabody Picture Vocabulary Test (PPVT-Spanish Edition)	557 6–8 years	u-As (μg/L) Mean (SD) 58.1 (33.2)	B (95% CI) *Visual–spatial abilities* −0.024 (−0.045, −0.004) *Peabody picture vocabulary* −0.064 (−0.115, −0.013) *WISC-RM digit span subscale* −0.014 (−0.025, −0.002) *Visual search* −0.007 (−0.011, −0.002) OR (95% CI) *Letter sequencing* 0.992 (0.987, 0.996)	Adjusted for age, sex, mother's school level, haemoglobin, B-lead and B-lead × u-As interaction when significant. They had further info on child anthropometry but this was not adjusted for
Parvez et al. (2011) Bangladesh Cross-sectional study	Bruininks-Oseretsky Test version 2. 4 subscales that are summarised into total motor composite score (TMC)	304 8–11 years	w-As (μg/L) Mean (SD) 43.3 (73.6)	β (95% CI) TMC −1.18 (−2.13, −0.10)	Adjustment for sex, school attendance, head circumference, mother's intelligence, B-manganese, B-lead and B-selenium

TABLE 20 (Continued)

Reference study population design	Outcome definition	Population size (*n*), age	Arsenic exposure	Results	Additional information/confounders
Hsieh et al. (2014) Taiwan Case–control study	Peabody Developmental Motor Scales, Gross Motor Function Measure, Preschool Language Evaluation Tool, Child Expression Evaluation Tool, Chinese Wechsler Intelligence Scale for Children (3rd ed.), Bayley III Scales of Infant and Toddler Development. Developmental delay defined as performance 2 SD below the mean on age-appropriate, standardised, norm-referenced tests	63/35 with and without developmental delays; 5 years 7/12 21/11 35/12	u-As (μg/g creatinine) Tertiles of the controls ≤ 13.56 13.57–24.71 > 24.71	OR (95% CI) Developmental delay 1.0 5.95 (0.64, 55.57) 11.83 (1.52, 91.82)	Adjusted for age, gender, birth weight of children, ethnicity of their mothers, gestational length, B-lead or B-mercury. Information about mothers' education but not different between delay groups and not included in the adjusted model
Wasserman et al. (2014) USA Cross-sectional study	The Wechsler Intelligence Scale for Children IV ed	272 8–11 years 141 46 52 33	w-As (μg/L) Mean (SD) 9.88 (15.06) Mean (SD) 1.24 (1.37) 7.37 (1.34) 14.80 (3.06) 42.55 (20.43)	B (SE, *p*-value) Full Scale IQ Ref −6.09 (1.98, < 0.01) −3.15 (1.91, 0.05) −2.51 (2.29, < 0.10)	Adjustment for maternal IQ, maternal education, HOME score, school district, number of siblings
Desai et al. (2018) Uruguay Cross-sectional study	Woodcock-Muñoz cognitive battery: 7 subtests from which the general intellectual abilities (GIA) score was derived	328 5–8 years	u-As (μg/L) children Median (range) 11.9 (1.4–93.9)	B (95% CI) *GIA score* −0.05 (−1.91, 1.82)	Adjusted for school clusters at the design stage, child's sex, BMI for age, serum ferritin, B-lead, haemoglobin, season, test administrator, mother's education, crowding at home, HOME score, parental smoking, source of drinking water, household possessions. No consistent effect modification by folate intake or %MMA
Signes-Pastor et al. (2019) Spain Cross-sectional study	McCarthy Scales of Children's Abilities (MSCA)	400 4–5 years	u-As (μg/L) Median (IQR) 4.85 (2.74–7.54)	B (95% CI) *Motor functions* global scores: −2.29 (−3.95, −0.63) gross scores: −1.92 (−3.52, −0.31) fine scores: −1.54 (−3.06, −0.03)	Adjusted for maternal education, child sex, BMI, age at testing, calorie adjusted consumption of rice and fish/seafood. In stratified analyses by sex, negative associations were observed with some scores only in boys

(Continues)

TABLE 20 (Continued)

Reference study population design	Outcome definition	Population size (*n*), age	Arsenic exposure	Results	Additional information/confounders
Desai, Barg, Vahter, Queirolo, Peregalli, Mañay, Millen, Yu, Browne, and Kordas (2020) Uruguay Cross-sectional study	Woodcock-Muñoz Cognitive Battery: 6 subtests from which Broad math score and Broad reading score were derived	239 5–8 years	u-As (μg/L) children Median (range) 11.7 (2.6, 50.1)	OR (95% CI) *Broad math score* 1.01 (0.98, 1.04) *Broad reading score* 1.00 (0.98, 1.03)	Adjusted for season, sex, maternal education, household possessions, HOME score, haemoglobin, B-lead, H-manganese. No effect modification by %MMA or B-vitamins
Desai, Barg, Vahter, Queirolo, Peregalli, Mañay, Millen, Yu, and Kordas (2020) Uruguay Cross-sectional study	Tests from Cambridge Neuropsychological Test Automated Battery (CANTAB): Stockings of Cambridge (SOC), Intra-dimensional/ extra-dimensional shift task (IED) and Spatial Span (SSP)	255 5–8 years	u-As (μg/L) children Median (range) 9.9 (2.2, 47.7) w-As (μg/L) Median (range) 0.45 (0.1, 18.9)	B (95% CI) *IED Stages completed*: −0.02 (−0.03, −0.002) *IED Pre-executive shift error*: −0.07 (−0.13, −0.01) *SSP Span length*: −0.02 (−0.02, −0.01)	Adjusted for age, sex, maternal education, possessions score, HOME score, season, school clusters, B-lead, haemoglobin, U-cadmium and H-manganese. No effect modification of B vitamin intake or %MMA

Abbreviations: As, arsenic; b, blood; BMI, body mass index; BSID-III, Bayley Scales of Infant and Toddler Development, Third Edition; CANTAB, Cambridge Neuropsychological Test Automated Battery; CI, confidence interval; GIA, general intellectual abilities; GM, geometric mean; HOME, Home Observation Measurement of the Environment score; IED, Intradimensional /extradimensional shift task; IQ, intelligence quotient; IQR, interquartile range; LOD, limit of detection; MAT, Math Achievement Test; MMA, sum of monomethylarsonous acid and monomethylarsonic acid; MSCA, McCarthy Scales of Children's Abilities; n, number; OR, odds ratio; PPVT, Peabody Picture Vocabulary Test; ref, reference; SD, standard deviation; SE, standard error; SOC, Stockings of Cambridge; SSP, spatial span; TMC, Total Motor Composite score; u, urine; u-As, urinary arsenic; USA, United States of America; w: water; w-As, water arsenic; WISC-IV, Weschsler Intelligence Scale for Children 4th edition; WISC-RM, Weschsler Intelligence Scale for Children Revised Mexican Version; u-tiAs, total urinary iAs (sum of iAs and its methylated metabolites MMA and DMA).

[a]Due to space limitations, not all outcomes reported in the studies are included in the table. For studies using Wechsler scales, the full score is presented; for studies with many tests, only outcomes that were associated with arsenic are presented.

Arsenic and autism spectrum disorder

For the present Opinion, the CONTAM Panel identified 27 studies on associations between As exposure and autism spectrum disorder (ASD) from a literature search (see Section 2 on methodology). Out of these, 16 studies did not meet the inclusion criteria and were thus not considered further (Adams et al., 2013; Amadi et al., 2022; Baj et al., 2021; Elsheshtawy et al., 2011; Fiore et al., 2020; Geier et al., 2012; Li, Li, et al., 2018; Majewska et al., 2010; Rahbar et al., 2012, 2021; Rezaei et al., 2022; Skogheim et al., 2021; Vergani et al., 2011; Wang, Hossain, et al., 2019; Yorbik et al., 2009; Zhao et al., 2022). Eleven studies that fulfilled the inclusion criteria are described in detail in Table 21.

In a case control study with Arab children, children with ASD had higher concentrations of As in hair compared with controls (Blaurock-Busch et al., 2011). Also, in an expanded population of the previous study, hair As concentrations were significantly higher in children with ASD compared with controls (Blaurock-Busch et al., 2012). In two further case control studies of Arab children, one study showed higher hair As among children with ASD compared with controls (Al-Ayadhi, 2005), but no differences were found in the second study (Fido & Al-Saad, 2016).

In case–control studies performed in Poland, USA and China, children with ASD had higher hair As concentrations compared with controls (Fiłon et al., 2020; Obrenovich et al., 2011; Zhai et al., 2019).

In a case–control study in Russia, hair As was not significantly different in children with ASD compared with controls (Skalny et al., 2017). In another and larger case control study from the same authors (possibly related to the previous study although there is no statement in the manuscript), hair As concentrations were not significantly different in children with ASD compared with controls (Skalny et al., 2016). Also, in a study in Italy, hair As concentrations did not differ between children with ASD and controls (De Palma et al., 2012), whereas in a US study, hair As concentrations were significantly lower children with ASD than in matched controls (Kern et al., 2007).

Overall, six studies found higher hair As levels in ASD cases, while four did not find any significant differences in hair As levels and one found lower levels of hair As in ASD cases compared to controls. All studies are case–control studies with relatively few cases/controls. This is important as the case–control study is not a relevant study design for a disease likely affecting life and family/child habits. All studies used hair As as exposure metric. It should be noted that hair As in some of the studies was surprisingly high, whereas hair As levels in most of the studies where no association was seen with autism as well as other investigations presented in this Opinion are below 0.1 µg/g.

In summary, there is insufficient evidence for an association between low to moderate exposure to iAs and ASD.

TABLE 21 Key epidemiological studies on autism and As exposure.

Reference study population age design	Outcome definition	Population size (*n*) case/control	Arsenic concentration/ exposure	Results	Additional information/confounders
Al-Ayadhi (2005) Arab/up to 14 years Case–control study	Autism spectrum disorder (autism, attention deficit disorder, Rett's syndrome, Asperger's syndrome)	77/80	Hair As	Cases versus control mean ppm (SEM): 1.8 (0.16) versus 0.23 (0.05), $p < 0.05$	Age and sex matched controls. Also results for 12 cases in total with attention deficit disorder, Rett's syndrome, Asperger's syndrome
Kern et al. (2007) USA 1–6 years, Case–control study	Autism spectrum disorder, Autism severity (Childhood Autism Rating Scale (CARS))	45/45	Hair As	Cases versus control mean µg/g (SD): 0.06 (0.06) versus 0.09 (0.08), $p < 0.05$. No association between As levels and CARS	Age, sex, race/ethnicity matched controls
Blaurock-Busch et al. (2011) Arab 3–9 years, Case–control study	Autism spectrum disorder (ASD), autism severity (Childhood Autism Rating Scale (CARS))	25/25	Hair As	Cases versus control mean µg/g (SD): 0.2 (0.26) versus 0.06 (0.04), *p*: 0.01	Age and sex matched controls. Significant differences regarding the amount of sea food eaten per month by mothers during pregnancy and by infants in the infancy period were noted
De Palma et al. (2012) Italy/mean 9 years Case–control study	Autism spectrum disorder, autism severity (Childhood Autism Rating Scale (CARS)	44/61	Hair As	Cases versus control median µg/g (IQR): 003 (0.01–0.06) versus 0.04 (0.012–0.07), *p*: NS	Age matched controls
Obrenovich et al. (2011) USA (authors)/under 6 years, Case–control study	Autism spectrum disorder	26/39	Hair As	Cases versus control $p < 0.001$	Age matched controls. No details for data
Blaurock-Busch et al. (2012) Arab 3–9 years, Case–control study	Autism spectrum disorder, autism severity (Childhood Autism Rating Scale [CARS])	44/146	Hair As	Cases versus control mean µg/g (SD): 2.94 (4.05) versus 0.7 (95th percentile), *p*: 0.01 No correlation between total or any subscale of CARS and As (*r*: −0.2).	Age matched controls. Expanded sample compared with Blaurock-Busch but only hair As measurement
Fido and Al-Saad (2016) Arab 4–7 years, Case–control study	Autism	40/40	Hair As	Cases versus control median µg/g (IQR): 013 (0.12–018) versus 0.13 (0.11–0.16) *p*: NS.	Age and sex matched controls
Skalny et al. (2016) Russia/2–9 years, Case–control study	Autism spectrum disorder	74/74	Hair As	Cases versus control median µg/g (IQR): 0.034 (0.021–0.044) versus 0.031 (0.021–0.058), *p*: NS	Age and sex matched controls. Additional data for selected age groups. Population of Skalny et al. (2016 and 2017) publications may partly overlap
Skalny et al. (2017) Russia 3–8 years, Case–control study	Autism spectrum disorder	33/66	Hair As	Cases versus control median µg/g (IQR): 0.0343 (0.026–0.0434) versus 0.0426 (0.021–0.0862), *p*: NS	Age and sex matched controls. Additional data for selected age groups and As correlation with age
Zhai et al. (2019) China mean 5 years, Case–control study	Autism spectrum disorder	79/58	Hair As	Cases versus control median (µg/g) (IQR): 0.21 (0.16–0.29) versus 0.09 (0.0–0.16), $p < 0.001$	Age and site matched. Data also for gut microbiota
Fiłon et al. (2020) Poland 2–8 years, Case–control study	Autism spectrum disorder	30/30	Hair As	Cases versus control mean µg/g (SD): 0.216 (0.09) versus 0.061 (0.03), $p < 0.001$	Controls < 8 years randomly selected

Abbreviations: As, arsenic; ASD, autism spectrum disorder; CARS, Childhood Autism Rating Scale; IQR, interquartile range; *n*, number; NS, not significant; ppm, parts per million; SD, standard deviation; SEM, standard error of the mean; USA, United States of America.

3.2.2.5 | *Effects on male fertility*

Associations between iAs and male fertility were not discussed in EFSA CONTAM Opinion (2009). For the current Opinion, the CONTAM Panel identified eight studies from a literature search, of which one study from China, summarised in Table 22, met the inclusion criteria (Wang et al., 2016). The study did observe a significant association between u-tiAs and unexplained male infertility. However, very wide confidence intervals clearly indicate the uncertainty in the risk estimates.

Six additional studies were also evaluated but did not fulfil the inclusion criteria and were accordingly not considered further (Calogero et al., 2021; Oguri et al., 2016; Sengupta et al., 2013; Sukhn et al., 2018; Tian et al., 2021; Xu et al., 2012).

In summary, the epidemiological studies provide insufficient evidence for an association between low to moderate exposure to iAs and effects on male fertility.

TABLE 22 Key epidemiological studies on male fertility in humans in relation to iAs exposure.

Reference study population design	Outcome definition	Population size (*n*) case/control	Arsenic exposure	Results	Additional information/ confounders
Wang et al. (2016) Nanjing Medical University, China Case–control	Unexplained male infertility	Cases: 101 infertile men with normal semen whose wives were evaluated to have normal reproductive function Controls: 61 fertile men with normal semen whose wives had successful pregnancy in last 3 months	**Urinary concentration (µg/g creatinine), Medians, Cases – Controls** As_i^{III} 4.10–3.97 As_i^{V} 71.59–0.63 AsB 12.03–7.80 MMA^{V} 4.20–2.93 DMA^{V} 28.23–18.30 u-tiAs 74.87–5.46	**Adjusted OR (95% CI) 4th versus 1st quartile** As_i^{III} 0.59 (0.19–1.83) As_i^{V} 36.51 (8.25–161.7) AsB 2.23 (0.70–7.12) MMA^{V} 1.97 (0.57–6.77) DMA^{V} 1.27 (0.40–4.03) u-tiAs 10.17 (2.72–38.11)	Adjusted for age, BMI, drinking and smoking

Abbreviations: As(III), arsenite; As(V), arsenate; AsB, arsenobetaine; BMI, body mass index; CI, confidence interval; DMA(V), dimethylarsinic acid; iAs, inorganic arsenic; MMA(V), monomethylarsonic acid; *n*, number; OR, odds ratio; u-tiAs, total urinary iAs (sum of iAs and its methylated metabolites MMA and DMA).

3.2.2.6 | *Neurotoxicity*

EFSA CONTAM Panel (2009) concluded that the available epidemiological studies indicated a relationship between high level oral exposures to iAs and sensitive endpoints for peripheral and central neurotoxicity.

Peripheral neuropathy is observed both at acute and chronic high exposure to arsenic. The clinical features of the arsenic-linked neuropathy are paresthesias, numbness and pain, particularly in the hands and the soles of the feet. In many cases a symmetrical peripheral neuropathy is one of the earliest symptoms of arsenic poisoning.

The CONTAM Panel identified 21 studies, of which 10 studies met the criteria. The relevant studies are summarised in Table 23. In 11 papers, arsenic and neurotoxicity were reported but the studies were not considered further, as they did not meet the inclusion criteria (Guha Mazumder et al., 2010; Ishii et al., 2017, 2018; Khan et al., 2019; Mathew et al., 2010; Guha Mazumder et al., 2010; O'Bryant et al., 2011; Peters et al., 2021; Shiue, 2015; Szabo et al., 2016; Valappil & Mammen, 2019; Yorifuji et al., 2016).

Mukherjee et al. (2014) found in pre-menopausal women of eastern India a higher risk of symptoms from the peripheral nervous system (for example burning sensation in extremities, tingling or numbness, reduced sense of taste and reduced sense of smell) in women who had been drinking water contaminated with As concentrations of 11–50 μg/L compared with women drinking water with As < 10 μg/L. Mochizuki et al. (2019) found in a study on adults and children in Myanmar that more subjective symptoms, possibly due to peripheral neuropathy, were reported at arsenic concentrations in drinking water > 10 μg/L compared with at concentrations < 10 μg/L. Objective peripheral nerve disturbances of both small and large fibres occurred at > 50 μg/L. However, no adjustments were performed in this study and the exposure assessment was crude.

Low chronic exposure to arsenic and associations with impairment of the central nervous system have been evaluated. Mukherjee et al. (2014) found a higher prevalence of depression and other neurobehavioral symptoms in the same pre-menopausal women mentioned above. Rahman, Niemann, and Yusuf (2022) evaluated in the NHANES survey for years 2015–16, associations between arsenic concentrations in urine and sleep disturbance. Compared with individuals with urinary arsenous acid below the lower level of detection, those with urinary arsenous acid at or above the detection limit had lower odds of sleep disturbance. There was no association for any other metabolites (total arsenic metabolites was not evaluated in the statistical analysis). Liu et al. (2017) reported in a study of Chinese men and women above 40 years, higher risk of cognitive impairment with higher arsenic in drinking water and the impairment was observed already at water arsenic concentrations of 11–50 μg/L compared to concentrations < 10 μg/L. Cognitive impairment with higher arsenic concentrations in drinking water was also found in adults from Bangladesh (Karim et al., 2019) exposed to drinking water with arsenic ranging 5.32–167.94 μg/L. Wang, Huang, et al. (2021) showed in a study from China higher risk of cognitive impairment with higher arsenic concentrations in hair, with a dose–response. The exposure assessment is though difficult in this study as the study participants lived in an area with historically high arsenic concentrations in drinking water polluted from a nearby plant that closed in 2011.

In three studies from Texas, arsenic exposure was estimated by a method based on geographic information system using information on arsenic in ground water (Edwards, Hall, et al., 2014; Edwards, Johnson, et al., 2014; Gong et al., 2011). The authors also reported on a comparison between estimated and measured arsenic values from seven wells and found a reasonable agreement (Edwards, Johnson, et al., 2014). They associated the estimated arsenic levels with different outcomes related to neurophysiological functions. However, the exposure assessment was rather crude. In Edwards, Johnson, et al. (2014), participants with Alzheimer's disease and mild cognitive impairment, were compared with participants with normal cognition. In the whole group, arsenic concentrations were positively associated with language abilities, but also associated with poorer verbal memory, immediate and delayed, as well as poorer visual memory, immediate and delayed. No association was found with depression. In Edwards, Hall, et al. (2014), where rural dwelling adults and elders over 40 years were examined with a battery of neurophysiological tests, estimated higher arsenic concentrations in water were negatively associated with language and executive functioning, and weakly with cognition. Gong et al. (2011) also evaluated estimated arsenic concentrations vs. global cognition in the same study area and same age group (it is not clear if these two latter studies represent independent samples) and found that those with estimated arsenic exposure > 10.0 μg/L had lower MMSE scores than those with arsenic exposure ≤ 10.0 μg/L). However, there were no adjustments in these analyses and no effect estimates presented (not in table).

Several studies have analysed the associations between arsenic and levels of different neurotransmitters or cholinesterase. Ali et al. (2010) investigated the association between arsenic exposure (measured in water) and the activity of plasma cholinesterase in Bangladeshi adults. When dividing the study participants in three exposure groups (low < 129 μg/L arsenic in drinking water; medium 130–264 μg/L and high > 265 μg/L), there was a dose–response with the highest plasma cholinesterase activity in the low exposure group followed by the medium and the high exposure groups (all group comparisons were statistically significant, but no exact values were provided for these comparisons). When dividing study participants according to ≤ 50 and > 50 μg/L As in drinking water, also a lower plasma cholinesterase activity was found in the higher arsenic exposure group. Plasma norepinephrine is used as a measure of sympathetic activity. In the already mentioned Mukherjee et al. (2014) study, levels of plasma neurotransmitters epinephrine, norepinephrine and serotonin were higher among premenopausal women exposed to water arsenic concentrations ranging 11–50 μg/L compared with women exposed to concentrations < 10 μg/L. The authors interpreted these findings as a stress response of the nervous system. In Karim et al. (2019), serum levels of the brain-derived neurotrophic factor (BDNF), a growth and survival factor for nervous cells, was lower with higher arsenic in water. BDNF and the Mini-Mental State Examination correlated positively, suggesting that arsenic may mediate its neurotoxicity via lower BDNF levels.

Overall, the available epidemiological studies (particularly Mukherjee et al., 2014; and Liu et al., 2017) indicate a relationship between low level of exposure to iAs and sensitive endpoints for both peripheral and central neurotoxicity. Moreover, studies including biomarkers of effect or mediation support the associations between low-level arsenic and neurotoxicity. Nevertheless, further epidemiological studies are warranted. It should be noted that in many of the studies, study participants may have been exposed since early in life, and the effects observed may be the result of exposure during developmental periods of the central and the peripheral nervous systems. In Table 23 the studies on neurotoxicity in adults are described.

In summary, the epidemiological studies provide insufficient evidence for an association between low to moderate exposure to iAs and neurotoxicity.

TABLE 23 Key epidemiological studies on As exposure and neurotoxicity among adults.

Reference study population design	Outcome definition	Population size (*n*)	Arsenic exposure	Results	Additional information/confounders
Ali et al. (2010) Bangladesh Cross-sectional	Plasma cholinesterase (PChE) activity	141 33 108	w-As (μg/L) ≤ 50 > 50	PChE (U/L) × 10^4 1.775 ± 0.371 1.365 ± 0.349	No exposure to pesticides during the last month among the study participants. No significant effects of age, sex and BMI on PChE activity
Edwards, Johnson, et al. (2014) USA Cross-sectional	Neuropsychology core battery for cognition, memory, depression	Full sample: 1390 733 Alzheimer's disease, 127 mild cognitive impairment, 530 with normal cognition	w-As, mean (SD) (μg/L) 3.97 (3.3) 3.9 (3.1) 3.2 (2.6) 4.0 (3.6)	B coefficient (SE, *p*-value) Full sample: Confrontation naming: 0.21 (0.08, 0.008) Immediate verbal memory: −0.23 (0.09, 0.008), Delayed verbal memory: −0.34 (0.10, < 0.001) Immediate visual memory: −0.23 (0.10, 0.02) Delayed visual memory: −0.58 (0.11, < 0.001)	Adjusted for age, gender, education, obesity, hyperlipidaemia, hypertension, diabetes and selenium level GIS-estimated
Edwards, Hall, et al. (2014) USA Cross-sectional	Attention, processing speed, verbal fluency, visuospatial abilities, immediate memory and delayed memory; executive functioning Mini Mental State Examination (MMSE) for global cognition	526 ≥ 40 years	w-As, mean (SD) (μg/L) 6.42 (2.99)	B (SD, *p*-value) Immediate memory raw index 0.15 (0.29, 0.60) Visuospatial raw index −0.39 (0.19, 0.05) Language raw index −0.48 (0.15, < 0.05) Attention raw index −0.66 (0.39, 0.09) Delayed memory index 0.53 (0.28, 0.06) Total raw index −0.82 (0.96, 0.39) Executive function 0.49 (0.13, < 0.05) MMSE −0.14 (0.08, 0.07)	Adjusted for age, gender, education, language of administration, selenium level and *APOE* ε4 presence

(Continues)

TABLE 23 (Continued)

Reference study population design	Outcome definition	Population size (*n*)	Arsenic exposure	Results	Additional information/confounders
Mukherjee et al. (2014) India Cross-sectional	Neurobehavioral symptoms and depression assessed by subjective symptoms questionnaire and Beck's 21-point depression inventory-II; plasma levels of neurotransmitters	654 women 312 342	w-As (μg/L) ≤ 10 (ref.) 11–50	OR (95% CI) transient loss of memory 2.02 (1.17–3.12) burning sensation in extremities 4.16 (1.89–7.27) tingling or numbness 3.08 (2.10–7.35) anxiety 1.49 (1.16–3.46) fatigue 1.92 (1.49–4.57) reduced sense of taste 2.29 (1.28–4.62) reduced sense of smell 1.36 (1.12–2.74) depression 1.37 (1.11–1.97) plasma epinephrine and norepinephrine 1.6-times higher ($p < 0.05$), plasma serotonin 1.8-times higher ($p < 0.05$); no difference in plasma dopamine ($p > 0.05$)	No exposure to pesticides during the last month among the study participants. Logistic regression controlling for age, education, cooking years, menstrual length, adverse reproductive outcome experienced in past 1 year
			≤ 10 (ref.) 11–50		
Liu et al. (2017) China Cross-sectional	Cognitive impairment by Mini-Mental State Examination	483 (> 40 years) 148 104 85 146	w-As (μg/L) < 10 10–50 50–100 > 100	OR (95% CI) 1.0 1.11 (1.01–1.43) 1.32 (1.21–2.75) 4.01 (2.77–11.03) Multivariable linear regression model: coefficient WAs = −0.73 ($p = 0.02$)	Crude odds ratio Adjusting for sex, age, education and BMI
Karim et al. (2019) Bangladesh Cross-sectional	Cognitive impairment by Mini-Mental State Examination (MMSE), serum BDNF	693 (18–60 years)/ sBDNF	w-As (μg/L) Range 0.03–1798.60 Interquartile range (IQR): 1.75, 214.0 IQR: 2.81, 207.28	β (95%CI) MMSE −0.021 (−0.026, −0.015) Change by IQR (95% CI) −0.113 (−0.161, −0.064) β (95%CI) sBDNF −0.082 (−0.105, −0.059) Change by IQR (95% CI) −0.437 (−0.609, −0.265)	Multi-variable linear regression adjusted for age, sex and education. Also, associations with As in hair and nails showed similar results.

TABLE 23 (Continued)

Reference study population design	Outcome definition	Population size (*n*)	Arsenic exposure	Results	Additional information/confounders
Mochizuki et al. (2019) Myanmar Cross-sectional	Peripheral neuropathy via subjective neurological symptoms and objective neurological examinations of sensory disturbances	1867 (above 5 years; out of which 456 children 5–15 years)	w-As (μg/L) < 10 ≥ 10 < 50 ≥ 50	Frequencies Subjective 'feeling of weakness': As < 10 μg/L 13% versus As ≥ 10 μg/L 17.6%; and 'chronic numbness or pain': 20.4% versus 24.7%. Objective pain sensation: As < 50 μg/L 4.7% versus ≥ 50 μg/L 9%); Vibration sensation: 3.8% versus 6.5%; two-point discrimination: 3.6% versus 7.2%. In children, no association between symptoms or signs and w-As	Aggregated water concentrations due to different sources depending on season. No adjustments in any analyses
Wang, Huang, et al. (2021) China Cross-sectional	Cognitive function via Chinese Mini-Mental State Examination	1556 Cognitive impairment (%) 56 (14.4) 76 (19.5) 87 (22.7) 102 (26.2)	Hair As (mg/kg) Quartiles: < 0.01–0.10 0.11–0.21 0.22–0.43 0.44–25.1	OR (95% CI) 1.0 1.480 (0.984, 2.228) 1.517 (1.014, 2.268) 1.919 (1.297, 2.840)	Adjusted for age, sex, education level and location
Rahman, Niemann, and Yusuf (2022) USA Cross-sectional	Sleep disturbance based on questionnaire	1611 (> 20 years)	u-tiAs (μg/L) Trouble sleeping 5.40 No trouble sleeping 5.65	OR 95% CI for having arsenous acid in urine above the lower limit of detection 1.0 ref 0.72 (0.51–1.00, *p*-value = 0.05)	Unclear whether arsenocbetaine is included in the u-tiAs concentrations Adjusted for age, serum Cotinine, ethnicity and depression

Abbreviations: *APOE* ε4, apolipoprotein E ε4-allele; As, arsenic; BDNF, Brain-Derived Neurotrophic Factor; BMI, body mass index; CI, confidence interval; GIS, geographic information system; IQR, interquartile range; MMSE, Mini-Mental State Examination; n, number; OR, odds ratio; PChE, plasma cholinesterase; ref, reference; sBDNF, serum Brain-Derived Neurotrophic Factor; SD, standard deviation; SE, standard error; u-tiAs, total urinary iAs (sum of iAs and its methylated metabolites MMA and DMA); U, enzyme unit; USA, United States of America; w-As, water-arsenic.

3.2.2.7 | *Effects on the cardiovascular system*

In the previous EFSA Opinion, 13 studies on cardiovascular disease were reviewed. All of them were retrieved from a systematic review by Navas-Acien et al. (2005). Eight of the 13 studies were performed in Taiwan with very high exposure to As in drinking water. Among the other five studies four (Engel & Smith, 1994; Lewis et al., 1999; Ruiz-Navarro et al., 1998; Varsanyi et al., 1991) did not fulfil our present inclusion criteria. One of them (Zierold et al., 2004) fulfilled the inclusion criteria, but this study has the risk of information bias since heart disease and hypertension were self-reported, and many of the 1185 respondents may have known if their water-As was high.

For the present Opinion, the CONTAM Panel identified 87 additional studies from a literature search and from nine systematic reviews (Abhyankar et al., 2012; Bao et al., 2022; Chowdhury et al., 2018; Karachaliou et al., 2021; Moon et al., 2012, 2017; Tsuji et al., 2014; Xu, Mondal, & Polya, 2020; Zhao et al., 2021). Out of these, 53 studies (Afridi et al., 2011; Ameer et al., 2015; Castiello et al., 2020; Cheng et al., 2021; Dastgiri et al., 2010; Desai et al., 2021; Dong et al., 2022; Gong & O'Bryant, 2012; Guha Mazumder et al., 2012; Gunduz et al., 2015; Guo et al., 2007; Hall et al., 2017; Jovanović et al., 2012; Liao et al., 2012; Lin, Hsu, et al., 2018; Lisabeth et al., 2010; Liu et al., 2022; McLeod et al., 2018; Meliker et al., 2007; Merrill et al., 2017; Nong et al., 2016; Nunes et al., 2022; Pichler et al., 2019; Qu et al., 2022; Rahman et al., 1999, 2014; Rahman, Niemann, & Munson-McGee, 2022c; Shiue, 2014; Sohel et al., 2009; Soria et al., 2021; Stea et al., 2016; Tang et al., 2022; Wang et al., 2002; Wang et al., 2011; Wang, Hao, et al., 2020; Wang, Karvonen-Gutierrez, et al., 2021; Wang, Wu, et al., 2007; Wei, Yu, et al., 2017; Wen et al., 2019; Wu et al., 2010; Xu et al., 2021; Xu, Liu, et al., 2022; Xu, Polya, et al., 2020; Yao et al., 2021; Yen et al., 2022; Yildiz et al., 2008; Yu et al., 2017; Yuan et al., 2017; Zhang et al., 2013, 2022; Zhong et al., 2019) did not fulfil the inclusion criteria.

The 34 additional studies that fulfilled the inclusion criteria examined ischemic heart disease (including the diagnoses of myocardial infarction and coronary heart disease), stroke, hypertension/blood pressure, atherosclerosis and overall cardiovascular disease.

Ischemic heart disease (IHD)

The 15 studies are summarised in Table 24. Among those based on As in water the studies performed in Inner Mongolia (Wade et al., 2009, 2015), Bangladesh (Chen, Graziano, et al., 2011; Chen, Wu, Liu, et al., 2013; Wu et al., 2015), Colorado (USA), (James et al., 2015) provide support for an association between water As and risk of IHD. The large study in Denmark (Monrad et al., 2017) provides only limited support for an association (in the Aarhus subcohort). Among the studies based on As in urine, the Strong Heart Study in the USA (Kuo et al., 2022; Moon et al., 2013), and the study of US NHANES (Nigra et al., 2021) also support an association with IHD. Analyses based on As content in toenails (Farzan et al., 2015; Wade et al., 2015) show conflicting results. The ecological (Medrano et al., 2010) and semi-ecological (D'Ippoliti et al., 2015) studies are considered less reliable, as are the studies with a small/unknown number of self-reported disease cases (Butts et al., 2015; Zierold et al., 2004).

Two studies were performed in the Ba Men region of Inner Mongolia, China, an agricultural region with elevated levels of As in well water. The first study was a retrospective cohort study in a village with about 12,000 inhabitants (Wade et al., 2009). Cause-specific mortality was examined during 1997 and 2004. As in the primary water source of each household was analysed. Adjusted rate ratios for mortality in heart disease was analysed by water-As categories. The adjusted incidence rate was significantly increased when water-As was treated as a continuous variable. For those exposed from the same water source since 1995, the IRR was 1.19 (95% CI 1.05–1.33) per increase of water As by 50 µg/L, based on 161 deaths. IRRs by categories of water As are shown in Table 24.

The next study from Ba Men was a case–control study (Wade et al., 2015). Cases were hospital patients with sign of ischemic heart disease (myocardial infarction, decreased ejection fraction without valvular disease or ECG changes indicating angina pectoris), and controls were patients from the same hospital with conditions unrelated to As. Cases and controls were recruited 2006–2011. The adjusted OR per 10 µg/L increase of water As was 1.19 (1.03–1.38). The adjusted OR per 1 µg/g increase of toenail As was 1.16 (0.98–1.38). ORs by categories of water As and nail-As are shown in Table 24.

Three studies were performed in Bangladesh as part of the HEALS project (Chen, Graziano, et al., 2011; Chen, Wu, Liu, et al., 2013; Wu et al., 2015). The first one (Chen, Graziano, et al., 2011) was a prospective cohort study of about 12,000 inhabitants in a defined area, recruited in 2000–2002. Mortality was followed up until 2009 (validated verbal autopsy). As in water was measured in the tube wells (about 6000 wells) used by cohort members, and 96% of participants also delivered a spot urine sample of analysis of total As. The adjusted trend for the HR regarding IHD mortality (71 cases), with water As as a continuous variable, was statistically significant ($p = 0.029$), and for u-tiAs as a continuous variable the corresponding p-value was 0.059. HRs by categories of water As and u-tiAs are shown in Table 24.

In the second paper (Chen, Wu, Liu, et al., 2013), the incidence of CVD (211 cases, mainly IHD) was studied using a case cohort design. The adjusted HR with water As as a continuous variable was statistically significant. HRs by categories of water As are shown in Table 24. There was also a significant association between MMA% in urine and HR for IHD.

In the third study of the HEALS cohort (Wu et al., 2015), the follow-up time was longer (2012) and the analysis was based on 237 cases of IHD. There was a significant association between water As as a continuous variable and the adjusted HR for CHD. HRs by categories of water As are shown in Table 24.

A case cohort study by James et al. (2015) in Colorado, US included 96 cases of CHD and showed a strong association between the time-weighted average lifetime As in water and risk of IHD. The HR was significantly increased already at 30–45 µg/L.

Monrad et al. (2017) performed a very large cohort study in two Danish cities (Copenhagen and Aarhus). There were 2707 incident cases of myocardial infarction. The As levels in drinking water were, however, low. In Copenhagen, about 60% of the population had As in water 0.5 µg/L, and none had levels > 2 µg/L. In Aarhus about 80% had As in water 2 µg/L, about 5% higher than that, and the remaining had As in water < 2 µg/L. Therefore, the analysis of the total cohort will to a large extent be a comparison between two cities. Even if the Aarhus cohort includes a larger range of water As levels, the exposure contrast is still limited. The medians in the third and the fourth quartile of water As is the same.

Two studies using u-iAs as exposure metric are based on the Strong Heart Study among American Indians in the US. The study by Moon et al. (2013) shows significantly increased risk of CHD incidence and mortality in the upper quartile (Table 24). The study by Kuo et al. (2022) found a significant association between water As and the broader outcome of CVD. The u-iAs were not very high; the median in upper quartile was 22 µg/g creatinine (Moon et al., 2013). According to the authors, As in water was the main source of iAs exposure in two of the three Strong Heart Study areas (Arizona and the Dakotas). This is consistent with the median inorganic fraction of u-iAs (8%), and the median MMA of 15% and DMA 78%.

The study by Nigra et al. (2021) based on u-tiAs after exclusion of those with u-AsB > 1.2 µg/L provides limited support for an association with heart disease mortality, but the study is relatively small.

Most of the longitudinal studies described above are large, and all of them adjusted their risk estimates for the most important potential confounders. There are no obvious sources of selection bias or information bias.

Several of the studies mentioned above (James et al., 2015; Wade et al., 2015; Wu et al., 2015) present results for relatively large data sets with strata of exposure to inorganic As, as concentrations in water. These studies were performed in several different countries (China, US, Bangladesh). The only European study was the Danish one, which also had the lowest exposure levels, but had a narrow range of exposure. Other studies, using As in water, were either based on the same study areas but with fewer cases (Chen, Graziano, et al., 2011; Chen, Wu, Liu, et al., 2013; Wade et al., 2009) or considered having a higher risk of bias (Butts et al., 2015; D'Ippoliti et al., 2015; Medrano et al., 2010; Zierold et al., 2004). Next to Wade et al. (2015), James et al. (2015) and Wu et al. (2015), two studies using u-tiAs (Moon et al., 2013; Nigra et al., 2021) have also been considered having an appropriate design.

The studies on ischemic heart disease meeting the inclusion criteria are described in Table 24.

In summary, the epidemiological studies provide sufficient evidence for an association between low to moderate exposure to iAs and IHD.

TABLE 24 Key epidemiological studies on As and cardiovascular disease: Ischemic heart disease (including coronary heart disease, myocardial infarction and 'heart disease').

Reference study population design	Outcome definition	Population size (*n*) case/control	Arsenic exposure	Results	Additional information/confounders
Zierold et al. (2004) Study in private well households in Wisconsin, USA Cross-sectional	Self-reported 'Bypass', 'heart attack'	Population 1185 Number of cases not presented	w-As 0–2389 µg/L, median 2 µg/L,16% > 10 µg/L < 2 2–10 > 10 µg/L < 2 2–10 > 10 µg/L	ORs in highest stratum: <u>Bypass surgery:</u> 1.0 1.77 (0.95–3.30) 2.34 (1.12–4.90) <u>Heart attack:</u> 1.0 1.31 (0.70–2.30) 2.08 (1.10–4.31)	Adjusted for age, sex, smoking, BMI. Methods and results incompletely described
Wade et al. (2009) study in Ba Men, Inner Mongolia, China Retrospective cohort	Heart disease mortality	78,251 person-years follow-up 1997–2004 161 deaths in heart disease in those exposed since before 1995 (results in this table)	w-As (µg/L) 0–5 5.1–20 20.1–100 100.1–300 > 300	Heart disease: Adj. IRR (cases) 1.0 (44) 1.07 (0.6–1.8) (26) 1.22 (0.8–1.8) (72) 1.55 (0.9–2.7) (17) 2.47 (0.5–12) (2)	Adjusted for age, sex, smoking, education, alcohol, farm work. Cause of death (blinded to w-As) from proxy interviews and medical records
Medrano et al. (2010) study in 651 municipalities in Spain Ecological	CHD mortality	Population 14.4 million Number of cases: 88,566 19,709 4725	w-As (µg/L) (median) < 1 (0.7) 1–10 (3.9) > 10 (23.3)	RR 1 1.05 (1.01–1.10) 1.02 (0.96, 1.08)	RR derived from reported % increase. *p* value trend 0.091 Adjusted for sex, age and covariates at municipal or provincial level (income, hospital beds, prevalence of smoking, hypertension, high serum cholesterol, diabetes, overweight/obesity, and low physical activity, dietary factors, water hardness, magnesium, pH and temperature)
Chen, Chiou, Hsu, Hsueh, Wu, & Chen (2010) Bangladesh (HEALS) Cohort study	IHD Mortality	Cases/Pyrs 14/20,064 16/19,109 15/18,699 26/19,380	w-As (µg/L) (mean) 0.1–12 (3.7) 12.1–62 (35.9) 62.1–148 (102.5) 148.1–864 (265.7) u-tiAs (µg/g creatinine) (mean) 6.6–105.9 (68.5) 106–199 (150.6) 199.1–351.8 (264.9) 352–1100 (641.5)	HR 1 1.22 (0.56, 2.65) 1.49 (0.70, 3.19) 1.94 (0.99, 3.84) HR 1 1.29 (0.66, 2.51) 1.47 (0.72, 3.01) 1.90 (0.91, 3.98)	*p* trend 0.03 (water) *p* trend 0.06 (u-As) Adjusted for sex and baseline age, BMI, smoking, education, changes in u-As over time u-tAs was considered a good measure of iAs (AsB and AsC only 3% in a random speciated subsample, and a high correlation between water-As and u-tAs)

TABLE 24 (Continued)

Reference study population design	Outcome definition	Population size (*n*) case/control	Arsenic exposure	Results	Additional information/confounders
Moon et al. (2013) USA (SHS) Cohort study	CHD Incidence	Cases/Pyrs 202/13,616 206/13,430 197/12,720 241/12,033	u-tiAs (μg/g creatinine) (median) < 5.8 (4.2) 5.8–9.7 (7.5) 9.8–15.7 (12.4) > 15.7 (21.8)	HR 1 1.05 (0.86, 1.28) 0.95 (0.77, 1.19) 1.30 (1.04, 1.62)	*p* trend = 0.006 (incidence) *p* trend < 0.001 (mortality) Adjusted for age, sex, education, smoking status, BMI and LDL cholesterol.
	CHD mortality	Cases/Pyrs 68 13,616 67 13,430 87 12,720 119 12,033	< 5.8 (4.2) 5.8–9.7 (7.5) 9.8–15.7 (12.4) > 15.7 (21.8)	1 0.99 (0.70, 1.41) 1.18 (0.83, 1.69) 1.71 (1.19, 2.44)	As in water the main source in most participants
Chen, Wu, Liu, et al. (2013) Bangladesh (HEALS) Case-cohort	Heart disease (mainly IHD) incidence.	211 cases of heart disease. Subcohort 1109.	w-As (μg/L) (*n* cases) 0.1–25 (61) 25.1–107 (72) 108–864 (75) Mean total u-As in subcohort 277 μg/g creatinine	HR 1.0 1.18 (0.75–1.84) 1.54 (1.02–2.31)	Adjusted for sex, age, smoking, BMI, education, hypertension, diabetes. Associations with u-iAs and heart disease not reported, but %MMA (median 13%) was positively associated with risk of heart disease. Same cohort as in Chen, Graziano, et al. (2011), but more cases.
Wade et al. (2015) Case control study in Ba Men, Inner Mongolia, China	IHD	Cases/controls (recruited 2006–2011) 168/137 105/131 11/4 168/305 105/236 11/26	w-As (μg/L) < 10 11–39 > 40 t-As (μg/g) in toenails 0.11–0.28 0.29–1.37 1.38–34.21	OR 1 1.23 (0.78, 1.93) 4.05 (1.10, 14.99) 1 0.67 (0.33, 1.34) 1.91 (0.73, 4.99)	*p* trend 0.06. Adj for diet, BMI, occupation, education, smoking, family history of hypertension, diabetes or heart disease *p* trend 0.21
D'Ippoliti et al. (2015) Cohort study, semi-ecological	IHD mortality	Population 165,609 Deaths Men: 380 310 567 Women: 304 263 447	w-As (μg/L (median) (municipality level) < 10 (7.4) 10–20 (12.9) > 20 (29.7) < 10 (7.4) 10–20 (12.9) > 20 (29.7)	HR 1 1.42 (1.15, 1.75) 1.70 (1.33, 2.16) 1 1.36 (1.06, 1.74) 1.23 (0.92, 1.65)	*p* trend < 0.001 Also significant for cumulative dose. HRs only reported by sex. Adj for age, calendar period, occupation in the ceramic industry. Area level: socioeconomic status, smoking sales and radon exposure.
Farzan et al. (2015) Cohort study in New Hampshire, USA	IHD mortality	Population 3939 IHD deaths 154	As (μg/g) in toenails range (median) 0.01–3.26 (0.09) w-As (μg/L) range (median) 0–158 (0.29)	HR per 1 unit ln-transformed toenail-As: 0.94 (0.74–1.19)	Cohort based on previous case–control study on skin cancer. Adjusted for smoking, education, skin cancer (and presumably age and sex, though not mentioned).

(Continues)

TABLE 24 (Continued)

Reference study population design	Outcome definition	Population size (*n*) case/control	Arsenic exposure	Results	Additional information/confounders
James et al. (2015) Case cohort study in Colorado, USA (SLVDS)	CHD incidence	96 CHD cases, subcohort 533 (74 cases) Cases/Pyrs 584,806 181,335 16,534 4 98	w-As (μg/L) estimated lifetime f (median) 1–20 (5.7) 20–30 (25.3) 30–45 (35.1) 45–88 (50.5)	HR 1 1.23 (0.56, 2.18) 2.18 (1.23, 4.02) 3.10 (1.10, 9.11)	Adjusted for LDL cholesterol and family history of CHD. Full model adjusted also for sex, smoking, BMI, ethnicity, SES, alcohol, other blood lipids, folate and Se showed very similar HRs.
Butts et al. (2015) Cross-sectional study in Romania	'Pilot study' of self-reported heart disease in pregnant women	295 women and 6 cases	w-As (μg/L) range 0–175, median 0.4	aOR per 1 unit ln-transformed w-As 1.6 (0.81–3.04)	Adjusted for age, smoking, education.
Wu et al. (2015) Case cohort study in Bangladesh (HEALS)	Incidence of CHD	238 cases of CHD Subcohort 1375	w-As (μg/L, (mean; number of cases) 0.1–16 (4.3; 69) 17–85 (47; 86) 86–864 (191; 82)	Adjusted HR 1.0 1.30 (0.83–2.01) 1.40 (0.88–2.23)	Same cohort as Chen, Wu, Liu, et al. (2013), but more cases. Mean u-As 119 μg/L (259 μg/g).
Monrad et al. (2017) Cohort study in Denmark Danish prospective cohort Diet, Cancer and Health (DCH) two cities, Copenhagen and Aarhus.	Myocardial infarction	Cohort 53,856 Incident MI cases 2707, 784 in the Aarhus cohort	w-As (μg/L 20 years mean). Total cohort median 0.7 0.05–0.57 (0.44) 0.57–0.76 (0.58) 0.76–1.93 (1.18) 1.93–25.3 (2.11) Aarhus cohort median 2.1 0.08–1.83 (1.30) 1.83–2.11 (2.09) 2.11–2.11 (2.11) 2.21–25.3 (2.11)	Adjusted IRRs 1.0 1.23 (1.11–1.37) 0.98 (0.87–1.10) 1.04 (0.93–1.16) 1.0 0.82 (0.67–1.02) 0.83 (0.68–1.02) 1.44 (1.16–1.78)	Adjusted for age, sex, smoking, BMI, waist, alcohol, physical activity, education, diabetes, hypertension, cholesterol, fruit intake, vegetable intake. Note low w-As and low contrast.
Nigra et al. (2021) Cohort study of NHANES participants 2003–2014	Heart disease mortality	4990 with available u-As and u-AsB 77 deaths	u-tAs (μg/L) <2.30 2.31–4.00 4.01–6.50 >6.50	HR 1.0 1.24 (0.58–2.68) 1.44 (0.65–3.21) 1.21 (0.46–3.14) Similar results for u-DMA.	Individuals with u-AsB ≥ 1.2 μg/L excluded. Overall median (IQR) for u-tAs 4.42 (2.52–7.20) and for u-DMA 2.71 (1.35–4.42). Adjusted for age, sex, ethnicity, u-creatinine, eGFR, education, BMI, cholesterol and serum cotinine.
Kuo et al. (2022) Cohort study in USA (SHS)	CVD mortality (484)	3600 484 deaths	u-tiAs median 11.2, IQR 12.5 μg/g creatinine	HR per IQR of u-tiAs: 1.28 (1.08–1.52). Similar HRs for MMA and DMA (per IQR). Larger HRs when MMA% or DMA% were high.	u-AsB was low (median 0.68, IQR 0.41–1.54 μg/g creatinine). Adjusted for age, sex, smoking, BMI, WHR, education, alcohol, u-creatinine, eGFR, LDL, diabetes, hypertension.

Abbreviations: adj, adjusted; aOR, adjusted odds ratio; As, arsenic; AsB, arsenobetaine; AsC, arsenocholine; BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; DCH, 'Diet, Cancer and Health' study; DMA, sum of dimethylarsinous acid and dimethylarsinic acid; eGFR, estimated glomerular filtration rate; f, female; HEALS, Health Effects of Arsenic Longitudinal Study; HR, hazard ratio; iAs, inorganic arsenic; IHD, ischemic heart disease; IQR, interquartile range; IRR, incidence rate ratio; LDL, low-density lipoprotein; MMA, sum of monomethylarsonous acid and monomethylarsonic acid; MI, myocardial infarction; n, number; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio; pyr(s), person year(s); RR, risk ratio; Se, selenium; SES, socioeconomic status; SHS, Strong Heart Study; SLVDS, San Luis Valley Diabetes Study; USA, United States of America; u-As, urinary arsenic; u-AsB, urinary arsenobetaine; u-DMA, urinary DMA; u-tAs, urinary total arsenic; u-tiAs, total urinary iAs (sum of iAs and its methylated metabolites MMA and DMA); w-As, water-arsenic; WHR ratio, waist-to-hip ratio.

Stroke

The eight studies are summarised in Table 25. Among those based on As in water, the HEALS study in Bangladesh (Wu et al., 2015) showed an association with stroke incidence in the highest stratum (water As 86–864, mean 191 µg/L), while in the stratum of 17–85 µg/L the point estimate was positive (HR 1.14) but with a broad confidence interval (0.65–1.98). The study performed in Inner Mongolia (Wade et al., 2009) showed no association with stroke mortality up to 100 µg/L. The large Danish study (Ersbøll et al., 2018) showed an association in the highest quartile in Aarhus, but the dose–response is difficult to interpret since most cases in the upper quartile had the same water As concentration (2.1 µg/L). The ecological study by Medrano et al. (2010) and the study with an unknown number of self-reported disease cases (Zierold et al., 2004) are considered less informative. The US studies based on u-As (Tsinovoi et al., 2018) or As in toenails (Farzan et al., 2015) had very few cases. The studies on stroke are described in Table 25.

In summary, the epidemiological studies provide insufficient evidence for an association between low to moderate exposure to iAs and stroke.

TABLE 25 Key epidemiological studies on arsenic and cardiovascular disease: Stroke.

Reference study population design	Outcome definition	Population size (*n*) case/control	Arsenic exposure	Results	Additional information/confounders
Zierold et al. (2004) Private well households in Wisconsin, USA Cross-sectional	Self-reported stroke	Population 1185 Number of cases not presented	w-As 0–2389 µg/L, median 2 µg/L,16% > 10 µg/L. < 2 2–10 > 10 µg/L	OR 1.0 0.94 (0.40–2.14) 1.53 (0.60–4.07)	Adjusted for age, sex, smoking, BMI. Risk of information bias.
Wade et al. (2009) Retrospective cohort study in Ba Men, Inner Mongolia, China	Stroke mortality	78,251 person-years during follow-up 1997–2004. 447 deaths in those exposed since before 1995 (results in this table), 118 of these in stroke.	w-As (µg/L) 0–5 5.1–20 20.1–100 100.1–300 > 300	Adj. IRR (cases) 1.0 (53) 0.47 (0.3–0.8) (16) 0.51 (0.3–0.8) (41) 0.52 (0.3–1.1) (7) 1.02 (0.2–6.7) (1)	Adjsted for age, sex, smoking, education, alcohol, farm work. Cause of death (blinded to w-As) from proxy interviews and medical records.
Medrano et al. (2010) Ecological study of mortality in 651 municipalities in Spain	Stroke mortality	Population 14.4 million Number of cases: 81,368 18,327 3895	w-As (µg/L) (median) < 1 (0.7) 1–10 (3.9) > 10 (23.3)	RR 1 1.00 (0.96–1.05) 1.02 (0.95, 1.09)	RR derived from reported % increase. *p* value trend 0.091 Adjusted for sex, age and covariates at municipal or provincial level (income, hospital beds, prevalence of smoking, hypertension, high serum cholesterol, diabetes, overweight/obesity and low physical activity, dietary factors, water hardness, magnesium, pH and temperature)
Chen, Wu, Liu, et al. (2013) Case-cohort study in Bangladesh (HEALS)	Stroke incidence	148 cases of stroke Subcohort 1109	w-As (µg/L) (*n* cases) 0.1–25 (50) 25.1–107 (46) 108–864 (52) Mean total u-As in subcohort 277 µg/g creatinine	aHR 1.0 0.86 (0.49–1.51) 1.38 (0.84–2.27)	Adjusted for sex, age, smoking, BMI, education, hypertension and diabetes. Associations with u-iAs and stroke not reported. %MMA (median 13%) was not associated with risk of stroke. Same cohort as in Chen, Graziano, et al. (2011), but more cases
Farzan et al. (2015) Cohort study in New Hampshire, USA	Stroke mortality	Population 3939 Stroke deaths 43	As (µg/g) in toenails range (median) 0.01–3.26 (0.09) w-As (µg/L) range (median) 0–158 (0.29)	HR per 1 unit ln-transformed toenail-As: 0.90 (0.61–1.33)	Cohort based on previous case–control study on skin cancer. Adjusted for smoking, education, skin cancer (and presumably age and sex, though not mentioned)
Wu et al. (2015) Case cohort study in Bangladesh (HEALS)	Incidence of stroke	165 cases of stroke Subcohort 1375	w-As (µg/L, mean; number of cases) 0.1–16 (4.3; 44) 17–85 (47; 50) 86–864 (191; 71)	Adjusted HR 1.0 1.14 (0.65–1.98) 1.87 (1.06–3.29)	Same cohort as Chen, Wu, Liu, et al. (2013), but more cases. Mean u-As 119 µg/L (259 µg/g)
Tsinovoi et al. (2018) Case cohort study in US (REGARDS)	Incidence of ischemic stroke	With u-iAs: Population 199, Cases: 41. Total data set 671 cases and subcohort 2486	u-iAs (µg/g creatinine) 0.1–3.52 3.53–66.8	Adjusted HR 1.0 2.18 (0.64–7.43)	Adjusted for analyses performed versus u-tAs based on the whole data set showed no association

TABLE 25 (Continued)

Reference study population design	Outcome definition	Population size (*n*) case/control	Arsenic exposure	Results	Additional information/confounders
Ersbøll et al. (2018) Cohort study in Denmark (Danish prospective cohort Diet, Cancer and Health (DCH), two cities, Copenhagen and Aarhus.	Stroke incidence	Cohort 53,941 Incident stroke cases 2195 (1801 ischemic and 381 haemorrhage, 13 other), 678 in the Aarhus cohort	w-As (μg/L 20 years mean). Total cohort median 0.7 0.05–0.57 (0.44) 0.57–0.76 (0.58) 0.76–1.93 (1.18) 1.93–25.3 (2.11) Aarhus cohort median 2.1 0.08–1.83 (1.30) 1.83–2.11 (2.09) 2.11–2.11 (2.11) 2.21–25.3 (2.11)	Adjusted IRRs 1.0 1.21 (1.07–1.36) 1.05 (0.92–1.19) 1.17 (1.04–1.32) 1.0 0.81 (0.62–1.04) 1.09 (0.88–1.34) 1.79 (1.41–2.26)	Adjusted for age, sex, smoking, BMI, waist, alcohol, physical activity, education, fruit intake, vegetable intake and calendar year. Note low w-As and low contrast. Results for ischemic and haemorrhagic stroke relatively similar

Abbreviations: adj, adjusted; aHR, adjusted hazard ratio; BMI, body mass index; DCH, 'Diet, Cancer and Health' study; HEALS, Health Effects of Arsenic Longitudinal Study; HR, hazard ratio; IRR, incidence risk ratio; MMA, sum of monomethylarsonous acid and monomethylarsonic acid; *n*, number; OR, odds ratio; REGARDS, Reasons for Geographic and Racial Differences in Stroke; RR, risk ratio; u-As, urinary arsenic; u-iAs, urinary inorganic arsenic; USA, United States of America; u-tAs, urinary total arsenic; w-As, water-arsenic.

Atherosclerosis

The eight studies are summarised in Table 26. Among those based on As in water, the Taiwanese studies (the largest one by Hsieh et al., 2011) showed clear associations with carotid artery atherosclerosis (increased intima-media thickness (IMT and/or plaque). The study in Bangladesh (Chen, Wu, Graziano, et al., 2013) also provides some support, but the association with intima-media thickness (IMT) was not quite significant on the 5% level.

Among the studies based on As in urine the study by Chen, Wu, Graziano, et al. (2013) found a significant association with IMT, and the study in Spain (Grau-Perez et al., 2022) found a significant association with IMT and plaque, while in the US SHS study (Mateen et al., 2017) and the US MESA study with very low u-iAs (Sobel et al., 2020) there was no association with IMT or plaque. The study by Grau-Perez had very low levels of u-tiAs but high u-AsB. Although the authors 'corrected' for the potential contribution of DMA from seafood to u-tiAs, the impact of iAs exposure on the carotid artery findings remain uncertain.

The data on atherosclerosis in the lower limbs (ABI) and the coronary arteries (CAC score) are limited.

In summary, the epidemiological studies based on As in water provide sufficient evidence for a causal association between moderate exposure to iAs and carotid artery atherosclerosis. For other arteries, the evidence is insufficient.

TABLE 26 Key epidemiological studies on As and cardiovascular disease: Atherosclerosis.

Reference study population design	Outcome definition	Population size (*n*) case/control	Arsenic exposure	Results	Additional information/confounders
Wu et al. (2006) Case–control study nested in a Taiwanese cohort	Carotid artery atherosclerosis based on IMT and/or plaque	163 cases and 163 controls	w-As (μg/L) ≤ 50 (25) 50–100 (46) ≥ 100 (89)	OR 1 1.9 (0.9–3.8) 2.6 (1.3–5.0)	Adjusted for age, sex, smoking, cholesterol, hypertension and *p*-homocysteine. Median MMA% about 13%, median DMA% about 77%
Hsieh et al. (2008) Case–control study nested in a Taiwanese cohort	Carotid artery atherosclerosis based on IMT and/or plaque	235 cases and 244 controls	w-As (μg/L) (cases) ≤ 10 (31) 10.1–50 (38) ≥ 50 (175)	OR 1 1.8 (1.0–3.2) 1.9 (1.1–3.1)	Adjusted for age, sex, smoking, diabetes, blood lipids. Same base cohort as Wu et al. (2006)
Hsieh et al. (2011) Case–control study nested in a Taiwanese cohort	Carotid artery atherosclerosis based on IMT and/or plaque	384 cases and 479 controls	w-As (μg/L) (cases) ≤ 10 (24) 10.1–50 (31) ≥ 50 (325)	OR 1 1.5 (0.7–3.5) 2.0 (1.1–3.9)	Adjusted for age, sex, smoking, blood glucose, hypertension, blood lipids, alcohol, BMI. Same base cohort as Wu et al. (2006) and Hsieh et al. (2008)
Chen, Wu, Graziano, et al. (2013) Cross-sectional study in Bangladesh (HEALS)	Carotid artery intima media thickness	959	w-As (μg/L): mean = 41, p10 – p90 = 1–225 u-As (μg/g creatinine): mean = 171, p10 – p90 = 60–439	w-As: Beta 5.1 (−0.2–10.3) per 1 SD (102 μg/L) u-As: Beta 11.7 (1.8–22) per 1 SD (358 μg/g creatinine)	Adjusted for sex, age, smoking, BMI, education, diabetes and blood pressure. Significant association with %MMA (median 13%), but not %DMA (median 72%)
Newman et al. (2016) Cohort study in USA (SHS)	Incident peripheral artery disease based on ABI < 0.9 or > 1.4	Population: 2891 Cases < 0.9280 Cases > 1.4206	u-tiAs (μg/g creatinine) (tertiles) ≤ 7.07 7.07–13.3 > 13.3 ≤ 7.07 7.07–13.3 > 13.3 MMA% 14 DMA% 78	HR ABI < 0.9 1.0 1.10 (0.66–1.72) 0.59 (0.33–1.04) ABI > 1.4 1.0 1.80 (0.93–3.35) 2.40 (1.11–4.95)	Adjusted for sex, age, smoking, education, BMI, LDL, diabetes, hypertension, estimated glomerular filtration rate and study centre. Note that ABI < 0.9 is a more accepted measure of atherosclerotic peripheral artery disease than ABI > 1.4
Mateen et al. (2017) Cohort study in USA (SHS)	Carotid artery atherosclerosis based on IMT and/or plaque	Population 2402 1550 with plaque	u-tiAs (μg/g creatinine) ≤ 5.64 5.65–9.24 9.25–14.75 14.75–123 ≤ 5.64 5.65–9.24 9.25–14.75 14.75–123	RR of plaques 1.0 1.05 (0.97–1.13) 1.04 (0.96–1.13) 1.03 (0.95–1.12) Mean diff. in IMT 0.00 0.01 (−0.01–0.02) 0.01 (0.00–0.03) 0.02 (0.00–0.04)	Adjusted for sex, age, smoking, education, BMI, LDL, diabetes, hypertension, estimated glomerular filtration rate Similar tendency for plaque score (no. of segments with plaque)

(Continues)

TABLE 26 (Continued)

Reference study population design	Outcome definition	Population size (*n*) case/control	Arsenic exposure	Results	Additional information/confounders
Sobel et al. (2020) Cross-sectional study in USA (MESA)	Carotid artery IMT Coronary artery calcium (CAC) ABI	u-iAs measured in 246 out of total population of 5050 (who had data on self-reported rice consumption)	Overall u-tiAs (µg/g creatinine) 3.08, IQR 1.96–4.69)	Beta per IQR of u-tiAs (2.7 µg/g creatinine) for IMT: (CCA) 1.00 (0.96–1.03) OR for CAC > P75: 1.27 (0.59–2.74). OR for ABI < 1.0: 1.01 (0.46–2.20)	Adjusted for age, sex, smoking, BMI, exercise, education, eGFR, diabetes, hypertension, high blood lipids, energy intake, site. The main iAs 'exposure' metric was rice intake. There was no association between rice intake and plaque, coronary calcium or ABI, but a positive association between rice intake and u-tiAs
Grau-Perez et al. (2022) Cross-sectional study in Aragon, Spain (AWHS)	Carotid artery plaque and IMT (CCA, ICA, ECA, bulb) Carotid artery plaque score (number of segments with plaque) Femoral artery plaque and IMT CAC	Population 1873. Carotid artery plaque 659 Femoral artery plaque 987 CAC positive (> 1) 691	u-tiAs (µg/g creatinine) median 1.83, IQR 1.25–2.72, P20 1.15 and P80 2.98. Means: AsB 105, DMA 13.1, MMA 1.38, AsIII0.51, AsV 0.05 µg/L. u-tiAs was 'corrected' possible DMA from seafood by a residual-based method. u-tiAs tertiles: < 1.42: 1.42–2.35 > 2.35 < 1.42: 1.42–2.35 > 2.35	OR for P80 versus P20: Carotid artery 1.24 (1.05–1.47) Femoral artery 1.10 (0.92–1.30) CAC positive 1.07 (0.91–1.27) CAC ≥ 10 1.11 (0.92–1.33) CAC ≥ 100 1.14 (0.88–1.49) OR for carotid artery plaque score 1.0 1.01 (0.96–1.07) 1.09 (1–02 – 1.16) OR for CAC score 1.0 0.99 (0.80–1.22) 1.12 (0.90–1.38)	Adjusted for age, sex, smoking, education, eGFR, diabetes, hypertension, high cholesterol

Abbreviations: ABI, Ankle-Barchial Index; AsB, arsenobetaine; As, arsenic; AsV, arsenate; AWHS, Aragon Workers' Health Study; BMI, body mass index; CAC, coronary artery calcium; CCA, common carotid artery; diff, difference; DMA, sum of dimethylarsinous acid and dimethylarsinic acid; ECA, external carotid artery; eGFR, estimated glomerular filtration rate; HEALS, Health Effects of Arsenic Longitudinal Study; HR, hazard ratio; iAs, inorganic arsenic; ICA, internal carotid artery; IMT, intima-media thickness; IQR, interquartile range; LDL, low-density lipoprotein; MMA, sum of monomethylarsonous acid and monomethylarsonic acid; MESA, Multi-Ethnic Study of Atherosclerosis; *n*, number; OR, odds ratio; RR, risk ratio; SD, standard deviation; SHS, Strong Heart Study; u-As, urinary arsenic; u-iAs, urinary inorganic arsenic; u-tiAs, total urinary iAs (sum of iAs and its methylated metabolites MMA and DMA); USA, United States of America; w-As, water-arsenic.

Blood pressure and hypertension

The 11 studies are summarised in Table 27. Eight of them (Chen et al., 2007; Hossain et al., 2017; Islam, Khan, Attia, et al., 2012; Li, Li, Xi, Zheng, Lv, & Sun, 2013; Li, Li, Xi, Zheng, Wang, & Sun, 2013; Mendez et al., 2016; Mordukhovich et al., 2012; Zierold et al., 2004) were cross-sectional. Two studies (Jiang et al., 2015; Spratlen et al., 2018) had a longitudinal design, and one (Kaufman et al., 2021) presented both cross-sectional and longitudinal analyses. In most of the studies, the outcome was hypertension, but the longitudinal study by Jiang et al. (2015) and the cross-sectional studies by Mordukhovich et al. (2012) and Li, Li, Xi, Zheng, Wang, and Sun (2013), examined associations between iAs exposure and blood pressure.

The study by Zierold et al. (2004) which had high risk of information bias, and the study by Hossain et al. (2017) which had few cases were considered less informative.

The longitudinal study of blood pressure by Jiang et al. (2015) provides relatively strong support for the hypothesis that iAs exposure increases blood pressure. Blood pressure was measured with appropriate methods at baseline and on several follow-up examinations in > 10,000 individuals. Systolic and diastolic blood pressure increased more in individuals with baseline water As in quartiles 2–4 than in the referent quartile (As < 12 μg/L), but there was no monotonic exposure-response relationship (Table 27). The finding is supported by the smaller cross-sectional study by Li, Li, Xi, Zheng, Wang, & Sun (2013), which found significant partial correlation coefficients between u-tiAs (and iAs, MMA, DMA) and SBP, and the study of nail As (Mordukhovich et al., 2012), but not by the study by Kaufman et al. (2021) which found no association between baseline u-tiAs and change of systolic blood pressure (SBP) or diastolic blood pressure (DBP).

An association between iAs exposure and increased blood pressure is biologically plausible. Vascular toxicity at As exposure is well-known (causing the so-called Blackfoot disease). *In vitro* work has shown that arsenic promotes inflammatory activity, oxidative stress and endothelial dysfunction through several mechanisms, including the activation of stress-response transcription factors such as activator protein-1 and nuclear factor-κB (Abhyankar et al., 2012).

Although there is considerable support for an association, it is based on relatively few studies, one study (Kaufman et al., 2021) showed no association, and the study with the highest quality (Jiang et al., 2015) showed no monotonic relationship. Therefore, the epidemiological studies provide insufficient evidence of a causal association between iAs exposure and blood pressure.

Hypertension

Among the studies of hypertension, two studies from Bangladesh, a very large one by Chen et al. (2007) and a small study by Islam, Khan, Attia, et al. (2012) found no associations with As in water. Two studies from China in areas with known As contamination of drinking water found clear associations between prevalence of hypertension and As in urine (Li, Li, Xi, Zheng, Wang, & Sun, 2013) and water (2013b). A study in Mexico (Mendez et al., 2016) found a somewhat elevated odds ratio for hypertension in the upper quartile of water As, but it was not statistically significant. Spratlen et al. (2018) found no increased incidence of hypertension versus u-tiAs in a follow-up of the US Strong Heart Study. Kaufman et al. (2021) analysed an extension of the same cohort (Strong Heart Family Study) and found a significant association between u-tiAs and prevalent hypertension at baseline, but no increased risk of incident hypertension in the longitudinal analysis. This study had, however, very low u-iAs concentrations.

The studies of hypertension adjusted for important confounders. The study by Chen et al. (2007) excluded hypertension cases on medication, but such medication was rare (Jiang et al., 2015). The study by Li, Li, Xi, Zheng, Lv, and Sun (2013) adjusted (for unknown reasons) the analysis of hypertension risk vs. As in water by cumulative (years of exposure x As concentration) which likely attenuated the association. The findings in the cross-sectional studies of hypertension were not consistent. Longitudinal studies are stronger when assessing causality. The longitudinal analyses of incident hypertension in the US SHS and SFHS (Kaufman et al., 2021; Spratlen et al., 2018) showed no association with u-tiAs.

In summary, the epidemiological studies provide insufficient evidence of an association between iAs exposure and hypertension.

The studies on blood pressure and hypertension are described in Table 27.

TABLE 27 Key epidemiological studies on As and cardiovascular disease: Blood pressure/hypertension.

Reference study population design	Outcome definition	Population size (*n*) case/control	Arsenic exposure	Results	Additional information/confounders
Zierold et al. (2004) Private well households in Wisconsin, USA Cross-sectional	Self-reported 'high blood pressure'	Population 1185 Number of cases not presented	w-As 0–2389 µg/L, median 2 µg/L,16% > 10 µg/L. Results per 3 categories: < 2, 2–10, > 10 µg/L	ORs in highest stratum: Hypertension: 1.7 (1.3–2.5)	Adjusted for age, sex, smoking, BMI. Risk of information bias
Chen et al. (2007) Cross-sectional study in Bangladesh (HEALS)	Hypertension	Population 10,910. Mean age about 35 years. Cases 1360 based on SBP and DBP	w-As quintiles TWA (µg/L) (mean) 0.1–8.0 (2.8) 8.1–40.8 (23.2) 40.9–91 (63.9) 91.1–176 (128) 176.1–864 (283)	OR (cases) 1.0 (289) 1.10 (0.90–1.33) (274) 1.03 (0.85–1.25) (273) 1.01 (0.83–1.22) (259) 1.02 (0.84–1.23) (265)	Adjusted for age, sex, BMI, smoking, education, water consumption. Those taking antihypertensive medications were excluded
Islam, Khan, Attia, et al. (2012) Cross-sectional study in rural Bangladesh	Hypertension	Population: 994 Mean age: 45 years Cases: 66	w-As (µg/L) (mean) 10–22 (16.5) 23–32 (28.5) 33–261 (141) ≥ 262 (459)	OR (Cases) 1 (22) 1.3 (0.7–2.6) (19) 1.1 (0.5–2.4) (13) 1.0 (0.4–2.2) (12)	Adjusted for age, sex, education, marital status, religion, income and BMI. Smoking was not a confounder. 12 cases were on antihypertensive medication. Pulse pressure was positively associated with w-As
Guha Mazumder et al. (2012) Cross-sectional and case–control study in rural India (West Bengal)	Hypertension	Village with elevated w-As *n* = 208, 66 cases (29%). Village with normal w-As *n* = 100, 20 cases (20%). Median age about 40 years	w-As (µg/L): mean in 'exposed' village 50 (range < DL – 326). Total u-As and hair-As also measured	Adjusted prevalence OR in 'exposed' village 2.9 (1.3–4.8)	Adjusted for age, sex, BMI. Methods unclear. Within 'exposed' village probably no association with cumulative As intake or u-As but positive association with hair As
Mordukhovich et al. (2012) Cross-sectional study of blood pressure in the Normative Ageing Study, USA	Blood pressure	639 men with toenail-As, BP and covariate data collected 1999–2009. Mean age 72 years. 60% on antihypertensive medication	Median nail-As 0.08 µg/g, IQR 0.06	Beta 0.93 (0.25–1.62) for SBP and 0.17 (−0.20–0.55) for DBP	Adjusted for age, smoking, season, year, education, race and alcohol. Somewhat higher betas when adjusted for other metals in nail
Li, Li, Xi, Zheng, Wang, and Sun (2013) Cross-sectional study in Shanxi, China	Blood pressure and hypertension	Population: 604 Mean age: 46 years HT cases: 168	u-tiAs 136 µg/g creatinine, and 91% was iAs, MMA or DMA (69%) < 94 94–251 > 251	HT aOR for t-As: 1.0 1.1 (0.6–1.8) 1.6 (1.0–2.7)	Adjusted for sex, age, smoking, BMI and alcohol. Significant association also with MMA. Significant association between u-tAs and SBP (partial correlation adjusted for variables mentioned above) but not DBP
Li, Li, Xi, Zheng, Lv, and Sun (2013) Cross-sectional study in Inner Mongolia, China	Hypertension	Population: 669 Mean age: 50 years HT cases: 182	w-As (µg/L) cases/*n* < 10 (24/124) 10–50 (48/207) > 50 (110/338) u-iAs measured but not reported	Hypertension aOR 1.0 1.42 (0.77–2.62) 1.94 (1.02–3.69)	Adjusted for age, gender, smoking, BMI, diabetes, alcohol and Cumulative As Exposure (!). This adjustment should cause underestimation of true OR. The aOR tended to be higher at high MMA%

TABLE 27 (Continued)

Reference study population design	Outcome definition	Population size (*n*) case/control	Arsenic exposure	Results	Additional information/confounders
Jiang et al. (2015) Cohort study in Bangladesh (HEALS)	Longitudinal change of blood pressure over 7 years of follow-up.	10,853. Mean age at baseline 37 years. Only 1% on antihypertensive medication	w-As (μg/L), baseline quartiles <12 12–62 62–148 >148 <12 12–62 62–148 >148	Change/year of SBP Ref 0.43 (0.29–0.56) 0.54 (0.40–0.67) 0.48 (0.35–0.61) Change/year of DBP Ref 0.41 (0.31–0.50) 0.41 (0.32–0.51) 0.39 (0.30–0.49)	Adjusted for age, sex, smoking, BMI, education, diabetes, change of U-iAs. Similar betas for U-iAs quartiles (mean u-tAs in μg/g creatinine): Q1: 100 Q2: 209 Q3: 317 Q4: 526
Mendez et al. (2016) Cross-sectional study in Mexico	Hypertension	1160. Age ≥ 18, mean 45 years. 28% on antihypertensive medication. 439 cases of HT	w-As (μg/L) quartiles (HT cases) <25.5 (106) 25.5–47.8 (106) 47.9–78.9 (109) ≥79 (118)	Adjusted OR 1.0 1.30 (0.84–2.00) 1.27 (0.82–1.94) 1.41 (0.91–2.17)	Adjusted for age, sex, smoking, alcohol, body weight, high waist circumference, education, recent seafood intake. No association was found with u-iAs
Hossain et al. (2017) Cross-sectional study in rural Bangladesh	Hypertension	Population 236 from one area with elevated w-As and one area with normal w-As. Mean age 36 years. 32 cases of HT	Water: GM 18 μg/L. Nail: 3.4 μg/g Hair: 1.3 μg/g	Adj. beta for log-transformed w-As vs. SBP: 1.10 (0.26–1.94). Versus DBP: 0.74 (0.19–1.29)	Probably adjusted for age, sex and smoking, but not clearly described. The focus of the study was the association between w-As and DNA methylation
Spratlen et al. (2018) Cohort study in the USA (SHS)	Incident hypertension over 5 years of follow-up	Population 877. Age at baseline 31 years. Number of incident cases not reported	u-tiAs median 6.5, IQR 4.5–10.8 μg/L	RR per IQR (6.3 μg/L): 1.03 (0.88–1.20)	Adjusted for u-creatinine, age, sex, region, smoking, alcohol, education, eGFR, BMI. Low u-AsB: median 0.51, IQR 0.34–1.00
Kaufman et al. (2021) Cross-sectional and cohort study in the USA (SHFS)	Hypertension	Cross-sectional: Population 1910, median age 35 years, 430 cases. Longitudinal: Population 1453, median age 31, median follow-up 5 years, 203 incident cases	u-tiAs (μg/L) quartiles <1.34 1.34–1.85 1.86–2.39 ≥2.40 <1.34 1.34–1.85 1.86–2.39 ≥2.40	Adj. prevalence 1.0 1.01 (0.81–1.27) 1.04 (0.82–1.32) 1.19 (1.04–1.82) Adj RR (incidence) 1.0 1.43 (0.99–2.06) 1.10 (0.75–1.61) 1.10 (0.69–1.74)	Adjusted for age, sex, region, smoking, alcohol, education, eGFR, diabetes, physical activity, dietary factors, u-creatinine and u-AsB. Some overlap between SHS (Spratlen et al., 2018) and SHFS (present study). Changes in SBP and DBP not significantly associated with u-iAs

Abbreviations: Adj, adjusted; aOR, adjusted odds ratio; As, arsenic; BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; DL, detection level; DMA, sum of dimethylarsinous acid and dimethylarsinic acid; DNA, deoxyribonucleic acid; eGFR, estimated glomerular filtration rate; GM, geometric mean; HEALS, Health Effects of Arsenic Longitudinal Study; HT, hypertension; iAs, inorganic arsenic; IQR, interquartile range; MMA, sum of monomethylarsonous acid and monomethylarsonic acid; *n*, number; OR, odds ratio; Q, quantile; ref, reference; RR, risk ratio; SBP, systolic blood pressure; SHFS, Strong Heart Family Study; SHS, Strong Heart Study; t-As, total arsenic; TWA, time-weighted average; u-As, urinary arsenic; u-AsB, urinary arsenobetaine; u-iAs, urinary inorganic arsenic, USA, United States of America; u-tiAs, total urinary iAs (sum of iAs and its methylated metabolites MMA and DMA); w-As, water-arsenic.

3.2.2.8 | *Respiratory disease*

In the previous EFSA Opinion (EFSA CONTAM Panel, 2009) studies on respiratory disease and arsenic exposure were not identified. For the present opinion, the CONTAM Panel identified 26 studies from a literature search. Out of these, eight studies did not meet the inclusion criteria (Bhattacharyya et al., 2014; Liao et al., 2011; Majumdar & Guha Mazumder, 2012; Sanchez et al., 2018; Scannell Bryan et al., 2021; Shih et al., 2019; Smith et al., 2011; Zhou, Wang, et al., 2022). The 19 studies that fulfilled the inclusion criteria (see Section 3.2.2.1) criteria were further considered (Table 28).

Prenatal/childhood exposure

In a case control study in children < 5 years in Bangladesh u-tiAs in the children was a risk factor for pneumonia hospitalisation (George et al., 2015).

In a cohort of children in rural Bangladesh, prenatal arsenic exposure (u-tiAs in pregnant mothers) or persistently high exposure in childhood was related to impaired lung function with decreases in FEV1 and FVC, mostly in boys (Ahmed et al., 2017).

In a cohort of US children gestational As exposure (assessed by u-tiAs) at levels relevant to the general US population were associated with reduced children's FVC and FEV1, but not FEV1/FVC. Of note, u-tiAs levels were low and > 75% of the participants were exposed to low As levels from household water (< 5 µg/L) (Signes-Pastor, Martinez-Camblor, et al., 2021).

In a cohort of children 0–14 years in Taiwan, prenatal As exposure (assessed by u-tiAs) was significantly associated with the occurrence of asthma but not with allergic rhinitis; in contrast childhood exposure (assessed by u-tiAs) was significantly associated with allergic rhinitis but not asthma (Tsai, Lei, et al., 2021).

In a cross-sectional study in children in Mexico water or urine As was not significantly associated with respiratory infections (Vega-Millán et al., 2021).

Adult populations

In a cohort (HEALS) study in adults in Bangladesh a dose–response relationship was observed between iAs exposure (assessed by water As and u-tiAs) and respiratory symptoms (Parvez et al., 2010).

Based in the same cohort a cross-sectional study showed that As exposure (assessed by water As and u-tiAs) was associated with dyspnoea in never-smokers (Pesola et al., 2012).

In an expansion of this cohort a significant inverse relationship between tiAs exposure (assessed by water As and u-tiAs) and post-bronchodilator forced expiratory volume during first second (FEV1) and FVC was reported in those individuals with respiratory symptoms (Parvez et al., 2013).

In a cross-sectional study in adults there were no associations between u-tiAs and asthma, emphysema, chronic bronchitis or respiratory symptoms in the general US population (NHANES 2003–2006), but the outcomes of interest were self-reported and adjustments for organic As were crude (Amster et al., 2011).

In a cross-sectional study of adults in Pakistan, high (> 100 µg/L and > 250 µg/L) As in drinking water was associated with a decrease in FVC but there was no association with respiratory symptoms (Nafees et al., 2011). However, the association with w-tiAs 100–250 µg/L is unclear.

In a cross-sectional study in male adults in India with elevated As in drinking water had higher prevalence of upper and lower respiratory symptoms, asthma and eye irritation, as well as lower lung function of restrictive and obstructive types at spirometry compared with controls (Das et al., 2014).

A study in adults in Chile, two studies showed that As exposure from drinking water was associated with respiratory symptoms. In addition, higher w-tiAs was associated with lower FVC, but statistically significant only in never smokers (Nardone et al., 2017; Steinmaus et al., 2016).

In a cohort with US adults focused on rice consumption, u-tiAs was measured in a subgroup but not significantly associated with impaired lung function assessed by spirometry or any CT finding except some that were consistent with interstitial lung disease (Sanchez et al., 2019).

In a cohort of US American Indians u-tiAs was associated with impaired lung function showing a significant association with restrictive pattern and a trend for obstructive pattern at spirometry. In addition, u-tiAs was associated with self-reported emphysema and stopping for breath but not with other symptoms examined (Powers et al., 2019).

In a cross-sectional study in female non-smoking adults in India iAs exposure (assessed by water As) was associated with reduction of FEV1 and FVC (Prasad et al., 2020).

In a cross-sectional study in adults in Bangladesh As exposure (assessed by As in water, hair and nail) was associated with decreased lung volumes and risk of asthma assessed by reversible airway obstruction, asthma-related symptoms and serum IgE levels (Siddique et al., 2020).

In a cross-sectional study in adults, u-As in any form (organic, inorganic or total) was not associated with chronic bronchitis in the general US population from the NHANES 2011–2016 datasets, but the outcome of interest was self-reported and the number of cases was limited (Rahman, Niemann, & Munson-McGee, 2022a).

In summary, the epidemiological studies provide sufficient evidence for an association between low to moderate exposure to iAs and impaired lung function (decreased lung volumes). This is also consistent with the conclusion in a recent meta-analysis (Sanchez et al., 2018). Associations have been reported both in children and in adults. Several biologically plausible mechanisms have been described, cellular injury caused by inflammation, increased ROS generation (Sanchez et al., 2018). There is insufficient evidence for associations between exposure to iAs and respiratory disease (infections and asthma).

TABLE 28 Key epidemiological studies on respiratory diseases and As exposure.

Reference, study population age, design	Outcome definition	Population size (*n*) case/control	Arsenic concentration/exposure	Results	Additional information/confounders
Parvez et al. (2010), Bangladesh/mean 39 years, cohort (HEALS)	Respiratory symptoms (chronic cough, breathing problems, blood in sputum) at follow-up	11,746 1874 with at least one symptom	w-As level (μg/L) Q1: < 7, Q2: 7–40 Q3: 40–90 Q4: 90–178 Q5: > 178 u-As (μg/g creatinine): Q1 < 90, Q2: 90–160 Q3: 160–246 Q4: 246–406 Q5 > 406	w-As HR (95% CI): 1.0 (ref), 1.27 (1.09 to 1.48) 1.39 (1.19 to 1.63) 1.43 (1.23 to 1.68) 1.43 (1.22 to 1.68) u-As: 1 (ref), 1.10 (0.94 to 1.27) 1.11 (0.95 to 1.29) 1.29 (1.11 to 1.49) 1.35 (1.16 to 1.56)	Adjusted for age, gender, smoking, BMI, education and As-related skin lesions. The association with w-As was present also in never-smokers. Data also available for each of the three questions. High correlation btw w-As and u-tAs, very low correlation btw u-tAs and u-AsB
Amster et al. (2011), US > 20 years, cross-sectional (from NHANES 2003–2006)	Self-reported physician diagnosis of asthma, chronic bronchitis and emphysema	2676 (asthma: 334, chronic bronchitis: 50, emphysema: 173)	u-tiAs estimated by subtracting organic As from u-tAs. Median: 5.8 μg/L. u-tiAs (mean μg/L case/control) Asthma: 8.46/9.36, Chronic bronchitis: 7.74/9.37, Emphysema: 6.51/9.30	OR with u-tiAs as a continuous variable: Asthma: 0.92 (0.83, 1.02), Chronic bronchitis: 1.10 (0.98, 1.19), Emphysema: 0.93 (0.84, 1.05). OR comparing P80 with P20: Asthma: 0.79 (0.43, 1.46), Chronic bronchitis: 0.76 (0.36, 1.61), Emphysema: 0.72 (0.13, 3.81)	Adjusted for gender, age, race/ethnicity, education, BMI, serum cotinine and urinary creatinine
Nafees et al. (2011), Pakistan/> 15 years, cross-sectional	Spirometry and respiratory symptoms	As exposed versus non-exposed 100/100	As exposed > 100 μg/L 'non-exposed' < 10 μg/L in drinking water	Decline in mean spirometry (mL, 95% CI) In 'exposed': FEV1: −154.3 (−324.7, 16.0; $p = 0.076$), FVC: −221.9 (−419.5, −24.3; $p = 0.028$), FEV1/ FVC: 2.0 (−25.3, 29.4; $p = 0.884$). No significant association between respiratory symptoms and w-As	Adjusted for age, sex, height and smoking. Analysis include also data for 60 participants with higher w-As (> 250 μg/L). Levels in the other 40 'exposed' not reported
Pesola et al. (2012), Bangladesh/mean 37 years, cross-sectional study (HEALS)	Dyspnea (interview)	11,746, 7568 of which were never-smokers	w-As (μg/L) Q1: < 7 Q2: 7–38 Q3: 39–90 Q4: 91–178 Q5 > 179 u-As (μg/g creatinine) quintiles (cut-offs not reported)	OR (95% CI) for never-smokers: 1.00 (ref) 1.36 (0.97–1.90) 1.96 (1.43–2.70) 2.14 (1.56–2.92) 1.80 (1.31–2.49) 1.00 (ref), 1.37 (0.97–1.92), 1.92 (1.38–2.65), 1.94 (1.41–2.68), 1.87 (1.36–2.58)	Adjusted for age, sex, education, BMI, systolic blood pressure.

(Continues)

TABLE 28 (Continued)

Reference, study population age, design	Outcome definition	Population size (*n*) case/control	Arsenic concentration/exposure	Results	Additional information/confounders
Parvez et al. (2013), Bangladesh/mean 42 years, cohort (HEALS)	Pre- and post-bronchodilator spirometry for subjects with respiratory symptoms	950 with good quality spirometry	w-As (μg/L) (tertiles, *n*) T1: < 19 (312) T2: 19–97 (315) T3:> 97 (315) T1: < 19 (312) T2: 19–97 (315) T3:> 97 (315) u-tAs (μg/g creatinine, *n*): T1 < 125 (298) T2: 125–285 (321) T3 > 285 (305) T1 < 125 (298) T2: 125–285 (321) T3 > 285 (305)	w-As beta (95% CI): FEV1 (mL): 0 (Ref) −33.1 (−114.6 to 48.4) −80.6 (−181.4 to −17.5) FVC (mL): 0 (Ref) −13.2 (−97.3 to 71.0) −97.3 (−181.8 to −12.7) FEV1 (mL): 0 (Ref) −67.0 (−148.3 to 14.1) −90.5 (−173.6 to −7.4) FVC (mL): 0 (Ref) −36.4 (−120.4 to 47.0) −81.0 (−166.7 to 4.8)	Adjusted for age, sex, BMI smoking, betel nut use, education and arsenical skin lesions. Data report post-bronchodilator findings. FEV1/FVC not significantly associated with w-As or u-tAs. Significant associations with FVC were present also in never-smokers. For FEV1 *p*-values about 0.1.
Das et al. (2014), India, non-smoking male adults, mean age 35 years Cross-sectional study	Respiratory symptoms assessed by questionnaire Spirometry	As exposed versus 'non-exposed' 446/388	As in drinking water (μg/L) Exposed: 11–50 (mean 22.9) 'non-exposed': ≤ 10 (mean 3.6)	OR (95% CI) for low spirometry values FEV1 < 80% predicted: 1.22 (1.04–1.72) FVC < 80% predicted: 1.37 (1.10–1.96)	Spirometry results adjusted for age and height by design, and also for biomass fuel and agricultural activities. Comparisons of respiratory symptoms were unadjusted, but group differences in age, and prevalence of ex-smokers (about 7%) were minor
George et al. (2015), Bangladesh/1–60 months children (nested in PERCH study), case control study	Hospitalisation for severe or very severe pneumonia (physician-diagnosed)	153/296	Total u-As (μg/L, median) cases: at hospitalisation 14 30 days later: 16 Controls: 14 At hospitalisation: Q1 < 5.9 Q2: 6–16.9 Q3: 17–50.9 Q4 ≥ 50 30-days later: Q1 < 5.9 Q2: 6.0–14.9, Q3: 15.0–41.9, Q4 ≥ 42	OR (95%CI): 1.00 1.75 (0.90–3.40) 2.11 (1.01–4.34) 2.04 (0.92–4.51) 1.00 2.25 (1.23–4.11) 2.29 (1.17–4.47) 2.56 (1.27–5.15)	Adjusted for weight, height, breastfeeding in the prior week, paternal education, age, number of people in the household and urinary creatinine. Sub-analysis for severe pneumonia with similar findings. Total u-As considered OK as marker of u-tiAs exposure in this Matlab area

TABLE 28 (Continued)

Reference, study population age, design	Outcome definition	Population size (*n*) case/control	Arsenic concentration/exposure	Results	Additional information/confounders
Steinmaus et al. (2016); Nardone et al. (2017) Chile/39–60 years, Cross-sectional study with retrospective exposure data	Spirometry, respiratory symptoms and self-reported disease	795 individuals from areas with elevated or low As in drinking water	As exposed (long-term average w-As (μg/L): Never-smokers: Around 60 (*N* = 107) versus < 11 (*N* = 60) Ever-smokers: Around 60 (*N* = 97) versus < 11 (*N* = 73)	**Steinmaus**: Multiple linear regression of FVC (mL, 90% CI): −192 (−351, −34) −62 (−189, 64) FEV1 not significant	Adjusted for age, gender, height (Steinmaus: also race and smoking). There were also similar associations with highest w-As any year (so not time-weighted average) over lifetime or in early age
Ahmed et al. (2017), rural Bangladesh/9 years, cohort of children (from MINIMat)	Spirometry data, FeNO, serum CRP and Club cell protein (CC16)	540 (total)	u-As (μg/L, median) At GW8: 76, At 4.5 years: 57 At 9 years: 53	Maternal log u-As association with spirometry (beta, 95% CI) in 9-year children: FVC (mL): −12 (−22, −1.5), FEV1 (mL): −12 (−22, −1.9). Not significant (NS) for VC, FEV1/FVC, MMF, PEF, CC16; FeNO: NS for maternal u-As. Significant association with log u-As at 4.5-years and 9 years in in boys, but not in girls or all children. Long-term cumulative As exposure (> 150 μg/L): Significant inverse associations btw spirometry and maternal u-As and u-As in children at 4.5 and 9 years	Adjusted for children's age, height-for-age z-score (HAZ), SES, sex, season, mothers' education, plasma concentrations of CRP and maternal micronutrient supplementation groups. Significant associations were restricted to boys, not girls.
Nardone et al. (2017) (the same study as Steinmaus et al. (2016))				Similar associations as in Steinmaus et al. (2016), but stronger associations in individuals with high BMI	Additional information between correlation of different BMI categories
Powers et al. (2019), USA American Indians/mean 57 years, cohort (Strong Heart Study)	Spirometry, respiratory symptoms, self-reported asthma, emphysema, chronic bronchitis	2132, obstructive spirometry in 458, restrictive in 307	u-tiAs (μg/g creatinine): T1 ≤ 7, T2 7.1–13.9, T3 ≥ 14	OR T3 versus T1 Obstructive 1.17 (0.99–1.40) Restrictive 1.18 (0.93–1.50 Emphysema 1.66 (1.29, 2.15) Asthma 0.76 (0.60, 0.96) Not associated with other symptoms and chronic bronchitis	Adjusted for age, sex, education, site, smoking, eGFR, tuberculosis, BMI, diabetes. Data also for lower limit of normal (LLN), as well as for FEV1, FVC in mL
Prasad et al. (2020), India/mean 41 years, only females, cross sectional study	Spirometry	281 from three areas with varying w-As	w-As level (μg/L) (*n*) > 50 (70) mean 68.5 11–50 (93) mean 22.5 Cont < 10 (118) mean 1.0 High > 50 (70) Low 11–50 (93) Controls < 10 (118)	FVC% predicted 73.2 ± 12.9, $p < 0.001$ versus controls 83.8 ± 19, NS versus controls 88.3 ± 22.4 FEV1% predicted 77.1 ± 17.8, $p < 0.001$ versus controls 90.5 ± 26.6, NS versus controls 91.1 ± 25.5	Only females and non-smokers were included. Associations between nail As concentration and As water concentration were significant. Associations btw nail As, and spirometry data showed significant dose–response relations

(Continues)

TABLE 28 (Continued)

Reference, study population age, design	Outcome definition	Population size (*n*) case/control	Arsenic concentration/exposure	Results	Additional information/confounders
Rahman, Niemann, and Munson-McGee (2022a), US > 20 years, cross-sectional (NHANES 2011–2016)	Chronic bronchitis (self-reported based on a specific question)	4186 88 cases	u-tAs, u-iAs, u-MMA, u-DMA, u-AsB, u-AsC (not u-tiAs)	No significant association with chronic bronchitis	Adjusted for gender, race/ethnicity, education, marital status, age, family income, BMI, cotinine, alcohol and country of birth
Sanchez et al. (2019), USA/ mean 63 years, cohort (MESA)	Spirometry, CT findings	310 (total)	u-tiAs median (IQR): 3 μg/g (2–5) increase u-tiAs per IQR (2.5 μg/g)	mean difference (95% CI): FEV1 (mL): −46 (−171, 79) FVC (mL): −15 (−30, 99) FEV1/FVC%: 0.01 (−0.02, 0.03) CT findings: non-significant except for interstitial lung abnormalities: OR (95% CI) 1.95 (0.44, 8.62)	Adjusted for sex, age, race/ethnicity, study site, education, height, weight, smoking. Also data on rice consumption are reported
Siddique et al. (2020), Bangladesh/18–60 years, cross sectional	Spirometry with reversibility test, asthma symptoms, serum IgE	842 Exposed/non-exposed 653/189 High *n*: 282, Medium *n*: 281, Low *n*: 279	w-As (μg/L) (tertiles, *n*) 0.03–5.30 (279) 5.32–134 (281) 135–1800 (286) 0.03–5.30 5.32–134 135–1800 0.03–5.30 5.32–134 135–1800 0.03–5.30 5.32–134 135–1800 0.03–5.30 5.32–134 135–1800	β (95% CI) FEV1: 0 (ref) −0.123 (−0.219 to −0.028) −0.203 (−0.334 to −0.071) FEV6 0 (ref) −0.122 (−0.211 to −0.033) −0.169 (−0.309 to −0.028) FEV1/FEV6 0 (ref) −0.0.18 (−0.040 to 0.005) −0.055 (−0.082, −0.028) Obstruction (OR, 95% CI, cases) 1.0 (ref) (14) 1.94 (1.03 to 3.65) (29) 3.65 (1.84 to 7.24) (54) Reversible obstruction (OR, 95% CI) 1.0 (ref) (10) 1.76 (1.01 to 3.06) (19) 3.81 (1.85 to 7.85) (41) Asthma related symptoms (OR, 95% CI) 1.0 (ref) 2.04 (1.06 to 3.92) 3.69 (2.23 to 6.11)	Adjusted for age, sex, BMI, smoking, income, education, occupation and clustering village. Airway obstruction defined as FEV1/FEV6 < 0.73. Reversibility defined as ≥ 12% increase in FEV1. There was also a dose–response association btw w-As and serum IgE. Data are reported also for As in hair and nail with similar results as for w-As
Signes-Pastor, Martinez-Camblor, et al. (2021), USA, cohort (New Hampshire Birth Cohort Study)	At 7.5-year children Spirometry	358	u-tiAs at GW 24–28. Median u-tiAs: 3.6 μg/L	β (95% CI) for doubling of u-tiAs: FEV1: −0.10 (−0.18, −0.02) FVC: −0.08 (−0.14, −0.01) FEV1/FVC: 0.002 (−0.003, 0.007)	Adjusted for maternal smoking status, children's age, sex and height

TABLE 28 (Continued)

Reference, study population age, design	Outcome definition	Population size (*n*) case/control	Arsenic concentration/exposure	Results	Additional information/confounders
Tsai, Lei, et al. (2021), Taiwan/children 0–14 years, cohort (Taiwan Maternal and Infant Cohort Study)	Asthma spirometry, self-reported allergic rhinitis	261 Allergy in 96	Maternal u-tiAs at GW 28–38 (Median u-tiAs: 24.9 µg/L), Children u-tiAs until 14 years of age (median u-tiAs: 17.2–41.1 at various visits)	Maternal u-tiAs-OR (95% CI): Asthma: 2.79 (1.52, 5.14). Allergic rhinitis: Not significant. Child u-tiAs: OR (95% CI) Allergic rhinitis: 1.81 (1.11, 2.93). Asthma: Not significant	Adjusted for child's sex, breastfeeding, ETS exposure, prenatal AsB, maternal allergy, paternal allergy, child's serum IgE.
Vega-Millán et al. (2021), Mexico/children (mean 10 years), cross-sectional	Respiratory infections	In three villages: 90/53/73	Mean w-As (µg/L) in three villages: 11.8, 23.3, 70.01 u-tAs: 37.3, 47.04, 132.57	Water or u-As not significantly associated with respiratory infections. OR 0.96 (0.87–1.05) with water As as a continuous variable	Adjusted for age, sex, tobacco/smoking, weight, community. Data also for CC16 and MMP9

Abbreviations: As, arsenic; AsB, arsenobetaine; BMI, body mass index; CC16, clara cell secretory protein; CI, confidence interval; cont, control; CRP, plasma c-reactive protein; CT, computed tomography; DMA, sum of dimethylarsinous acid and dimethylarsinic acid; eGFR, estimated glomerular filtration rate; ETS, environmental tobacco smoke; FeNo, fractional exhaled nitric oxide; FEV(1/6), forced expiratory volume (in 1/6 seconds); FVC, forced vital capacity; GW, gestational week; HAZ, height-for-age-z-score; HEALS, Health Effects of Arsenic Longitudinal Study; HR, hazard ratio; IgE, immunoglobulin E; IQR, interquartile range; LLN, lower limit of normal; MESA, Multi-Ethnic Study of Atherosclerosis; MINImat, Maternal and Infant Nutrition Interventions in Matlab; MMA, sum of monomethylarsonous acid and monomethylarsonic acid; MMF, maximum mid-expiratory flow; MMP9, matrix metalloproteinase 9; *n*, number; NHANES, National Health and Nutrition Examination Survey; NS, not significant; OR, odds ratio; PEF, peak expiratory flow; PERCH, Pneumonia Etiology Research for Child Health; Q, quantile; RAO, reversible airway obstruction; ref, reference; SES, socioeconomic status; T, tertile; u-As, urinary arsenic; u-AsB, urinary arsenobetaine; u-AsC, urinary arsenocholine; u-DMA, urinary DMA; u-MMA, urinary MMA; USA, United States of America; u-As, urinary arsenic; u-tAs, total urinary arsenic; u-tiAs, total urinary inorganic arsenic (iAs and its methylated metabolites DMA and MMA); VC, vital capacity; w-As, water arsenic.

3.2.2.9 | *Effects on diabetes and insulin resistance*

In the previous EFSA Opinion (2009) it was concluded that there remained uncertainty whether arsenic contributes to the occurrence of type 2 diabetes and that there was inadequate data from which to inform on dose response at lower level of exposure. In addition to type 2 diabetes, the current Opinion also includes gestational diabetes and type 1 diabetes.

The CONTAM Panel identified 65 studies from a literature search. Out of these, 13 studies met the criteria (Table 29).

Gestational diabetes

Two studies, one from the U.S. and one from Chile, investigated the association between u-tiAs and gestational diabetes (Chen, Davis, et al., 2021; Muñoz et al., 2018). The outcome was based on either clinical diagnoses or medical charts. These studies observed no association between iAs exposure measured as u-tiAs and gestational diabetes (Chen, Davis, et al., 2021; Muñoz et al., 2018).

Ten additional studies were also evaluated but did not fulfil the inclusion criteria and were accordingly not considered further (Ashley-Martin et al., 2018; Farzan et al., 2016; McKeating et al., 2021; Peng et al., 2015; Shapiro et al., 2015; Wang, Gao, et al., 2020; Wang, Zhang, et al., 2019; Xia et al., 2018; Zhang, Chen, et al., 2021; Zhang, Zhang, et al., 2021).

Type 1 diabetes

One cross-sectional study included in this review investigated the association between iAs and type 1 diabetes (Grau-Pérez et al., 2017). The study, which was from the U.S., observed no association between the total concentrations of inorganic As and its metabolites (iAs + MMA + DMA) in plasma and type 1 diabetes. However, increased concentrations of iAs in serum decreased the risk for type 1 diabetes, whereas concentrations of MMA and DMA, respectively, tended to increase the risk for type 1 diabetes. These associations were somewhat more pronounced when fractions were investigated instead of concentrations.

One study did not fulfil the inclusion criteria and was not considered further (Chafe et al., 2018).

Type 2 diabetes

The five cross-sectional study populations included in this Opinion are from the U.S., China, Bangladesh and Mongolia (Chen, Ahsan, Slavkovich, Peltier, Gluskin, Parvez, et al., 2010; Li, Li, Xi, Zheng, Lv, & Sun, 2013; Nizam et al., 2013; Steinmaus et al., 2009; Zhang et al., 2020). Four of these studies showed no associations between iAs and type 2 diabetes (Chen, Ahsan, Slavkovich, Peltier, Gluskin, Parvez, et al., 2010; Li, Li, Xi, Zheng, Lv, & Sun, 2013; Nizam et al., 2013; Steinmaus et al., 2009), whereas one did so regarding fractions of arsenic (Zhang et al., 2020). This study, which was from China, did not observe an association between u-tiAs and type 2 diabetes, whereas the concentrations of iAs and MMA were significantly lower among the individuals with type 2 diabetes. In adjusted analyses, the tertile with highest fraction of MMA had decreased occurrence of type 2 diabetes and the tertile with the highest fraction of DMA had increased occurrence of type 2 diabetes (Zhang et al., 2020).

Three prospective studies from the U.S. investigated the association between iAs and risk of developing type 2 diabetes (Grau-Perez et al., 2017; Kuo et al., 2015; Yang et al., 2019). Kuo and colleagues found no significant differences in iAs concentrations at baseline between those who developed type 2 diabetes and those who did not (Kuo et al., 2015). However, arsenic metabolism was prospectively associated with type 2 diabetes incidence, higher percentage of MMA being consistently associated with lower risk of diabetes. In a study by Grau-Perez and colleagues no overall association was indicated between u-tiAs and type 2 diabetes (Grau-Perez et al., 2017). However, higher concentrations were associated with an increased risk for type 2 diabetes among those with normal fasting glucose at baseline but not among those with impaired fasting glucose at baseline. A third study by Yang and colleagues with very long follow-up (up to 28 years) and up to seven follow-up exams did not find associations between arsenic and type 2 diabetes (Yang et al., 2019). This study analysed arsenic concentrations in toenails and did not perform arsenic specification. However, according to the authors toenails have been suggested to preferentially sequester iAs and its metabolites. In addition, sensitivity analyses with adjustment for fish/seafood consumption did not change the results.

Thirty-one additional studies were also evaluated but did not fulfil the inclusion criteria and were accordingly not considered further (Arab YarMohammadi et al., 2021; Becker & Azelrad, 2014; Bräuner et al., 2014; Castriota et al., 2018; Currier et al., 2014; Dai et al., 2020; Del Razo et al., 2011; Eick et al., 2019; Feseke et al., 2015; Grau-Perez et al., 2018 ; Gribble et al., 2012; Hansen et al., 2017; Hsu et al., 2013; Huang et al., 2014; Islam, Khan, Hassan, et al., 2012; Jovanovic et al., 2013; Kim et al., 2013; Kim & Lee, 2011; Konkel, 2020; Liu et al., 2016; Lucio et al., 2020; Makris et al., 2012; McLeod et al., 2019; Pan, Kile, et al., 2013; Pan, Seow, et al., 2013; Rehman et al., 2019; Rhee et al., 2013; Simic et al., 2017; Sripaoraya et al., 2017; Wang, Karvonen-Gutierrez, et al., 2020; Yuan et al., 2018).

Insulin resistance

A cross-sectional study in the U.S. did not find an association between u-tiAs and HOMA2-IR, i.e. insulin resistance (Li et al., 2021). However, lower MMA% was associated with higher HOMA2-IR levels among obese participants but not among non-obese participants. Another cross-sectional study among students from Taiwan observed that higher concentrations of u-tiAs was associated with higher HOMA-IR (Lin et al., 2014).

Ten additional studies were also evaluated but did not fulfil the inclusion criteria and were accordingly not considered further (Fleisch et al., 2022; Lampron-Goulet et al., 2017; Mondal et al., 2020; Ourshalimian et al., 2019; Park et al., 2016; Paul et al., 2019; Su et al., 2012; Tinkelman et al., 2020; Wang, Mukherjee, et al., 2020; Zhou, Zhao, & Huang, 2022).

In summary, most of the studies were cross-sectional which might be affected by reverse causality. Although some studies indicate associations, especially in subgroup analyses, the epidemiological studies provide insufficient evidence for an association between low to moderate exposure to iAs and diabetes or glucose metabolism.

TABLE 29 Key epidemiological studies on diabetes and insulin resistance in humans in relation to iAs exposure.

Reference study population design	Outcome definition	Population size (*n*) case/control	Arsenic exposure	Results	Additional information/confounders
Gestational diabetes					
Chen, Davis, et al. (2021) Oklahoma, USA Case–control	Clinical diagnoses	Cases: 64 Controls: 237	**u-tiAs (µg/L), medians** Cases: 3.02, Controls: 3.42 iSumAs = Sum of inorganic and methylated arsenic ≤ 4.54 4.55–6.75 > 6.76	**Adjusted OR (95% CI)** 1.00 0.66 (0.29–1.49) 0.73 (0.34–1.61) No associations with AsIII, AsV, iAs, MMA or DMA	Adjusted for age, race/ethnicity, BMI, smoking, history of GDM
Muñoz et al. (2018) Arica, Chile Cross-sectional	From medical charts (WHO criteria)	21 out of 244 had GD	**u-tiAs (µg/L)** Medians were 15.12 among cases and 14.72 among controls 2.05–11.08 11.09–19.90 19.91–69.30	**Adjusted OR (95% CI)** 1.0 2.98 (0.87–10.18) 1.07 (0.26–4.33) No association with MMA% or DMA%	Adjusted for age, education, ethnicity and BMI
Type 1 diabetes					
Grau-Pérez et al. (2017) Five sites in the USA Cross-sectional case–control	Clinical diagnoses	Cases: 429 Controls: 174 (in addition 85 with type 2 diabetes)	**iAs in plasma (ng/L)** Medians among cases and controls: ΣAs: 81.7 and 83.1 iAs: 46.6 and 50.2 MMA: 8.9 and 8.1 DMA: 22.8 and 21.0 ΣAs = sum of iAs, MMA and DMA As metabolism iAs%: 58.7 and 63.4 MMA%: 11.2 and 10.3 DMA%: 28.9 and 25.2	**Adjusted OR (95% CI)** Interquartile range increases ΣAs (ng/L): 0.90 (0.71–1.13) iAs (ng/L): 0.85 (0.73–1.00) MMA (ng/L): 1.21 (0.93–1.57) DMA (ng/L): 1.15 (0.94–1.42) iAs%: 0.70 (0.53–0.92) MMA%: 1.29 (1.01–1.65) DMA%: 1.27 (1.01–1.58)	Adjusted for age, sex, BMI, educational level and ethnicity
Type 2 diabetes					
Steinmaus et al. (2009) NHANES, USA Cross-sectional case–control	Self-reported diagnoses or fasting glucose serum measurements	Cases: 98 Controls: 697	**u-tiAs (µg/L)** Median and Mean (SD) All 6.0 and 9.4 (12.9) T2D 6.2 and 11.1 (16.9) No T2D 6.0 and 9.2 (12.3)	**Adjusted OR (95% CI)** Estimated iAs ≥ 80th versus ≤ 20th percentile (11.9 vs. 2.7 µg/L) 1.15 (0.53–2.50) A reanalysis of a former study which observed strong association but did not subtract arsenobetaine from total As	Adjusted for sex, age, ethnicity, education, BMI, cotinine, hypertension medication

TABLE 29 (Continued)

Reference study population design	Outcome definition	Population size (*n*) case/control	Arsenic exposure	Results	Additional information/confounders
Chen, Ahsan, et al. (2010) Araihazar, Bangladesh Cross-sectional	Self-reported physician diagnosed T2D HbA1c was analysed for part of the participants	241 out of 11,319 had T2D	- Time-weighted As concentrations (TWA) was estimated as a function of drinking durations and well arsenic concentrations - Total As urine concentrations - As metabolites measured in a random 10% of the populations	**Adjusted OR (95% CI)** No significant associations between TWA and T2D TWA and glucosuria	Adjusted for age, sex, BMI, smoking, education and creatinine
Li, Li, Xi, Zheng, Lv, and Sun (2013) Inner Mongolia, China Cross-sectional	Fasting blood glucose levels	42 out of 669 participants had T2D	**w-As, µg/L** (cases/*n*) < 10 7/124 10–50 14/207 > 50 21/338	**Adjusted OR (95% CI)** < 10 1.00 10–50 1.36 (0.52–3.57) > 50 1.57 (0.58–4.26)	Adjusted for sex, age, smoking, BMI and alcohol
Nizam et al. (2013) Faridpur, Bangladesh Case–control study	Physician-diagnosed T2D	140 cases 180 controls	**Urine As, µg/L,** mean Cases – Controls u-tiAs: 252.2–235.3 iAs: 20.0–21.2 MMA: 23.9–22.22 DMA: 208.3–192.0	***p*-values** case versus controls u-tiAs: 0.56 iAs: 0.65 MMA: 0.60 DMA: 0.81 **from adjusted models** iAs%: 0.34 (higher among controls) MMA%: 0.08 (higher among controls) DMA%: 0.14 (higher among cases)	Adjusted for sex, union, age, water arsenic, income, duration of drinking water, family history of diabetes, smoking and BMI
Kuo et al. (2015) The Strong Heart Study, USA Follow-up study Baseline 1989–91 Followed through 1998–99.	Fasting plasma glucose level, self-reported diabetes history or use of anti-diabetic medications	Out of 1694 diabetes-free 396 developed diabetes	**Urine As, µg/g (median)** No DM / DM u-tiAs 8.7 / 9.1 iAs 0.7 0.7 MMA 1.3 / 1.2 DMA 6.4 / 7.0 iAs% 8.4 / 8.1 MMA% 15.5 / 14.0 DMA% 75.9 / 77.4	**Adj HR 95% CI** Per doubling increase u-tiAs: 0.96 (0.85–1.08) iAs: 0.98 (0.90–1.06) MMA: 0.90 (0.81–1.00) DMA: 0.98 (0.87–1.11) Methylation – Conventional approach (per 5% increase)	Adjusted for age, sex, education, smoking, alcohol, BMI, waist-to-hip ratio. Also 'leave-one-out' approaches were reported
Grau-Perez et al. (2017) Strong Heart Family study, USA Follow-up	Two outcomes: – T2D at follow-up via fasting plasma glucose or self-reported physician diagnoses or treatments – HOMA2-IR, fasting glucose and insulin values	252 out of 1838 developed T2D	**Urine As (median)** u-tiAs 4.4 µg/g creatinine iAs% 9.5% MMA% 14.4% DMA% 75.6%	**Adjusted HR (95%CI)** per interquartile range u-tiAs Overall: 1.16 (0.94–1.42) Normal Fasting Glucose at Baseline (NFG): 1.57 (1.18–2.08) Impaired Fasting Glucose at Baseline (IFG): 0.92 (0.67–1.27) As metabolism was not associated with incident diabetes or insulin resistance	Adjusted for sex, age, education, BMI, waist circumference, smoking, glomerular filtration rate, glucose status (only overall), estimated dietary vitamin B2, vitamin B6 and folate, and AS3MT genotype

(Continues)

TABLE 29 (Continued)

Reference study population design	Outcome definition	Population size (*n*) case/control	Arsenic exposure	Results	Additional information/confounders
Yang et al. (2019) CARDIA study, USA Follow-up study Baseline 1987–1988 Followed through 2015–16.	Fasting glucose level	599 out of 4102 developed T2D during the 28 years follow-up (individuals completed up to 7 follow-up exams)	**Total toenail As level, ppm** Median in respective quintile Q1: 0.047 Q2: 0.071 Q3: 0.097 Q4: 0.135 Q5: 0.237	**Adjusted HR (95% CI)** 1.00 0.95 (0.75–1.22) 1.04 (0.81–1.33) 1.00 (0.77–1.30) 0.96 (0.73–1.27)	Adjusted for age, sex, race, study centre, baseline glucose levels, BMI, education, smoking, physical activity and family history for diabetes
Zhang et al. (2020) Northern China Cross-sectional	Fasting plasma glucose levels or self-reported physician diagnoses or medications	49 out of 1003 had T2D	**Urine As concentrations, µg/g Cr** T2D – Non-T2D (medians) iAs: 7.6–15.4 MMA: 11.7–17.5 DMA: 95.7–101.7 u-tiAs: 112.8–138.1 Urine As metabolism iAs%: 7.0–10.4 MMA%: 10.3–13.6 DMA%: 82.2–74.2	*p*-values for U-As concentrations between T2D – Non-T2D iAs: 0.005 MMA: 0.019 DMA: 0.591 u-tiAs: 0.196	Adjusted for gender, age, education, job, smoking, drinking, BMI, study area and u-tiAs in urine.
Insulin resistance					
Li et al. (2021) NHANES (2003–2016), USA Cross-sectional	HOMA2-IR was calculated based on participants fasting glucose and insulin values	3730 individuals	**Urine As concentrations (µg/g Cr),** Medians u-tiAs: 5.96 iAs: 0.63 MMA: 1.21 DMA: 3.98	**The Geometric Mean Ratio (95% CI) of HOMA2-IR** Per doubling increase u-tiAs: 0.99 (0.97, 1.01) *p*-value = 0.14	Adjusted for age, sex, race/ethnicity, BMI, smoking, alcohol, education, physical activity, fish consumption, B-Hg
Lin et al. (2014) Taiwan Cross-sectional	Insulin resistance determined by HOMA-IR	303 elementary school students and 319 junior school students	**Urine As concentrations (µg/L),** Mean Elementary/Junior u-tiAs: 24.54 /25.92 As metabolism iAs%: 5.06/7.57 MMA^{V}%: 5.00/5.30 DMA^{V}%: 90.52 /87.5	**Adjusted B (95% CI) from linear regression models** u-tiAs (µg/L) All students: 0.024 (0.017–0.047) Elementary: 0.044 (0.017–0.071) Junior: 0.017 (0.001–0.034)	Adjusted for age, sex, BMI, lipid profiles, liver function, paternal and maternal education, smoking

Abbreviations: As, arsenic; AsIII, arsenite; AsV, arsenate; AsB, arsenobetaine; AS3MT, arsenite methyltransferase; BMI, body mass index; B-Hg, blood mercury; CAE, cumulative arsenic exposure; CARDIA, Coronary Artery Risk Development in Young Adults; CI, confidence interval; Cr, creatinine; DM, diabetes mellitus; DMA, sum of dimethylarsinous acid and dimethylarsinic acid; GD, gestational diabetes; GDM, gestational diabetes mellitus; GM, geometric mean; HbA1c, glycated haemoglobin A1c; HOMA-IR, homeostasis model assessment-insulin resistance; HR, hazard ratio; iAs, inorganic arsenic; IFG, impaired fasting glucose; iSumAs, sum of inorganic and methylated arsenic; MMA, sum of monomethylarsonous acid and monomethylarsonic acid; *n*, number; NFG, normal fasting glucose; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio; ppm, parts per million; Q, quantile; SD, standard deviation; T2D, type 2 diabetes; t-As, total arsenic; TWA, time-weighted average; USA, United States of America; u-tiAs, total urinary inorganic arsenic (sum of iAs and its methylated metabolites MMA and DMA); w-As, water-arsenic; WHO, World Health Organization.

3.2.2.10 | *Metabolic syndrome*

The CONTAM Panel identified eight studies from a literature search. Out of these, four studies met the criteria. The relevant studies are summarised in Table 30.

Two cross-sectional studies and two follow-up studies investigated the associations between iAs and metabolic syndrome (Chen et al., 2012; Kazemifar et al., 2020; Pace et al., 2018; Spratlen et al., 2018). A cross-sectional study from Iran did not find associations between urinary concentrations of iAs and metabolic syndromes (Kazemifar et al., 2020). However, increased MMA% was associated with decreased occurrence of metabolic syndrome whereas increased DMA% was associated with increased occurrence of metabolic syndrome. Neither did the second cross-sectional study, which was performed in the U.S., report an association between urinary concentrations of iAs and metabolic syndrome (Pace et al., 2018). When gender specific analyses were performed in this study, the %MMA was statistically significantly associated with metabolic syndrome among men but not among women. On the other hand, the ratio DMA/MMA gave a significant association among women but not among men. None of two follow-up studies, one from Taiwan and one the U.S., showed an association between the baseline concentrations of u-tiAs in urine and the risk of developing metabolic syndrome (Chen et al., 2012; Spratlen et al., 2018). However, both studies showed that increased MMA% was associated with decreased risk of developing metabolic syndrome and that increased DMA% was associated with increased risk of developing metabolic syndrome. Even in longitudinal studies it is difficult to judge whether such associations are causal, since a metabolic syndrome may affect the metabolism of iAs.

Four additional studies were also evaluated but did not fulfil the inclusion criteria and were accordingly not considered further (Asprouli et al., 2019; Bulka et al., 2019; Choi et al., 2014; Martínez-Barquero et al., 2015).

In summary, the evidence for an association between iAs exposure and metabolic syndrome is insufficient.

TABLE 30 Key epidemiological studies on metabolic syndrome in humans in relation to iAs exposure.

Reference study population design	Outcome definition	Population size (*n*) case/control	Arsenic exposure	Results	Additional information/confounders
Chen et al. (2012) Southwestern Taiwan Cohort study Recruited in 1990 and follow-up in 2002–03	Metabolic syndrome (MetS) based on criteria for fasting plasma glucose, triglycerides, high density lipoprotein, increased systolic of diastolic blood pressure and waist girth	247 individuals, 111 with MetS and 136 with no MetS	**u-As (mean) at follow-up** No Mets – Mets AsIII (µg/g creatinine)3.79–4.12 AsV 1.78–1.47 iAs 5.57–5.58 MMA 4.51–3.08 DMA 32.79–35.52 u-tiAs 42.87–44.19 iAs% 17.2–16.8 AsIII% 10.1–10.4 AsV% 7.3–6.9 MMA% 10.6–9.4 DMA% 72.3–73.5 PMI 0.92–0.75 (MMA/(AsIII+AsV)) SMI 16.12–19.98 (DMA/MMA) As concentrations in well-water (µg/L) 570–684 Cumulative As exposure, CAE (mg/(L*years)) 13.96–17.71	**Age-adjusted *p*-values** No Mets versus Mets AsIII 0.79 AsV 0.29 iAs 0.97 MMA 0.03 DMA 0.42 u-tiAs 0.66 iAs% 0.98 AsIII% 0.98 AsV% 0.99 MMA% 0.06 DMA% 0.37 PMI 0.06 SMI 0.42 **Adjusted OR (95% CI)** Highest versus lowest tertile In well water 1.24 (0.65–2.37) CAE 1.73 (0.72–4.19) In urine: AsIII% 0.78 (0.41–1.49) AsV% 0.80 (0.43–1.49) MMA% 0.35 (0.18–0.66) DMA% 2.01 (1.05–3.86) PMI 0.39 (0.20–0.76) SMI 2.61 (1.35–5.08)	Adjusted for age and betel nut chewing

TABLE 30 (Continued)

Reference study population design	Outcome definition	Population size (*n*) case/control	Arsenic exposure	Results	Additional information/confounders
Kazemifar et al. (2020) Qazvin province, Iran Cross-sectional	Metabolic syndrome using the criteria suggested by the Third National Cholesterol Education Program (NCEP) report	45 with metabolic syndrome and 87 without	**Urinary concentrations**, Means, (μg/L) cases – controls iAsIII 2.32–2.36 iAsV 0.69–0.74 iAs 3.01–3.10 MMA 2.90–3.12 DMA 15.53–14.15 %iAs 14.45–14.46 %MMA 13.69–15.33 %DMA 71.85–68.19 MMA/iAs 0.97–0.99 DMA/MMA 5.28–4.59	***p*-values for comparisons between cases and controls** iAsIII 0.43 iAsV 0.14 iAs 0.15 MMA 0.06 DMA 0.07 %iAs 0.017 %MMA < 0.001 %DMA < 0.001 MMA/iAs 0.45 DMA/MMA < 0.001 **Adjusted OR (95% CI) by unit increase** %iAs 0.90 (0.75–1.08) %MMA 0.76 (0.59–0.97) %DMA 1.18 (1.07–1.39) MMA/iAs 0.39 (0.04–3.73) DMA/MMA 1.86 (1.05–3.31)	Adjusted for age and BMI
Spratlen et al. (2018) Strong Heart Family Study, USA Follow-up study (Baseline visits 1998–99 and 2001–03 and Follow-up visits 2001–03 and 2006–09)	Metabolic syndrome was characterised according to the National Cholesterol Education Program Adult Treatment Panel III guidelines	1047 participants with no MetS at baseline 338 developed MetS during follow-up	**Urinary concentrations at baseline Medians, No MetS – MetS** u-tiAs (μg/L) 6.3–7.0 iAs% 10.0–9.9 MMA% 16.0–14.2 DMA% 72.1–75.1	***p*-values for comparisons between cases and controls** u-tiAs (μg/L) 0.21 iAs% 0.01 MMA% < 0.001 DMA% < 0.001 **Adjusted RR (95% CI)** per IQR increase u-tiAs 1.03 (0.90–1.18) per 5% increase iAs% 0.94 (0.88–1.01) MMA% 0.87 (0.79–0.95) DMA% 1.07 (1.02–1.12)	Adjusted for urinary creatinine concentration, sex, region, education, alcohol, smoking, kidney function and BMI.

(Continues)

TABLE 30 (Continued)

Reference study population design	Outcome definition	Population size (*n*) case/control	Arsenic exposure	Results	Additional information/confounders
Pace et al. (2018) NHANES, USA Cross-sectional	A diagnose was given based on the following variables: Fasting glucose, systolic or diastolic blood pressure, triglycerides, waist circumferences, HDL-cholesterol	957 individuals participated whereof 331 had MetS	**Urinary As species, mean** (μg/L) iAsIII: 0.51 MMA III + V: 0.63 DMA III + V: 4.68 %iAs: 9.68%MMA: 11.69 %DMA: 78.63 MMA/iAs: 1.89 DMA/MMA: 10.44	***p*-values obtained from adjusted logistic regression** Gender specific analyses Men - Women %iAs 0.950–0.977% MMA 0.021–0.153 %DMA 0.150–0.078 MMA/iAs 0.173–0.876 DMA/MMA 0.152–0.037	Adjusted for age, Poverty Income Ratio, ethnicity, smoking

Abbreviations: As, arsenic; AsIII, arsenite; AsV, arsenate; BMI, body mass index; CAE, cumulative arsenic exposure; CI, confidence interval; DMA, sum of dimethylarsinite and dimethylarsinate; DMA(III), dimethylarsinous acid; DMA(V), dimethylarsinic acid; HDL, high-density lipoprotein; iAs, inorganic arsenic; iAsIII, arsenite; iAsV, arsenate; IQR, interquartile range; MMA, sum of monomethylarsonous acid and monomethylarsonic acid; MMA(III), monomethylarsonous acid; MMA(V), monomethylarsonic acid; MetS, metabolic syndrome; *n*, number; NCEP, National Cholesterol Education Program; OR, odds ratio; NHANES, National Health and Nutrition Examination Survey; PMI, primary methylation index; RR, risk ratio; SMI, secondary methylation index; u-As, urinary arsenic; USA, United States of America; u-tiAs, total urinary iAs (sum of iAs and its methylated metabolites MMA and DMA).

3.2.2.11 | *Renal effects*

In the previous EFSA Opinion (EFSA CONTAM Panel, 2009) the only mention of possible effect on the kidney was that a Chinese study had shown a possible interaction between arsenic and cadmium on excretion of biomarkers of renal damage, but the CONTAM Panel concluded that further studies were needed to clarify this.

The CONTAM Panel identified 15 studies on associations between As exposure and renal effects from a literature search. Out of these, 10 studies met the inclusion criteria, while 5 studies did not meet the inclusion criteria (Chen, Chen, et al., 2011; Jiménez-Córdova et al., 2018; Smith et al., 2012; Tsai et al., 1999; Weidemann et al., 2015).

Chronic kidney disease (CKD)

The most important studies are those that examine the risk of chronic kidney disease (CKD). Five such studies are reviewed below.

Meliker et al. (2007) examined cause-specific mortality in an ecological study in six counties in Michigan, US with elevated water As concentrations. The population-weighted water As in the six counties was 7.6 µg/L, based on 9152 water analyses. In the remainder of Michigan, it was 1.3 µg/L, based on 23,691 analyses. The standardised age- and race-specific mortality ratio for kidney disease in the six counties was 1.28 (1.15–1.42) in males and 1.38 (1.25–1.52) in females, based on 614 and 679 deaths. The results were similar when urban/rural counties were considered.

Hsueh et al. (2009) performed a case–control study in Taiwan, selecting 125 patients with CKD (eGFR < 60 mL/min per 1.73 m^2 for 3 months) and 229 controls with eGFR ≥ 60, frequency-matched for age, from a hospital pool. U-tiAs was significantly ($p < 0.001$) higher in cases (mean 31.95 µg/g creatinine) than in controls (20.71 µg/g creatinine). The adjusted OR in the upper tertile (based on u-tiAs in controls) was 4.34 (1.94–9.69).

Zheng et al. (2015) examined incident CKD in 3119 adults from the US Strong Heart Study. The adjusted HR for CKD (502 cases based on low eGFR, dialysis or kidney transplant at follow-up) was significantly associated with baseline u-tiAs. In the upper quartile of u-tiAs the HR was 1.6 (1.2–2.2) in a model adjusted for potential confounders, and 1.3 (0.9–1.8) in a model additionally adjusted for diabetes. The latter model would be over-adjusted if As associated diabetes is not a confounder but a factor in the causal chain.

Hsu, Hsieh, et al. (2017) examined the incidence of CKD in relation to concentrations of As in drinking water in a cohort of 6093 individuals in Taiwan followed up over 14 years. The adjusted HR for incident CKD (447 cases from National insurance registry) was significantly associated with water As (p for trend 0.01). The HR was 1.36 (1.05–1.76) in the category 50–150 µg/L.

Cheng et al. (2018) performed a nation-wide cohort study in Taiwan consisting of about 330,000 members of the National Health Insurance, free of CKD, living in 323 townships with measurements of As in drinking water. About one third of the cohort members had been exposed to elevated As (≥ 50 µg/L) in drinking water before the 1990s. Incidence of end-stage renal disease (ESRD, serious CKD, requiring dialysis treatment) in the cohort was followed up over 12 years and compared with exposure to As in drinking water aggregated on township level. The adjusted data (data on potential confounders available on individual level) hazard ratio of ESRD was 1.12 (1.06–1.19) in individuals with water As concentrations ≥ 50 µg/L, based on 5442 cases. The authors state in the text that the risk at water As concentrations 50–349 µg/L was similar as the risk at ≥ 350 µg/L, without presenting any details.

Other renal outcomes

Several studies examined associations between iAs exposure and biomarkers of renal function or damage. Such results may suffer from reverse causation, the kidney disease causing changes in renal biomarkers, or confounding due to physiological factors affecting both u-iAs excretion and renal biomarkers.

In a cross-sectional study in Korea As exposure was not significantly associated with tubular damage in the kidney assessed by biomarkers (Huang et al., 2009).

In a mixed cohort and cross-sectional analysis in Bangladesh in adults As exposure (assessed in water and urine) was positively associated with proteinuria prevalence at baseline but not associated with development of proteinuria over time (Chen, Parvez, et al., 2011).

In a mixed cohort and cross-sectional analysis in Bangladesh in adults a positive association of As exposure (assessed in water and urine) with both prevalence and incidence of dipstick haematuria was found (McClintock et al., 2014).

In two cross-sectional studies of 478 (Peters et al., 2014) and 379 (Peters, Hall, et al., 2015) adults in Bangladesh no significant association was found between As in water or u-tiAs and estimated GFR (eGFR) as a continuous variable.

Cheng et al. (2017) examined associations between As in water (aggregated on township) and rapid decrease of eGFR in 8854 individuals participating in two health screenings in a period of 12–24 months. The adjusted OR of a decrease of eGFR by > 5 mL/min/1.73 m^2 per year was 1.22 (1.05–1.42) in individuals with As in tap water ≥ 50 µg/L compared with < 50 µg/L.

In summary, three longitudinal studies from Taiwan (Cheng et al., 2018; Hsu, Hsieh, et al., 2017; Hsueh et al., 2009) and two from the US (Meliker et al., 2007; Zheng et al., 2015) show associations between As in drinking water or u-tiAs and risk of CKD. Although one of the studies (Meliker et al., 2007) had an ecological study design, there is sufficient evidence of an association between low to moderate exposure to iAs and risk of CKD. For biomarkers of renal damage, the evidence of an association is insufficient.

The studies meeting the inclusion criteria for renal effects are described in Table 31.

TABLE 31 Key epidemiological studies on renal effects and As exposure.

Reference study population design	Outcome definition	Population size (*n*) case/control	Arsenic exposure	Results	Additional information/confounders
Meliker et al. (2007) Population in six counties in Michigan, USA, ecological study	Mortality from kidney disease	Population in the six counties 740,000 and 1293 deaths 1979–1997. Compared to the entire state	Population-weighted w-As in the six counties 7.6 µg/L and 1.3 for the rest of Michigan	SMR 1.28 (1.15–1.42) in males and 1.38 (1.25–1.52) in females	Adjusted for age and race by design
Hsueh et al. (2009) Taiwan Case control study	CKD (eGFR < 60 over at least 3 months) from hospital files	125 cases and 229 controls from hospital pool of patients with eGFR	u-tiAs, µg/g creatinine (cases/controls) ≤ 11.78 (19/75) 11.78–20.74 (30/78) > 20.74 (76/76)	OR 1.0 1.41 (0.62–3.19) 4.34 (1.94–9.69)	Adjusted for age, sex, education, ethnicity, smoking, coffee, analgesics, hypertension, diabetes from interviews
Zheng et al. (2015) USA (Strong Heart Study) Cohort study	Incident CKD based on eGFR < 60, dialysis or kidney transplant	3119 individuals free of CKD at baseline. 502 incident cases	u-tiAs, µg/g creatinine (cases/non-cases) ≤ 5.7 (109/663) 5.8–9.7 (110/671) 9.7–15.6 (128/656) ≥ 15.6 (155/627)	HR by quartiles 1 1.1 (0.8–1.4) 1.2 (0.9–1.7) 1.6 (1.2–2.2)	Adjusted for age, gender, location (state), education, smoking status, BMI, hypertension medication, SBP and baseline eGFR. Also, cross-sectional analyses were performed, showing a positive association (reverse causation)
Hsu, Hsieh, et al. (2017) Taiwan Cohort study	Incident CKD from National Health Insurance Registry over 14 years	6093 individuals free of CKD at baseline, 447 incident cases	w-As (µg/L) (individuals/cases) ≤ 10 (2029/132) 10.1–49.9 (1850/140) 50–149.9 (1281/101) ≥ 150 (933/74)	HR 1.0 1.15 (0.91–1.46) 1.36 (1.05–1.76) 1.35 (1.02–1.80)	Adjusted for age, sex, BMI, education, smoking, alcohol, regular analgesic use, hypertension, diabetes, dyslipidaemia.
Cheng et al. (2018) Cohort study Taiwan Cohort study	Incident End Stage Renal Disease (ESRD = CKD requiring dialysis) in members of National Health Insurance Registry over 12 years, 1998–2010	362,505 individuals, born before 1958 and free of ESRD at baseline. 5442 incident cases of ESRD	w-As (µg/L) aggregated by 323 townships < 50 ≥ 50	HR 1.0 1.12 (1.06–1.19)	Adjusted for age, sex, income, urbanisation level, hypertension, hyperlipidaemia, coronary artery disease, diabetes, anaemia, congestive heart failure. Many individuals in the category ≥ 50 µg/L had very high w-As, but the authors state in the text that the risk was similar in a category 50–349 µg/L and ≥ 350 µg/L without presenting details

TABLE 31 (Continued)

Reference study population design	Outcome definition	Population size (*n*) case/control	Arsenic exposure	Results	Additional information/confounders
Chen, Parvez, et al. (2011), Bangladesh/mean 37 years, cohort for follow-up, cross-sectional for baseline proteinuria (HEALS)	Proteinuria	Proteinuria yes/no 1030/9130	w-As (μg/L) Q1: 0.1–7 Q2:8–39 Q3: 40–91 Q4: 92–179 Q5: 180–864	Cohort: HR (95% CI): 1.00 (ref), 0.84 (0.70–1.01), 0.79 (0.65–1.07), 0.85 (0.70–1.04), 0.84 (0.69–1.06), *p*: NS. Cross sectional: OR (95% CI): 1.00 (ref), 1.01 (0.79–1.31), 1.33 (1.04–1.70), 1.54 (1.22–1.96), 1.65 (1.31–2.09), $p < 0.01$	Adjusted for urinary creatinine, age, gender, BMI, cigarette smoking status, education length, SBP, DBP, diabetes status. Also, data for u-As changes over time
Huang et al. (2009), Korea/unknown age, cross sectional	Kidney biomarkers of (tubular) toxicity: ß2-microglobulin (β2 MG), *N*-acetyl-b-D-glucosaminidase (NAG) activity in urine	Total 290	u-tiAs μg/g (50th percentile) < 3.94 versus > 3.94	High versus low u-As mean (SD): β2 MG: 74.3 (152) versus 78.3(171), *p*: NS; NAG: 1.82 (1.91) versus 1.66 (2.36), *p*: NS. No significant correlation for u-As and β2-MG or NAG	No data for adjustments
McClintock et al. (2014), Bangladesh/18–75 years, cross-sectional (prevalence of hematuria at baseline) and cohort (incidence of hematuria at follow-up) (HEALS)	Haematuria (dipstick test)	Cross-sectional: 1189/6654; cohort 5362/949	w-As (mean 99 μg/L), 0.1–3 3–25 25–66 66–142 142–949.1 per SD increase	Cross sectional, OR (95%): 1.00 (Ref) 1.07 (0.87–1.31) 0.95 (0.76–1.17) 1.30 (1.06–1.59) 1.66 (1.37–2.02) 1.20 (1.13–1.27) $p < 0.01$ Cohort, HR (95%): 1.00 (Ref) 1.10 (0.88–1.37) 0.96 (0.77–1.20) 1.05 (0.84–1.31) 1.34 (1.09–1.65) 1.10 (1.04–1.16), $p < 0.01$	Adjusted for age, BMI, cigarette smoking status, education length, SBP, DBP, occupational dye exposure and change in u-As before incident visit

(Continues)

TABLE 31 (Continued)

Reference study population design	Outcome definition	Population size (*n*) case/control	Arsenic exposure	Results	Additional information/confounders
Peters et al. (2014), Bangladesh/mean 36 years, cross-sectional (HEALS)	Renal function using plasma cystatin C and calculated the estimated glomerular filtration rate (eGFR)	Total 478, CKD stages 1–5: 95	w-As (mean 96.5 µg/L)	eGFR prediction and log u-As B(SE): 22.55 (1.44), *p*: NS, *r*-square: 29. eGFR prediction and log water-As B(SE): 20.67 (0.56), *p*: NS, r-square: 29.2	Adjusted for log(age), sex, current smoking, log (u-creatinine), recruitment year. Also data for urinary methylated metabolites
Peters, Hall, et al. (2015), Peters, Liu, et al. (2015), Bangladesh/30–65 years, cross-sectional (FOX)	Renal function using plasma cystatin C and calculated the estimated glomerular filtration rate (eGFR)	Total 374 eGFR< 90 versus > 90: 153/222	w-As (mean 138 µg/L), w-As (mean 138 µg/L)	Nean change (95% CI) in eGFR (mL/min/1.73 m^2) for a 10% increase in w-As: −0.03 (−0.12, 0.07), *p*: NS; u-As: −0.16 (−0.37, 0.04), *p*: NS GFR < 90 versus > 90: mean (SD) w- As µg/L: 1legend 40.67 (129.4) versus 135.9 (120.1), *p*: NS; u-As µg/L: 248.1 (215.3) versus 219.4 (196.4), *p*: NS	Adjusted for log (age), sex, log (BMI), ever smoking. Also, data for glutathione

Abbreviations: As, arsenic; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ESRD, end stage renal disease; FOX, Folate and Oxidative Stress; GFR, glomerular filtration rate; HEALS, Health Effect of Arsenic Longitudinal Study; HR, hazard ratio; MG, macroglobulin; n, number; NAG, *N*-acetyl-b-D-glucosaminidase; NS, not significant; OR, odds ratio; Q, quantile; ref, reference; SBP, systolic blood pressure; SD, standard deviation; SE, standard error; SMR, standardised mortality ratio; tiAs, total inorganic arsenic; USA, United States of America; u-As, urinary arsenic; u-tiAs, total urinary inorganic arsenic (sum of iAs and its methylated metabolites MMA and DMA); vs., versus; w-As, water arsenic.

3.2.2.12 | *Other effects*

For the present Opinion, the CONTAM Panel identified, from a literature search, 26 studies on associations between As exposure and effects other than those discussed above from a literature search (see Section 2 on methodology). Out of these, 12 studies did not meet the inclusion criteria (Akbal et al., 2014; Burchiel et al., 2014; Cárdenas-González et al., 2016; Jimenez-Cordova et al., 2018; Jochem et al., 2016; Gong et al., 2015; Linares et al., 2021; Galvez-Fernandez et al., 2021; Osorio-Yáñez et al., 2021; Ruan et al., 2022; Rahman, Islam, et al., 2021; Wang, Ding, et al., 2021).

Fourteen studies that fulfilled the eligibility criteria were further considered (Table 32).

Mortality

In a cohort study in Bangladesh in adults chronic As exposure through drinking water was associated with an increase in the mortality rate (Argos et al., 2010).

In a cohort study with a 7-years follow-up in Bangladesh in individuals 5–18 years, water As exposure was associated with increased risk of deaths from all-causes, cancer and cardiovascular-related conditions (Rahman et al., 2013).

In the same cohort with a 13-years follow-up, higher As concentration in water increased the risk of mortality due to cerebrovascular-, cardiovascular- and respiratory disease but no association was found for cancer related mortality (Rahman et al., 2019).

In a cohort study in Bangladesh in subjects > 15 years of age, As exposure through drinking water was associated with excess mortality after 20–30 years of exposure (Sohel et al., 2009).

In a cross-sectional study in China heart disease mortality but not all-cause-, cancer- or stroke related mortality was associated with As exposure in water (Wade et al., 2009).

Endocrine effects

In a birth cohort in Bangladesh in children < 15 years of age increased levels of prenatal As exposure in water were associated with older age at menarche (2.8 months delay), with exposure above Bangladesh's acceptable As level (≥ 50 µg/L) (Rahman, Kippler, et al., 2021).

Viral infections serology

In a cross-sectional analysis from NHANES 2003–2004, 2009–2010 in US individuals 6–49 years, U-As was inversely associated with Varicella zoster virus (VZV) IgG seroprevalence (Cardenas, Smit, et al., 2015).

In a cross-sectional study from NHANES 2003–2012 in US individuals > 6 years old, As exposure was positively associated with the seroprevalence of total anti-hepatitis A virus (HAV) in participants receiving > 2 doses of HAV vaccine and for individuals unable to recall their immunisation history (Cardenas et al., 2016).

In a cross-sectional study from NHANES 2003–2014 in US individuals > 6 years, higher u-As levels were associated with a greater odd of having a serological classification consistent with a past (natural) hepatitis B infection (HBV) (Cardenas et al., 2018).

Hepatic effects

In a cross-sectional study in Bangladesh in individuals aged 15–60 years, a significant association between As exposure (assessed in water, hair, nail) and serum hepatic enzymes activity (alanine transaminase (ALT), argininosuccinate lyase (ASL), alkaline phosphatase – ALP) was found (Islam et al., 2011).

In a cross-sectional analysis of NHANES 2005–2014 in US subjects > 12 years of age there was a positive association between U-As exposure and risk of non-alcoholic fatty liver disease (NAFLD) estimated by increased levels of ALT (Frediani et al., 2018).

Hearing loss

In a cross-sectional study in young adults in Bangladesh, As in toenails but not in urine was associated with hearing loss (Li, Ohgami, et al., 2018).

In a cross-sectional study in adolescents and young adults in Iran, As in water was not significantly associated with hearing loss (Shokoohi et al., 2021).

Allergy

In a birth cohort in Taiwan in children aged < 4 years, prenatal exposure assessed by u-As was associated with a higher risk of atopic dermatitis in young children, most evident when the mothers had a history of dermatitis (Tsai, Wang, et al., 2021).

In summary, there is insufficient evidence for a causal association between low to moderate exposure to iAs and liver function, endocrine function (not covered in other outcomes mentioned previously), hearing loss, allergy, anaemia and reduced bone mineral density. For these outcomes the number of studies is very limited. Regarding mortality the major

disease groups affecting mortality, such as cancer, ischemic heart disease, stroke, chronic kidney disease and infant mortality have already been assessed in previous sections. Therefore, it is not relevant to consider separately the evidence for all-cause mortality.

TABLE 32 Key epidemiological studies on other effects and As exposure.

Reference, study population age, design	Outcome definition	Population size (*n*) case/control	Arsenic concentration/ exposure	Results	Additional information/confounders
Mortality					
Sohel et al. (2009), Bangladesh/> 15 years, cohort study	Cancer, cardiovascular mortality, infectious, nonaccidental mortality	Deaths/survived: 9015/106888	w-As (μg/L) (average in well water) < 10 10–49 50–149 150–299 > 300	HR (95% CI) for cancer mortality: 1.00 (ref), 1.10 (0.77–1.59), 1.44 (1.06–1.95), 1.75 (1.28–2.40), 1.56 (1.06–2.30), *p* trend: 0.007. HR (95% CI) for cardiovascular mortality: 1.00 (ref), 1.03 (0.82–1.29), 1.16 (0.96–1.40), 1.23 (1.01–1.51) 1.37 (1.07–1.77), *p* trend: 0.026. HR (95% CI) for infectious mortality: 1.00 (ref), 1.09 (0.92–1.30) 1.30 (1.13–1.49), 1.51 (1.31–1.75), 1.59 (1.33–1.91), *p* trend: < 0.001. HR (95% CI) for nonaccidental mortality: 1.00 (ref), 1.16 (1.06–1.26), 1.26 (1.18–1.36), 1.36 (1.27–1.47), 1.35 (1.23–1.48), *p* trend: < 0.001	Adjusted for age, sex, asset score, education
Wade et al. (2009), China/age data not reported, cross sectional study	All-cause mortality, cancer mortality, heart disease mortality, stroke mortality	Deaths/ survived: 572/12600	w-As, for 50 μg/L As increase	IRR (95% CI) and all-cause mortality: 1.02 (0.94, 1.11), *p*: NS; cancer mortality: 1.07 (0.89, 1.28), *p*: NS; heart disease: 1.12 (1.01, 1.23), *p*: 0.034; stroke: 0.82 (0.65, 1.03), *p*: NS	Adjusted for age, sex, education, smoking, drinking, farm work. Data also for different time of exposure
Argos et al. (2010), Bangladesh/18–75 years, cohort study (HEALS)	All-cause mortality, mortality due to chronic disease	Deaths/survived: 407/11339	w-As (μg/L) 0–10, 10.1–50, 50.1–150, > 150	HR (95% CI) for all-cause mortality: 1.00 (ref), 1.34 (0·99–1·82), 1.09 (0·81–1·47), 1.68 (1·26–2·23). HR (95%CI) for chronic-disease mortality: 1.00 (ref), 1.33 (0·94–1·87), 1.22 (0·87–1·70), 1.68 (1·21–2·33)	Adjusted for age, sex, body-mass index, systolic blood pressure, education, smoking status. Data also for As dose and relation to change in u-As over time

(Continues)

TABLE 32 (Continued)

Reference, study population age, design	Outcome definition	Population size (*n*) case/control	Arsenic concentration/ exposure	Results	Additional information/confounders
Rahman et al. (2013), Bangladesh/5–18 years, cohort (7-years follow-up)	All-cause mortality, cancer and cardiovascular mortality	Deaths/survived: 185/58221	Baseline w-As (μg/L) <10 10–50 51–150 151–300 >300 Cumulative As exposure (μg-years/L) <1000 1000–4000 >4000	HR (95% CI) for baseline w-As and all-cause mortality: 1.00 (ref), 1.13 (0.65–1.96), 0.81 (0.45–1.46), 1.35 (0.92–1.97), 1.51 (1.01–2.23), *p* trend <0.05. HR (95% CI) for cumulative w-As and all-cause mortality: 1.00 (ref), 1.17 (0.84–1.65), 1.90 (1.25–2.89), *p* trend <0.05. HR (95%CI) for baseline w-As and cancer and cardiovascular mortality: 1.00 (ref), 1.53 (0.51–4.57), 1.29 (0.43–3.87), 2.18 (1.15–4.16), *p* trend <0.05.	Adjusted for baseline age, educational attainment, socioeconomic status. Data also for time-weighted lifetime average arsenic in well water.
Rahman et al. (2019), Bangladesh/5–18 years, cohort (13-years follow-up)	Cancer and cerebrovascular-cardiovascular-respiratory mortality	Deaths/survived: cancer 48/58358; Cerebro vascular-cardiovascular-respiratory: 40/58366	Current w- As (μg/L) <90.9 90.9–223.1 >223.1 cumulative w-As exposure (μg-years/L) <1013.3 1013.3–2711.0 >2711 average or lifetime average As in well water (μg/L) <90.9 90.9–223.1 >223.1	HR (95% CI) for average w-As and cancer mortality: 1.00 (ref), 1.2 (0.6–2.3), 0.8 (0.4–1.6), *p* trend: NS. HR (95% CI) for cumulative w-As and cancer mortality: 1.00 (ref), 0.9 (0.5–1.8), 0.7 (0.3–1.5), *p* trend: NS. HR (95%CI) for average w-As and cardio-cerebro-respiratory mortality: 1.00 (ref), 2.7 (1.0–7.6), 4.8 (1.8–12.8), *p* trend: 0.01. HR (95%CI) for cumulative water As and cardio-cerebro-respiratory mortality: 1.00 (ref), 4.0 (1.3–12.0), 5.1 (1.7–15.1), *p* trend: 0.01	Adjusted for baseline age, sex, educational attainment, socioeconomic status. Data also for time-weighted lifetime average arsenic in well water.
Endocrine effects					
Rahman, Kippler, et al. (2021), Bangladesh/1–15 years, birth cohort study (MINIMat/AsMat)	Age at menarche	Total 809	w-As, median 80 μg/L (IQR 2–262). <10 10–49 50–99 100–199	HR (95% CI): 1.0 (Ref), 0.82 (0.59–1.14), 0.89 (0.58–1.36), 0.82 (0.64–1.05)	Adjusted for maternal socioeconomic status, education, BMI. Data also for As level >200 μg/L

TABLE 32 (Continued)

Reference, study population age, design	Outcome definition	Population size (*n*) case/control	Arsenic concentration/ exposure	Results	Additional information/confounders
Viral infections serology					
Cardenas, Smit, et al. (2015), USA/6–49 years, cross-sectional (NHANES 2003–2004, 2009–2010)	Seroprevalence of VZV IgG antibody	Seropositive/ seronegative 3250/98	u-tiAs (1) geometric mean 6.57 µg/L (95% CI: 6.26, 7.9). u-As minus AsB / AsC (2) geometric mean (total As minus AsB and AsC) 5.64 µg/L (95% CI: 5.20, 6.12). 1-unit increase in ln-transformed u-As (1) (µg/L) 1-unit increase u-As (2)	u-As (1) GM (SE) seropositive versus seronegative: 6.77 (1.02) versus 8.31 (1.08), *p*: 0.01; u-As (2) GM (SE) seropositive versus seronegative: 5.85 (1.04) versus 7.62 (1.12), *p*: 0.02. OR (95% CI): 1.87 (1.03, 3.44) 1.40 (1.00, 1.97)	Adjusted for age, sex, race, family poverty–income ratio, BMI classification, ln urinary creatinine, survey cycle.
Cardenas et al. (2016), USA/> 6 years, cross-sectional study (NHANES 2003–2012)	Hepatitis A antibodies (total anti-HAV: IgG and IgM)	Seropositive/ seronegative 5064/6028	u-tiAs (1) geometric mean 6.34 µg/L (SE 1.01). u-tAs minus AsB, AsC (2) geometric mean (total As minus AsB and AsC) 5.06 µg/L (SE 1.02) 1-unit increase in ln-transformed u-As (1) (µg/L) 1-unit increase u-As (2)	OR (95% CI): > = 2 doses vaccination 1·42 (1·11–1·81); < 2 doses: 1·46 (0·83–2·59; 0 dose: 1·12 (0·98–1·30); unknown vaccination history: 1·75 (1·22–2·52), > = 2 doses vaccination: 1·17 (1·04–1·31) < 2 doses: 1·26 (0·95–1·67) 0 dose: 1·07 (0·99–1·16) unknown vaccination history: 1·20 (0·97–1·48)	Adjusted for log-transformed creatinine, age, sex, race, family income/poverty ratio, country of birth, body mass index and survey year.
Cardenas et al. (2018), USA/> 6 years, cross-sectional study (NHANES 2003–2014)	Hepatitis B antibodies (total anti-HAV: IgG and IgM)	Current HBV/ past HBV infection/ Vaccinated/ seronegative 33/636/3491/ 8520	u-As: DMA residual adjusted for arsenobetaine For 1-unit increase in ln-transformed u-As (DMA residual)	OR (95% CI): for natural infection versus susceptible: 1.40 (1.15, 1.69); natural infection versus vaccine induced immunity: 1.65 (1.34, 2.04); seronegative versus vaccine induced immunity: 1.18 (1.05, 1.33)	Adjusted for log-transformed creatinine, age, sex, race, family poverty-income ratio, country of birth, BMI, survey year, log-transformed serum cotinine, recent seafood consumption, self- reported Hepatitis B immunisation. Data also for how many doses of vaccination.

(Continues)

TABLE 32 (Continued)

Reference, study population age, design	Outcome definition	Population size (*n*) case/control	Arsenic concentration/ exposure	Results	Additional information/confounders
Hepatic effects					
Islam et al. (2011), Bangladesh/15–60 years, cross-sectional study	AST, ALT, ALP	Quartiles Q1/ Q2/Q3/Q4: 50/50/50/50	w-As (μg/L): Q1: 0.11–24.7, Q2: 34–142, Q3: 145–242, Q4:249–546 hair As: Q1: 0.05–1.43, Q2: 1.57–2.80, Q3: 2.81–5.52, Q4: 5.66–37.24 nail As: Q1: 0.15–3.17, Q2: 3.21–6.25, Q3: 6.26–11.27, Q4: 11.4–37.42	Coefficient (95% CI) for w-As and ALP: 1.0 (ref), 0.039 (−0.008, 0.085), 0.087 (0.041, 0.134), 0.165 (0.119, 0.212). W-As and AST: 1.0 (ref), 0.025 (−0.020, 0.070), 0.023 (−0.022, 0.067), 0.124 (0.080, 0.169). w-As and ALT: 1.0 (ref), 0.060 (−0.011, 0.132), 0.071 (0.00, 0.143) 0.186 (0.115, 0.257). Hair As and ALP: 1.0 (ref), 0.028 (−0.023, 0.078), 0.044 (−0.005, 0.093), 0.117 (0.066, 0.168). Hair As and AST: 1.0 (ref), 0.028 (−0.020, 0.075), 0.054 (0.008, 0.099), 0.096 (0.049, 0.144). Hair As and ALT: 1.0 (ref), 0.064 (−0.010, 0.139), 0.086 (0.014, 0.158), 0.151 (0.076, 0.225). Nail As and ALP: 1.0 (ref), 0.037 (−0.014, 0.088), 0.057 (0.005, 0.110), 0.109 (0.055, 0.163). Nail As and AST: 1.0 (ref), −0.007 (−0.055, 0.040), 0.010 (−0.039, 0.060), 0.062 (0.012, 0.113). Nail As and ALT: 1.0 (ref), 0.043 (−0.033, 0.118), 0.055 (−0.024, 0.133), 0.084 (0.004, 0.165)	Adjusted for age, sex, BMI, smoking habit, skin lesions

TABLE 32 (Continued)

Reference, study population age, design	Outcome definition	Population size (*n*) case/control	Arsenic concentration/ exposure	Results	Additional information/confounders
Frediani et al. (2018), USA/> 12 years, cross-sectional study (NHANES 2005–2014)	ALT as a biomarker for NAFLD	NAFLD yes/no: 2713/5805	u-tAs minus AsB/AsC arsenocholine) µg/L Q1: < 2.42 Q2: 2.42–4.08 Q3: 4.08–6.99 Q4: > 6.99	 1.00 (ref) 1.2 (0.7, 1.9), 1.6 (1.0, 2.8), 2.0 (1.2, 3.4)	Adjusted for age, survey cycle, gender, PIR, BMI Weight status, race/ethnicity.
Hearing loss					
Li et al. (2018), Bangladesh/23–45 years, cross-sectional study	Hearing threshold	Total 145, high versus low toenail As group: 97/48	Toenail As High > 0.6 µg/g Low < 0.6 µg/g	High versus low OR (95% CI): 1.28 (0.43–3.83) for 1 kHz, 4.27 (1.51–12.05) for 4 kHz, 3.91 (1.47–10.38) for 8 kHz, 4.15 (1.55–11.09) for 12 kHz	Adjusted for age, sex, smoking history, BMI.
Shokoohi et al. (2021), Iran/10–49 years, cross-sectional	Hearing threshold (Pure Tone Audiometry)	Exposed/non-exposed 120/120	w-As (µg/L) non-exposed: 0.179 exposed: 200 (region A), 76.6 (region B), 74.5 (region C)	Exposed versus non-exposed OR (95% CI): 2.03 (0.96–4.31) overall, 1.49 (0.24–9.18) for 2 kHz, 2.07 (0.92–4.62) for 4 kHz, 1.85 (0.74–4.66) for 8 kHz	Adjusted for age, smoking.
Allergy					
Tsai, Wang, et al. (2021), Taiwan/4 years, birth cohort study (TMICS)	Atopic dermatitis (questionnaire)	Dermatitis yes/no: 110/260	u-tiAs (inorganic) 30 trimester of pregnancy 2-fold increase u-As	Dermatitis versus control u-As µg/g creatinine median (IQR): 30.91 (27.51–37.25) versus 28.62 (25.97–33.14), $p < 0.001$. OR (95% CI): 2.42 (1.33–4.39)	Adjusted for child's sex, parental allergies, geographic area, exposure to tobacco smoke during pregnancy, exposure to tobacco smoke at age 4 years, maternal educational level. Data also for sensitivity analysis based on the existence of maternal allergy.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; As, arsenic; AsB, arsenobetaine; AsC, arsenocholine; AsMat, Health Consequences of Arsenic in Matlab; AST, aspartate transaminase; BMI, body mass index; CI, confidence interval; DMA, sum of dimethylarsinous acid and dimethylarsinic acid; GM, geometric mean; HAV, hepatitis A virus; HBV, hepatitis B virus; HEALS, Health Effects of Arsenic Longitudinal Study; HR, hazard ratio; IgG, immunoglobulin G; IgM, immunoglobulin M; IQR, interquartile range; IRR, incidence rate ratio; kHz, kilohertz; MINIMat, Maternal and Infant Nutrition Interventions in Matlab; MMA, sum of monomethylarsonous acid and monomethylarsonic acid; *n*, number; NAFLD, non-alcoholic fatty liver disease; NHANES, National Health and Nutrition Examination Survey; NS, not significant; OR, odds ratio; PIR, poverty income ratio; Q, quartile; ref, reference; SE, standard error; tAs, total arsenic; TMICS, Taiwan Maternal and Infant Cohort Study; u-As, urinary arsenic; u-tiAs, urinary total inorganic arsenic (sum of iAs and its methylated metabolites MMA and DMA); USA, United States of America; VZV, Varicella-Zoster Virus; w-As, water arsenic.

3.2.3 | Critical effects

In the sections on Observations in humans (Section 3.2.2), the CONTAM Panel assessed a large number of epidemiological studies on different adverse health outcomes. Most of these studies were not available for the previous opinion in 2009. Exposure was based on As in drinking water, urine, toenails or in hair.

The following outcomes were considered as potential critical effects, because for these adverse effects the evidence of association with exposure to low to moderate levels of iAs was considered sufficient to assume causality and because they were considered biologically plausible: lung cancer, bladder cancer, skin cancer, skin lesions, decreased birth weight, spontaneous abortion, stillbirth, infant mortality, congenital heart disease, neurodevelopmental effects, ischemic heart disease and atherosclerosis. Additional information about biologically plausible mechanisms per endpoint is provided in the text below.

3.2.3.1 | *Skin, bladder and lung cancer*

The CONTAM Panel considers the evidence from epidemiological studies sufficient for an association between low to moderate exposure to iAs and increased risk of basal and squamous cell carcinomas of the skin, bladder and lung.

There are several biologically plausible mechanisms for arsenic causing cancer in the tissues where it is metabolised, distributed to or excreted. iAs can induce DNA damage via generation of RONS (reactive oxygen and nitrogen species) and interferes with genome maintenance systems. iAs has been shown to increase the frequency of CA and MN in chronically exposed populations, to cause epigenetic alterations (e.g. changes in DNA-methylation, histone post-translational modifications), to contribute to the epithelial-to-mesenchymal transition during cell transformation and to target key signalling pathways associated with cancer (see Sections 3.1.2. Biomarkers and 3.1.3. Genotoxicity).

These genotoxic and epigenetic effects have been detected in a variety of *in vitro* and *in vivo* model systems including cells relevant for these cancer types, such as primary human keratinocytes and lung cells, and exfoliated urothelial cells derived from exposed subjects where increased frequency of MN has been reported. Moreover, there are characteristic features of arsenic-induced skin and lung cancer. Bowen's disease is the most common skin cancer induced by arsenic. Cases of Bowen's disease related to arsenic exposure tend to have multi-focal cancer in sun-protected skin (Yu et al., 2006), whereas cases not related to arsenic exposure mainly have solitary cancer in sun-exposed skin (Yu et al., 2006). Recently a compelling study (Speer et al., 2023), has provided evidence that iAs acts as a powerful co-mutagen and co-carcinogen alongside UV radiation in a mouse skin carcinogenesis model. By examining a group of human basal cell carcinomas and melanomas, this study has successfully identified, within a subset of tumours, the same distinctive mutational pattern resulting from the combined exposure to these two environmental carcinogens in the mouse model. The carcinogenicity of iAs on lung seems to be cell-type specific: iAs-related lung tumours are more often squamous cell carcinomas (Kuo et al., 2017). In addition, there is some preliminary evidence of specific genetic and epigenetic changes in tumours seen after iAs exposure when compared with histologically matched tumours that developed in an iAs-free environment (reviewed in Hubaux et al., 2013).

The CONTAM Panel considers the association between low to moderate exposure to iAs and cancers of the skin, bladder and lung to be causal.

3.2.3.2 | *Skin lesions*

The CONTAM Panel considers the evidence from epidemiological studies sufficient for an association between low to moderate exposure to iAs and increased risk of skin lesions, i.e. pigmentation changes and hyperkeratosis.

Arsenic tends to accumulate in the skin and there are several biologically plausible mechanisms for arsenic causing skin lesions. Some of the mechanisms are overlapping with skin cancer, since arsenic-related skin lesions are a risk factor for skin cancer. The CONTAM Panel considers the association between low to moderate exposure to iAs and skin lesions to be causal. It should be noted that because these studies were performed in low and medium income regions in Bangladesh and China and nutrition and health status are important modifying factors, it is difficult to translate these risks to populations with more adequate nutrition such as in Europe.

3.2.3.3 | *Decreased birth weight*

The CONTAM Panel considers the evidence from epidemiological studies performed in Bangladesh (Kile, Cardenas, et al., 2016; Rahman et al., 2009) sufficient for an association between low to moderate exposure to iAs and decreased birth weight, while results from other countries (Chile, Taiwan, Mongolia, Mexico, US) are inconsistent and the evidence therefore insufficient.

Arsenic readily crosses the placenta. Proposed mechanisms for decreased birth weight include disruption of placental vascular function, inflammation, RONS formation and epigenetic effects on the fetus (Bloom et al., 2014). The CONTAM Panel considers this association to be causal. However, the average birth weight in Europe is much higher and undernutrition is less common. Therefore, it is uncertain if an association between iAs exposure and birth weight is present in European populations.

3.2.3.4 | *Spontaneous abortion and stillbirth*

The CONTAM Panel considers the evidence from epidemiological studies performed in Bangladesh sufficient for an association between low to moderate exposure to iAs and increased risk of spontaneous abortion and stillbirth. Embryotoxic

effects at high doses of iAs have been shown in animal studies (Wang et al., 2006). Specific mechanisms proposed regarding spontaneous abortion and stillbirth include enzyme inhibition due to thiol reactivity, and cytotoxicity due to altered cell–cell signalling and RONS generation (Milton et al., 2017). The mechanisms mentioned above regarding birth weight are also relevant. The CONTAM Panel considers the association between exposure to arsenic and spontaneous abortion and stillbirth to be causal. However, as discussed above on birth weight, the relevance for Europe is unclear since maternal and fetal undernutrition, low birth weight (BW) and preterm birth (PTB) in Bangladesh is much more common than in Europe. These factors are likely mediators, increasing the risk of spontaneous abortion and stillbirth.

3.2.3.5 | *Infant mortality*

The CONTAM Panel considers the evidence from epidemiological studies sufficient for an association between low to moderate exposure to iAs and increased risk of infant mortality, both in the first 28 days (neonatal period) and later. Associations have been shown in Bangladesh, Mongolia and Chile. Decreased birth weight and preterm birth likely contribute to increased risk of infant mortality. The same is true for effects of iAs on lung function and possible risk of respiratory disease in infancy. Therefore, the CONTAM Panel considers the association of iAs exposure and infant mortality to be causal.

3.2.3.6 | *Congenital heart disease*

The CONTAM Panel considers the evidence from epidemiological studies sufficient for an association between low to moderate exposure to iAs and increased risk of congenital heart disease. The key epidemiological studies by Rudnai et al. (2014) from Hungary and by Richter et al. (2022) from Denmark, are large and of good quality. However, the CONTAM Panel notes that the exposure-response relation between water As concentrations and risk of congenital heart disease seemed to be supralinear. In the study by Richter et al. (2022) most of the increase in risk was reported from the reference category (< 0.5 μg/L) up to a few μg/L, and in the study by Rudnai et al. (2014), the increased risk was mainly found when mothers' drinking water As was 10–30 μg/L.

The teratogenicity of iAs in experimental animals is well established (EFSA CONTAM Panel, 2009), but the mechanisms are not well characterised. At least two studies in experimental animals have shown heart malformations, mainly septum defects (Lin, Zhuang, et al., 2018; Na et al., 2020). Folate supplementation protected against heart malformations in both these studies. With the support from experimental studies, it seems reasonable to assume that the associations reported in humans are causal.

3.2.3.7 | *Neurodevelopmental effects*

The CONTAM Panel considers the evidence from epidemiological studies sufficient for an association between low to moderate exposure to iAs and effects on cognitive function during childhood.

Several biologically plausible mechanisms for impaired neurodevelopment, including cognition, have been described such as epigenetic alterations (e.g. changes in DNA methylation profiles and histone post-translational modifications) alterations in neurotransmitter homeostasis, oxidative stress, impaired DNA repair, mitochondrial dysfunction and neuroinflammation (reviewed in Thakur et al., 2021). The CONTAM Panel considers the association between low to moderate exposure to iAs and impaired cognition during childhood to be causal.

3.2.3.8 | *Ischemic heart disease*

The CONTAM Panel considers the evidence from epidemiological studies sufficient for an association between low to moderate exposure to iAs and ischemic heart disease.

Several biologically plausible mechanisms have been described, e.g. inflammatory responses, increased ROS in endothelial cells and signs of compromised endothelial-dependent vasodilatation (Chowdhury et al., 2018; Ellinsworth, 2015; Karachaliou et al., 2021). The CONTAM Panel considers the association between low to moderate exposure to iAs and ischemic heart disease to be causal.

3.2.3.9 | *Carotid artery atherosclerosis*

The CONTAM Panel considers the evidence from epidemiological studies sufficient for an association between low to moderate exposure to iAs and carotid artery atherosclerosis. As shown in Table 26 of Section 3.2.2, several of the studies show associations between As in water or urine and carotid artery plaque or intima media thickness (IMT). This is biologically plausible, and likely mechanisms are endothelial dysfunction and injury in the arterial vessels, in line with the well-known risk of so-called Blackfoot disease at high iAs exposure. Endothelial damage and inflammation increase the risk of plaque formation (Karachaliou et al., 2021). Carotid artery atherosclerosis increases the risk of ischemic stroke and myocardial infarction (Spence et al., 2002). The CONTAM Panel considers the association between low to moderate exposure to iAs and carotid artery atherosclerosis to be causal.

3.2.3.10 | *Lung function*

The CONTAM Panel considers the evidence from epidemiological studies sufficient for an association between low to moderate exposure to iAs and impaired lung function, in children as well as in adults. Several biologically plausible mechanisms have been described, including cellular injury caused by inflammation and increased ROS generation (Sanchez et al., 2018). The CONTAM Panel considers the association between low to moderate exposure to iAs and impaired lung function to be causal.

3.2.3.11 | *Chronic kidney disease*

The CONTAM Panel considers the evidence from epidemiological studies sufficient for an association between low to moderate exposure to iAs and risk of CKD. Several mechanisms for arsenic-mediated nephrotoxicity have been described including the production of ROS and other free radicals, inflammation and apoptosis (Robles-Osorio et al., 2015). The CONTAM Panel considers the association with iAs exposure to be causal.

3.2.4 | Dose–response analyses

3.2.4.1 | *Previous dose response analyses*

In the previous Opinion on arsenic (EFSA CONTAM Panel, 2009) the data for cancers of the bladder, lung and skin, and skin lesions were considered as possibly providing an appropriate Reference Point.

In the previous Opinion on arsenic, it was noted that the EFSA guidance on the use of benchmark dose modelling (EFSA CONTAM Panel, 2009) provided neither guidance on an appropriate BMR for human data nor on calculation of confounder-adjusted BMDs and BMDLs. Because the individual data from the studies were not available to the CONTAM Panel, it estimated a 1% extra risk (and its lower 95% CI) based on the unadjusted incidence data reported. The Panel noted that although it would have been possible to estimate a 5% or 10% extra risk, a 1% extra risk would be within the observed data range and was therefore used for dose response modelling.

The CONTAM Panel calculated BMCLs for two studies on dermal lesions considered as potentially relevant (in all of which the exposure metric was iAs concentrations in drinking water) and used BMCLs for lung and bladder cancer calculated by NRC (2001) and for skin cancer identified a so-called change point for the water level based on Karagas et al. (2002). These BMCLs were then transformed into ranges of BMDLs by applying assumptions for the possible range of daily iAs exposure via food and water consumption, together with body weights relevant to the study populations used in the different studies. Briefly, the CONTAM Panel applied a range of scenarios for estimating total dietary exposure to iAs in the study populations. For rural Asian communities, 50–200 µg iAs/day from food and 3–5 L per day for water consumption including use in cooking, were applied. For North and South American populations, the corresponding ranges were 10–20 µg/day from food and 1–2 L per day. Average body weights were assumed to be 55 kg for rural Asian populations and 70 kg for North and South America (EFSA CONTAM Panel, 2009).

For skin lesions, the studies from Ahsan et al. (2006), and Xia et al. (2009) were used for analysis. With Ahsan et al. (2006), applying the log-logistic model as the best fitting model a BMC_{01} of 26.47 µg and a $BMCL_{01}$ of 22.92 µg iAs/L were obtained. The corresponding $BMDL_{01}$ values ranged between 2.2 and 5.7 µg iAs/kg bw per day. Modelling the results of the study by Xia et al. (2009) resulted in a BMC_{01} of 0.56 and a $BMCL_{01}$ of 0.31 iAs/L, corresponding to a $BMDL_{01}$ ranging from 0.93 to 3.7 µg iAs/kg bw per day.

Karagas et al. (2002) found an association between skin cancer (basal and squamous cell carcinoma) and toenail iAs in a US population. A regression analysis resulted in a non-linear curve with a maximum likelihood 'change point' (the concentration where the dose–response started to increase, and which might be considered as a NOAEL) of 0.105 µg iAs/g (95% CI 0.093–0.219). This change point was found at a concentration of 1–2 µg iAs/L in drinking water corresponding to a 'change point' exposure ranging from 0.16 to 0.31 µg iAs/kg bw per day for skin cancer.

Karagas et al. (2004) found a two-fold (statistically not significant) increase in bladder cancer in the group with the highest toenail arsenic in a study in New Hampshire (US). A regression analysis showed a non-linear curve with a maximum likelihood change point of 0.326 µg iAs/g (95% CI 0.121–0.446 corresponding to a 'change point' exposure ranging from 0.9 to 1.7 µg iAs/kg bw per day.

In an analysis carried out by the NRC (2001) the data from Chiou et al. (2001) showed a significant trend for urinary tract and transitional cell carcinoma with increasing iAs concentrations in water. The BMC_{01}[18] (and BMCL01) were 129 (42) and 281 (92) µg/L for males and females, respectively from the Chiou data (NRC, 2001), from which the EFSA CONTAM Panel estimated $BMDL_{01}$ values ranging from 3.2 to 7.5 µg iAs/kg bw per day.

In the study of Ferreccio et al. (2000) increases in lung cancer cases in a Chilean population at 30–49 µg iAs/L and above were observed and the NRC (2001) calculated BMC01 (and BMCL01) values by linear regression of 17 (14) and 27 (21) µg/L for males and females, respectively. The CONTAM Panel transformed the $BMCL_{01}$ of 14 µg/L (for increased lung cancer incidences in males) to a $BMDL_{01}$ range of 0.34 to 0.69 µg iAs/kg bw per day.

3.2.4.2 | *Current dose–response analyses*

Overview of the approach

The criteria for inclusion of critical effects and reasoning for inclusion of studies for dose–response analyses are described in detail in Section 3.2.3 on critical effects above. Studies that were considered for dose–response modelling had to meet three criteria: (i) the overall risk of bias was considered low, (ii) the statistical analysis on the association between iAs exposure and the risk of the outcome reported by the authors had to show a statistically significant association with iAs as a continuous variable, a statistically significant trend test and/or a statistically significant increase of risk in the upper exposure category/ies, (iii) results for at least three exposure categories (including the reference category) had to be reported.

[18]The NRC in their publication used the term 'ED_{01}' as the dose corresponding to a theoretical 1% excess risk of cancer mortality in a US population. The CONTAM Panel considered such a value as equivalent to a BMC_{01} since the NRC ED_{01} actually related to concentrations of arsenic in water and not doses.

In the studies selected for dose–response modelling the CONTAM Panel first transformed iAs concentrations in drinking water and urine to daily total iAs exposures per kg/bw for use in BMD calculations. The data analysed are adjusted incidences and resulting number of cases based on the risk ratios reported in these studies and the provided (cohort studies) or provided/estimated (case–control studies) population sizes (see Section 'Transformations of relative risk estimates to quantal data' below). The models for quantal data are used to perform BMD analysis. As BMR the CONTAM Panel decided to use a relative increase of 5% of the background incidence after adjustment for confounders. These modelling results are used as the basis for the selection of the Reference Point.

Studies selected for dose–response modelling

Skin cancer

The studies from Leonardi et al. (2012) and Gilbert-Diamond et al. (2013) meet the above-mentioned criteria for dose–response modelling.

Bladder cancer

The studies by Chen et al. (2010b) and Steinmaus et al. (2013) meet the above-mentioned criteria for dose–response modelling. The study by Huang et al. (2018) was not modelled because the study results might be influenced by the presence of high amounts of DMA in the urine.

Lung cancer

The studies from Ferreccio et al. (2000), Smith et al. (2009), Chen et al. (2010a) and Steinmaus et al. (2013, 2014a) meet the above-mentioned criteria for dose–response modelling. However, since the Chilean case–control studies by Steinmaus et al. (2013, 2014a) are larger and have better methodological quality than the studies based on the previously used case–control study by Ferreccio et al. (2000) and reanalyzed by Smith et al. (2009) and are from the same Chilean region, these results were not modelled.

Skin lesions

The studies from Ahsan et al. (2006), Xia et al. (2009) and Pierce et al. (2011) meet the above-mentioned criteria for dose–response modelling.

Decreased birth weight

No studies were modelled in this health outcome category (See section 3.2.3.3 Decreased birth weight). Studies on associations between iAs exposure and birth weight usually present the results from regression analyses with iAs exposure as a continuous variable, rather than analyses based on exposure categories. For example, the study by Rahman et al. (2009) presents the decrease of birth weight per one µg/L of As in water (linear model) and the study by Kile, Cardenas, et al. (2016) presents the decrease of birth weight in gramme per one unit of log-transformed water As. Therefore, normal dose–response modelling cannot be performed for these studies. In addition, these studies were performed in Bangladesh and the relevance for Europe is unclear since maternal and fetal undernutrition, low birth weight and preterm birth in Bangladesh are much more common than in Europe.

Spontaneous abortion and stillbirth

The studies by Milton et al. (2005) and Rahman et al. (2010) on spontaneous abortion meet the above-mentioned criteria for dose–response modelling, and the same is true for the studies by Milton et al. (2005), Cherry et al. (2008) and Rahman et al. (2010) on stillbirth. However, as discussed above on birth weight, the relevance for Europe is unclear since maternal and fetal undernutrition, low BW and PTB are more common in Bangladesh than in Europe, and these factors also increase the risk of spontaneous abortion and stillbirth. Studies on birthweight were not included in dose–response modelling.

Infant mortality

The studies by Milton et al. (2005), Rahman et al. (2007) and Rahman et al. (2010) meet the above-mentioned criteria for dose–response modelling. These studies are from Bangladesh, but associations have also been shown in Mongolia and Chile.

Congenital heart disease

The studies by Rudnai et al. (2014) from Hungary and by Richter et al. (2022) from Denmark meet the above-mentioned criteria for dose–response modelling.

Neurodevelopmental effects

The studies by Vahter et al. (2020) and Wasserman et al. (2004, 2014) meet the above-mentioned criteria for dose–response modelling. However, only the study by Vahter et al. (2020) was finally selected for modelling, since it is the largest and it is a longitudinal study with data both for prenatal exposure and postnatal exposure, and the dose–response may depend on the timing of exposure.

Ischemic heart disease

The studies by Moon et al. (2013), Wade et al. (2015), James et al. (2015) and Wu et al. (2015) meet the above-mentioned criteria for dose–response modelling. The study by Monrad et al. (2017) had the lowest exposure levels, but a very narrow range of exposure. In the total data set, there was no significant dose–response and in the city of Aarhus, where there was a significant association, the median water-As was the same (2.11 µg/L) in the third and fourth quartiles. This study was therefore not considered appropriate for dose–response modelling. The other studies using As in water, mentioned in Table 24 of this Section, were either based on the same study areas but with fewer cases (Chen, Graziano, et al., 2011; Chen, Wu, Liu, et al., 2013; Wade et al., 2009) or considered to have a high risk of bias (Butts et al., 2015; D'Ippoliti et al., 2015; Medrano et al., 2010; Zierold et al., 2004) and therefore not appropriate for dose–response modelling.

Carotid artery atherosclerosis

No studies were modelled within this health outcome category. Among the studies in a Taiwanese cohort (Table 26), the largest study by Hsieh et al. (2011) meets the above-mentioned criteria for dose–response modelling. Since carotid artery atherosclerosis is a subclinical outcome, and there was only one study of carotid artery plaque (but several studies on atherosclerotic cardiovascular disease), it was decided not to use the study by Hsieh et al. (2011) for BMD modelling. The study of IMT by Chen, Wu, Graziano, et al. (2013) only presented data on associations with water As as a continuous variable.

Lung function

Among the studies in Table 28, the studies by Parvez et al. (2013), Powers et al. (2019) and Siddique et al. (2020) meet the above-mentioned criteria for dose–response modelling.

Chronic kidney disease

The studies by Hsueh et al. (2009) and Zheng et al. (2015) meet the above-mentioned criteria for dose–response modelling.

Risk of bias analysis

The risk of bias was considered already as part of the review of studies in Section 3.2.2, as described in Section 3.2.2.1, albeit not being carried out formally. A formal extensive comparative risk-of-bias assessment, however, was conducted for the studies selected for dose–response modelling (Table 33). The rationale behind this additional level of scrutiny was that a comparative assessment of the evidence providing the modelling inputs across different endpoints and health outcome categories would enhance the informed deliberations related to the derivation of reference points. For these studies, which had been already assessed as of low risk of bias, the risk of bias was classified as either low (L) or moderate (M) separately for selection bias ('Sel'), information bias ('Inf') and confounding ('Con'). In addition, the assumed direction (Dir) of the potential bias on the reported risk estimate is commented on. No specific tool was used for the risk of bias assessment. However, the general structure is in agreement with the draft SC guidance on appraisal of epi studies (EFSA Scientific Committee, 2020). An explanation of the basis for the assessment of risk of bias is provided in Annex C. Risk of bias for the studies listed in Table 33 was assessed independently by two experts, the assessments were compared, discussed and consensus was reached on all points.

One type of information bias is misclassification of exposure, which deserves a special comment. The ideal situation for an epidemiological study is that the exposure for each study participant is known for each day over a long-time period. The studies reviewed in this Opinion are based either on As in drinking water or on iAs in urine.

Arsenic in drinking water has generally been measured once or a couple of times in the drinking water of the study participants. The mean arsenic concentrations over time are usually relatively stable, but they can vary from day to day. In addition, the water intake may vary somewhat within individuals (between days) and between individuals. It may also have changed over the years preceding the collection of water samples. Therefore, there will always be some misclassification of long-term intake of iAs from drinking water. For studies using As in water as exposure metric, it is also necessary to take into account the exposure from other dietary sources. This contribution from other food is known only on a group level. So when estimating the total daily dose of iAs, a fixed estimate of the intake of iAs from other food (different for different countries) must be added. In reality, the iAs intake in other food will vary between individuals. In summary, the iAs exposure in all studies based on As in water plus assumed intake from other food will be subject to misclassification. In

general, non-differential misclassification leads to a bias toward the null, so a reported increased risk can be assumed to be underestimated.

The studies using iAs in urine (including their metabolites; u-tiAs) have the advantage that the excretion of u-tiAs mirrors the total intake of iAs (water + other food) on the day of sampling and the day before. This is an advantage compared with the above-mentioned studies based on As in water and an assumed intake of iAs from other food. A disadvantage of using u-tiAs is that it mirrors exposure to iAs only in the past 1 or 2 days. This is not important when exposure is stable, but if exposure (from drinking water or other food) changed over the years preceding urine collection, this is not captured by u-tiAs. The within-individual variability of u-tiAs in urine (between days) is usually small, as shown by studies using repeated sampling (Steinmaus et al., 2005). This is in contrast to total As in urine, which has a higher variability due to the impact of variable intake of organic As species (Barregard et al., 2021). The concentration of u-tiAs in a spot sample must be transformed into an estimated 24 h u-tiAs to estimate the daily intake of iAs. This is another source of misclassification, since a fixed estimate of the 24 h urine volume (2 L used in this Opinion for adults) is used, while in real life the average 24 h urine volume differs between individuals. In summary, as for the studies based on As in water plus an assumed intake from other food, studies based on u-tiAs will also be subject to misclassification. It is likely that when the iAs from water is low, misclassification in studies based on u-tiAs is somewhat smaller than in the studies based on As in drinking water. Also, for studies based on iAs in urine, the misclassification will almost always be non-differential (not associated with the outcome) and attenuate a true association. An exception is when u-tiAs is used in studies of CKD since then the disease can be assumed to decrease the excretion of u-tiAs, which will partly mask a true positive association between iAs exposure and CKD, meaning that the underestimation of risk may be higher than in the case of non-differential misclassification alone.

Conversion of water and urine iAs concentrations to inorganic arsenic exposures

The results of the epidemiological studies are based upon associations of adverse outcomes with either concentrations of arsenic measured in drinking water (w-tiAs, which is inorganic As) or measured in urine (u-tiAs). Unlike in the 2009 Opinion, where BMCLs were first derived and then transformed to BMDLs after adding exposure via food (EFSA CONTAM Panel, 2009), for the present Opinion the CONTAM Panel decided to follow an approach applied by JECFA (FAO/WHO, 2011) and to first transform iAs concentrations in drinking water and urine to daily total iAs exposures per kg/bw for use in BMD calculations. The CONTAM Panel considered this approach to be the most appropriate method to derive BMDs for iAs. For the derivation of default dietary exposures for studies where water concentrations were reported for the present Opinion, the EFSA CONTAM Panel refined some of the values used in the previous Opinion (EFSA CONTAM Panel, 2009), taking into account additional information. For studies with populations from Europe, North and South America an average bodyweight of 70 kg was assumed while for Asian populations (China, Bangladesh) the corresponding value was 55 kg. These values are the same as those applied by the EFSA CONTAM Panel (2009) and JECFA (FAO/WHO, 2011).

For studies, where iAs concentrations in water were reported, dietary exposures were used as follows.

For European populations, for average iAs exposure via food, a value of 7.7 µg iAs/day was assumed. This value is based on the UB median mean exposure of European adults of 0.11 µg iAs/kg bw per day estimated by EFSA in the recent report on iAs dietary exposure (EFSA, 2021; see also Table 34 of Section 3.5.1) and a body weight of 70 kg.

For U.S. populations (only the study of James et al., 2015), a value of 15 µg iAs/day for average exposure via food was assumed based on information provided in a study also dealing with a population from Colorado from the same authors (James et al., 2013). In that paper, estimating exposures based on drinking water As concentrations, the group with the lowest w-As concentrations (≤ 2 µg/L) had a mean u-tiAs of 11.3 µg/g creatinine. Assuming a water concentration of 1 µg/L iAs, and taking into account 24 h creatinine excretion, the CONTAM Panel estimated exposure from diet of about 15 µg/day.

For Chilean populations, a value of 20 µg iAs/day has been applied for average exposure via food based on the estimates from Sancha (2000) and Muñoz et al. (2005). Sancha (2000) estimated an iAs dietary exposure of 13 µg/day for the inhabitants of urban populations of Northern Chile while Muñoz et al. (2005) estimated a substantially higher exposure of 39 µg iAs/day for the inhabitants of Santiago de Chile. In addition, Díaz et al. (2004) studied the dietary intake of iAs in a rural village in Northern Chile and ended up with a dietary exposure estimate ranging from 38 to 58 µg iAs/day. The CONTAM Panel concluded that a lower estimate of 20 µg iAs/day was most appropriate for the Chilean studies considered for risk characterisation. This was mainly based on two publications. In the publication of Ferreccio and Sancha (2006) it was noted that the relatively high iAs levels estimated in food in the studies by Díaz et al. (2004) was only relevant for a certain population of indigenous people in the Andes. In the second publication Muñoz et al. (2005) transformed the measured total As concentrations to iAs levels with a single conversion factor of 50%, which was assumed to overestimate the true dietary exposure of the Chilean population.

For populations from Taiwan/China, an average dietary exposure of 36 µg iAs/day was assumed. This estimate is based on a dietary intake estimate of 0.65 µg iAs/kg per day from a survey of Taiwanese eating habits carried out by the Taiwan Department of Health (TDOH, 2007) reported in the publications by Mendez et al. (2020) and Allen et al. (2020), and assuming a body weight of 55 kg.

Finally, for populations from Bangladesh, a value of 60 µg iAs/day as average exposure via food was used based on an estimate published by Vahter et al. (2006). There, the authors found a significant association between arsenic in urine and drinking water for pregnant women in gestational weeks 6–8 (linear regression: ln UAs = 3.0 + 0.70 $WAs^{0.2}$, $R^2 = 0.39$, $p < 0.001$). The ratio U-As to water As was 76. The average dietary exposure of the inhabitants of Bangladesh was then estimated from this linear regression, assuming a urine volume of 2 L and a water intake of 4 L. In support of this estimate,

Lindberg et al. (2008) calculated that the contribution to urinary arsenic from arsenic exposure from food and other water sources was about 45 µg/L for populations from Bangladesh, including both men and women of wide age ranges. Overall, the estimate of 60 µg/day is uncertain.

An average water consumption of 1.5 L per day was assumed for populations in Europe, North and South America (i.e. the mid-point of the range assumed in the EFSA CONTAM Panel, 2009). The EFSA guidance on default values (EFSA Scientific Committee, 2012) recommends a 2 L default value for chronic daily total liquid intake (including milk, tap water and other beverages). In the epidemiological studies selected, only iAs concentrations in drinking water were reported. The CONTAM Panel considered it justified to apply a consumption value of 1.5 L per day for European, US and Chilean populations, unless other data were provided by the authors. The corresponding values for China/Taiwan and Bangladesh were 3 and 4 L respectively (FAO/WHO, 2011). The JECFA noted that water consumption can vary greatly based on for instance, region, temperature and food consumption. In particular, when the habitual diet includes foods like rice that take up large quantities of water, the total water consumption can increase from 1.5 L up to 5 L per day (FAO/WHO, 2011).

For studies where concentrations of u-tiAs were provided in µg/L, a urinary output of 2 L per day was assumed for all populations (Sieniawska et al., 2012), and total daily exposure was estimated using average body weights of 70 kg and 55 kg, as noted above. Note that for the study by Vahter et al. (2020), a urinary output of 1 L per day and a body weight of 23 kg (reported) were used for children of 10 years.

If u-tiAs was given in µg/g creatinine, then the concentration in µg/g was multiplied by the normal 24 h creatinine excretion in order to transform the concentration (in µg/g) to µg/24 h. For women in Europe and the Americas the multiplication factor was 1.2 (Pouillot et al., 2022; Sallsten & Barregard, 2021) and 1.0 for Asian populations (due to lower body weight and muscle mass). For men in Europe and the Americas this factor was 1.8 (Pouillot et al., 2022; Sallsten & Barregard, 2021) and 1.5 for Asians (due to lower body weight and muscle mass).

The exposure estimates have been derived as described above for each individual study and are presented in detail in Annex D.

Calculation of benchmark doses

The benchmark dose (BMD) analyses were performed using the EFSA 'Bayesian BMD' webtool, an online application that uses the *R*-package BMABMDR to perform data preparation, model fitting, model averaging and plotting. The guidance of the Scientific Committee on BMD modelling (EFSA Scientific Committee, 2022) was taken into account. The CONTAM Panel recognised that the guidance did not specifically address modelling of epidemiological data.

Transformations of relative risk estimates to quantal data

The results of the epidemiological studies were reported as crude and adjusted risk estimates in the form of incidence rate (IR), incidence rate ratio (IRR), hazard ratio (HR), odds ratio (OR) and prevalence ratios (PRs). In some instances, these indices were named relative risk (RR). The adjusted risk estimate reflects the risk estimate adjusted for potential confounders, such as age, sex, smoking, socioeconomic status etc. and is therefore a better estimate of the true risk from exposure than the crude risk estimates.

Since the current BMD approach is not designed to model relative risk estimates such as IRR, HR or OR, it was necessary to transform the relative risks to natural numbers/integers. This was based on the approach used by JECFA (FAO/WHO, 2011).

For cohort studies, the incidence rate or the cumulative incidence in the reference category was calculated. This incidence was multiplied by the adjusted risk estimate to obtain an adjusted incidence estimate, which was then used to calculate the 'adjusted number of cases' (as integers). Having obtained the 'adjusted number of cases' and the population size (provided in the papers or calculated from number of cases and incidence rates) in each exposure category, these data could be used as input into the EFSA BMD webtool.

For case–control studies, the approach was similar. A case–control study usually uses the OR as the estimate of the RR. When the outcome (e.g. a disease) has a low incidence (e.g. < 1% of a population), the OR can be considered a good approximation of the RR.

In order to make inferences about the source population, its distribution of exposure had to be derived. In a case–control study the number of controls in each exposure category reflects the distribution of exposure in the source population from which the controls were selected, and this was used to distribute the source population into exposure categories. The 'adjusted number of cases' was calculated in a similar way as for the cohort studies. To obtain the 'adjusted number of cases' in a specific exposure category (e.g. 'A'), first the number of cases in the reference category was multiplied by the adjusted OR in 'A'. It was then multiplied by the ratio of the number of controls in 'A' and the reference category ('R'). This is because the ratio of controls in A and R reflects the relative distribution of exposure categories in the source population. Finally, the adjusted case numbers were 'normalised' so that their sum was identical to the initial sum of cases.

If the outcome was not one with a low incidence (< 1%), the OR can be used to obtain the RR using the following formula: $RR = OR/(1 - p0 + (p0 \times OR))$ where p0 is the baseline risk (Grant, 2014).

The cross-sectional studies usually used the adjusted OR (the prevalence odds ratio) as the risk estimate, and therefore the approach was in line with that used for case–control studies.

In most studies also the number of outcome cases (e.g. cancer) by exposure category (e.g. water As concentration) was reported. For cohort studies and case cohort studies the size of the cohort (or the subcohort) was reported (as the number

of individuals or the number of person-years) and in most studies these data were also reported by exposure category. For most of the case–control studies, the number of cases and controls in total and by exposure category were reported, as well as the approximate size of the source population from which the controls were selected. The source populations in the respective dose categories were set to have the same relative sizes as the number of controls. If the source populations were not presented in the papers, they were retrieved from national statistics for the areas from which the cases were recruited. If there was an age inclusion of cases, this was taken into account when estimating the source populations. For cross-sectional studies, the number of cases, the population sizes and or the prevalence (proportion) were presented by exposure category.

The transformations have been performed (including the number of cases and the sizes of the source populations) as described above for each individual study and are presented in detail in Annex D.

Selection of the benchmark response for critical effects

The EFSA guidance on benchmark dose modelling (EFSA Scientific Committee, 2022) does not provide formal guidance on modelling of epidemiological data, including the selection of the appropriate BMR for human data. The default BMR for quantal experimental animal data is 10% (extra risk). EFSA (2005) considers that such a value is the lowest statistically significant increased incidence that can be measured in most experimental animal studies. Previous risk assessments based on human data, which generally have larger numbers of subjects than in animal studies, have considered appropriate BMRs on a case-by-case basis, and arrived at lower response values (see EFSA CONTAM Panel, 2009). In the arsenic Opinion in 2009, the CONTAM Panel decided to use 1% extra risk when modelling the risk of skin lesions (see Section 3.2.4.1). In addition, BMCLs, for 1% extra risk for lung and bladder cancer derived by NRC (2001) were taken into account. For lung cancer, the NRC (2001) calculations were based on the relative risks in one of the studies. The JECFA (FAO/WHO, 2011) used a BMR of 0.5% extra risk considering that the low end of the observed data range was 0.5% increased (cancer) incidence. Also, EPA (US EPA, 2012) and Haber et al. (2018) noted that for epidemiological data response rates of 10% extra risk may involve upward extrapolation, in which case a lower BMR value needs to be applied.

In the subsection on Endpoints used for calculation of benchmark doses the 'adjusted number of cases' was calculated in each exposure category for human studies selected for modelling. The source population for the cases was provided in cohort studies or estimated in case–control studies. This allowed for the use of quantal data and the EFSA software. But the observation time during which the cases occurred varied between studies and for most of them it was short. For the cancer outcomes the cumulative incidence (the ratio between the number of cases and the size of the source population over the observation time) in the case–control studies was only around 0.02%. The CONTAM Panel considers it not to be appropriate to model the dose at which the incidence of an outcome increases from – for example – 0.02% to 1.02%, since this would correspond to a very large (50-fold) relative increase of the background incidence after adjustment for confounders. The fact that the observation time and the time period for recruiting cases in control studies differs a lot between studies makes it inappropriate to add an extra (absolute) incidence to the background incidence. Therefore, the BMR was instead expressed in terms of relative risk, i.e. a relative increase of the background incidence after adjustment for confounders. This response definition better accounts for the variation in 'observation times' which is regarded to increase the comparability of BMD results across studies.

More specifically, the CONTAM Panel decided to use a BMR of 5%, expressed as relative increase of the background incidence after adjustment for confounders by 5% as the BMR and use the modelling results for the derivation of an appropriate Reference Point. For considered endpoints a BMR of 1%–5% (relative increase of the background incidence after adjustment for confounders) is regarded to be relevant for public health. Depending on the background response such BMRs can represent very low absolute increases, which may have an impact on the BMD estimation. However, model averaging used in the BMD modelling process improves the estimation precision. It allows to estimate more accurately the BMD associated with smaller BMRs compared to using a single model only. The Bayesian model averaging allows to incorporate additional information in the modelling process, which also influence the estimation precision. In particular, ensuring that the background incidence is centred around the observed incidences for the lowest exposure group (as expected based on expert knowledge) contributes as well to improved precision in the BMD estimation for lower BMR values. The inferences used to estimate corrected number of cases (after adjustment for confounders) to build the associated incidence, entailing large sample sizes, allows in addition to improve estimation precision. Results from the analyses fulfilled criteria in the EFSA guidance (2022) related to BMD uncertainty (see next Section). The uncertainty in BMDs across different BMRs (1%–10%, relative increase of the background incidence after adjustment for confounders) was also assessed in more detail, promoting a value of 5% (Section 3.7). The consequence of using a BMR that is substantially higher than 5% is also discussed in Section 3.7. However, this is not regarded as a better option than the modelling approach taken.

In addition, the CONTAM Panel used the estimated incidence in the reference category as an informative prior for the background parameter in the dose–response modelling. As a general approach, it is regarded to be more appropriate, as this is additional information that can be incorporated in the modelling process guiding the model rather than allowing the model to estimate a theoretical background response. The latter would imply extrapolations below the observed exposure ranges that would be dependent on the models used in the analysis.

When the midpoint of the highest exposure category was not reported, both the lower limit (in most cases the most conservative approach) and twice this value were used. For some outcomes the incidence or prevalence of the outcome was high (in some cases > 10%), and an increase of extra (absolute) risk was meaningful, but for consistency, the relative increase of background incidence was modelled also for these studies.

Results of dose–response analyses

Table 33 shows an overview of the results of the benchmark dose analyses and the potential RP for the studies selected for dose–response modelling.

The EFSA guidance (2022) includes recommendations for assessing when the BMD is too uncertain for the BMDL to be used as a Reference Point (RP). The CONTAM Panel considers that these criteria are also applicable when modelling epidemiological studies. According to the criteria, the BMDL was not recommended as an RP when (i) none of the candidate models fit the data sufficiently well, (ii) BMD/BMDL > 20, (iii) the BMD is 10 times lower than the lowest non-zero dose or (iv) BMDU/BMDL > 50. If one or more of these criteria were not met the study was not considered further.

The following studies were excluded from further consideration since none of the candidate models adequately fitted the data: Richter et al. (2022) and Rudnai et al. (2014) on congenital heart disease; Parvez et al. (2013) on FEV_1 and FVC; Powers et al. (2019) on asthma-related symptoms; Siddique et al. (2020) on obstruction, reversible obstruction asthma-related symptoms, FEV_1 and FEV_6, and Milton et al. (2005) on infant mortality. Additionally, the following endpoints did not comply with the BMD/BMDL and/or BMDU/BMDL criteria: Rahman et al. (2010) on infant mortality and stillbirth; Siddique et al. (2020) on obstruction and asthma-related symptoms and were therefore not considered further. Rahman et al. (2010) on spontaneous abortion was rejected following visual screening due to the non-monotonic dose response seen.

BMDLs are only listed in Table 33 if all recommendations are fulfilled. Further information and BMD reports are listed in Annex E. In addition, the table shows the evaluation of the risk of bias (selection bias, information bias and confounding) and its assumed direction.

TABLE 33 Summary of benchmark analysis and potential reference points for inorganic arsenic using a BMR of a 5% relative increase of the background incidence after adjustment for confounders (prevalence for the cross-sectional studies).

Critical effect	Reference	Population	Study design	Matrix	Input parameters for exposure estimate[1,2,3,4,5,6,7,8,9,10]	Results in μg t-iAs/kg bw per day[11]			Risk of bias analysis			
						BMDL	BMD	BMDU	Sel[$]	Inf[&]	Con	Dir
Skin cancer	Leonardi et al. (2012)	Hungary, Slovakia, Romania	Lo	w-tiAs	1	0.01	0.05	0.08	L/M	L/L	L	U
	Gilbert-Diamond et al. (2013)	USA	Lo	u-tiAs	6	0.06	0.15	0.21	L/L	L/L	L	U
Bladder cancer	Chen et al. (2010b)	Taiwan	Lo	w-tiAs	4	0.15	1.33	5.46	L/L	L/L	M	U
	Steinmaus et al. (2013)	Chile	Lo	w-tiAs	3	0.57	1.09	1.64	L/L	L/L	M	U
Lung cancer	Chen et al. (2010a)	Taiwan	Lo	w-tiAs	4	1.21	4.97	10.80	L	L/L	M	U
	Steinmaus et al. (2013)	Chile	Lo	w-tiAs	3	2.07	2.79	3.79	L/L	L/L	L	U
	Steinmaus et al. (2014a)	Chile	Lo	w-tiAs	3	0.17	0.76	1.71	L/L	L/L	L	U
Skin lesions	Ahsan et al. (2006)	Bangladesh	CS	w-tiAs	5	0.08	0.31	0.60	L	L/L	L	U
	Xia et al. (2009)	China	CS	w-tiAs	4	0.11	0.18	0.25	L	L/L	L	U
	Pierce et al. (2011)	Bangladesh	Lo	w-tiAs	5	0.80	1.61	2.86	L	L/L	L	U
Spontaneous abortion and stillbirth	Milton et al. (2005), stillbirth	Bangladesh	CS	w-tiAs	5	0.87	4.08	6.71	L	L/M	L	U
	Milton et al. (2005), spontaneous abortion	Bangladesh	CS	w-tiAs	5	0.58	2.66	5.54	L	L/M	L	U
	Cherry et al. (2008), stillbirth	Bangladesh	Lo	w-tiAs	5	1.37	2.02	2.64	L	M/L	M	↓
Infant mortality	Rahman et al. (2007)	Bangladesh	Lo	w-tiAs	5	0.98	5.34	12.06	L	L/L	M	↓
Neuro developmental effects[12]	Vahter et al. (2020), full developmental score, children u-tiAs 10 years	Bangladesh	CS	u-tiAs	10	0.54	1.53	2.05	L	L/L	L	U
	Vahter et al. (2020), full developmental score, mothers u-tiAs at GW 8	Bangladesh	Lo	u-tiAs	7	1.36	1.81	2.12	L	L/L	L	U
Ischemic heart disease	Wade et al. (2015)	China	Lo	w-tiAs	4	1.23	1.67	2.28	L	L/L	L	U
	James et al. (2015)	USA	Lo	w-tiAs	2	0.17	0.48	0.92	L	L/L	L	U
	Wu et al. (2015)	Bangladesh	Lo	w-tiAs	5	0.81	3.58	11.51	L	L/L	L	U
	Moon et al. (2013)	USA	Lo	u-tiAs	8	0.15	0.31	0.40	L	L/L	L	U

(Continues)

TABLE 33 (Continued)

Critical effect	Reference	Population	Study design	Matrix	Input parameters for exposure estimate[1,2,3,4,5,6,7,8,9,10]	Results in μg t-iAs/kg bw per day[11]			Risk of bias analysis			
						BMDL	BMD	BMDU	Sel[$]	Inf[&]	Con	Dir
Lung function	Powers et al. (2019), airflow obstruction	USA (American Indians)	Lo	u-tiAs	8	0.07	0.17	0.26	L	L/M	L	U
	Powers et al. (2019), restrictive pattern	USA (American Indians)	Lo	u-tiAs	8	0.10	0.23	0.28	L	L/M	L	U
	Powers et al. (2019), emphysema	USA (American Indians)	Lo	u-tiAs	8	0.04	0.15	0.25	L	L/M	L	U
Chronic kidney disease	Hsueh et al. (2009)	Taiwan	Lo	u-tiAs	9	0.12	0.28	0.40	L/M	M/L	L	↓
	Zheng et al. (2015)	USA	Lo	u-tiAs	8	0.06	0.15	0.24	L/M	M/M	L	U

Abbreviations: BMD, benchmark dose; BMDL, benchmark dose lower confidence limit; BMDU, benchmark dose upper confidence limit; BMR, benchmark response; bw, body weight; CS, cross-sectional study; GW, gestational week; Con, Confounding bias; Dir, Assumed direction; L, low risk of bias; H; high risk of bias; Inf, Information bias; Lo, longitudinal (cohort, case–control, case-cohort) study; M, medium risk of bias; Sel, Selection bias; U, unclear; USA, United States of America; u-tiAs, urinary total inorganic arsenic; w-tiAs, water total inorganic arsenic; ↓ underestimation of true risk (so overestimation of BMD).

[$]In the case of case–control studies the ranking was carried out for cases (left side of '/') and controls (right side of '/') separately.

[&]For all studies, this was carried out separately for exposure misclassification (left side of '/') and exposure misclassification/case diagnosis (right side of '/'). The exposure misclassification due to estimating iAs from food in studies based on As in drinking water will be more pronounced in the reference category with low water As (see section Risk of bias analysis).

[1]Total daily exposures (μg/kg bw per day) were calculated assuming a default water consumption of 1.5 L per day, a default exposure via food of 7.7 μg iAs/day and a default body weight of 70 kg.

[2]Total daily exposures (μg/kg bw per day) were calculated assuming a default water consumption of 1.5 L per day, a default exposure via food of 15 μg iAs/day and a default body weight of 70 kg.

[3]Total daily exposures (μg/kg bw per day) were calculated based on daily water arsenic intakes, assuming a default exposure via food of 20 μg iAs/day and a default body weight of 70 kg.

[4]Total daily exposures (μg/kg bw per day) were calculated assuming a default water consumption of 3 L per day, a default exposure via food of 36 μg iAs/day and a default body weight of 55 kg.

[5]Total daily exposures (μg/kg bw per day) were calculated assuming a default water consumption of 4 L per day, a default exposure via food of 60 μg iAs/day and a default body weight of 55 kg.

[6]Total daily exposures (μg/kg bw per day) were calculated using reported urinary concentrations and assuming, a urinary output of 2L per day and using bodyweights of 70 kg.

[7]Total daily exposures (μg/kg bw per day) were calculated using reported urinary concentrations and assuming, a urinary output of 2L per day and using bodyweights of 55 kg.

[8]Total daily exposures (μg/kg bw per day) were calculated by multiplying the concentration in μg creatinine/g reported by the normal creatinine excretion in 24 h in order to transform the concentration (in μg/g) to μg/24 h. The multiplication factor (normal creatinine excretion) was 1.2 for women and 1.8 for men.

[9]Total daily exposures (μg/kg bw per day) were calculated by multiplying the concentration in μg creatinine/g reported by the normal creatinine excretion in 24 h in order to transform the concentration (in μg/g) to μg/24 h. The multiplication factor (normal creatinine excretion) was 1.0 for women and 1.5 for men.

[10]Total daily exposures (μg/kg bw per day) were calculated using reported urinary concentrations and assuming, a urinary output of 1 L per day and using bodyweights of 23 kg (as reported in the publication).

[11]A BMR of 5% (relative increase of the background incidence after adjustment for confounders) was applied to all calculations.

[12]For these studies continuous data was modelled, applying 5% extra risk.

3.2.5 | Identification of a reference point for hazard assessment

The lowest BMDLs (< 0.1 μg/kg bw per day) in Table 33 (Section 3.2.4.2) based on a BMR of 5% relative increase of the background incidence after adjustment for confounders were calculated for skin cancer, skin lesions, lung outcomes and chronic kidney disease. Low BMDLs (≤ 0.17 μg/kg bw per day) were also calculated for lung cancer, bladder cancer and ischemic heart disease.

The CONTAM Panel decided to use the $BMDL_{05}$ (0.06 μg/kg bw per day) for the case–control study on skin cancer (type: squamous cell carcinoma) in the US by Gilbert-Diamond et al. (2013) as a Reference Point (RP). The association between iAs exposure and skin cancer is well established. The study was considered to have a low risk of bias. Exposure categories were based on u-tiAs. The confounder-adjusted risk of skin cancer was positively associated with u-tiAs (untransformed as well as log-transformed) with statistical significance, although the adjusted OR in the upper tertile was not statistically significant (OR 1.43, 95% CI 0.91–2.27), Table 11.

The $BMDL_{05}$ of 0.01 μg/kg bw per day derived for the other case–control study on skin cancer (type basal cell carcinoma), performed in Hungary, Romania and Slovakia by Leonardi et al. (2012) was also considered as RP. This study too showed a statistically significant association between iAs exposure, as measured by As in drinking water, Table 11. The $BMDL_{05}$ derived from this was much lower than that from study by Gilbert-Diamond et al. (2013) (0.06 μg/kg bw per day). Both these studies were considered as being of good quality. The study by Leonardi et al. (2012) had the advantage of five doses compared to three for the Gilbert-Diamond study.

However, the study by Leonardi et al. (2012) used hospital controls and was therefore considered having a slightly higher risk of bias than the study by Gilbert-Diamond et al. (2013), which used population controls.

Moreover, when modelling the study by Gilbert-Diamond et al. (2013), which was based on u-tiAs, there was no need to use a fixed default additional intake of iAs from other food than drinking water, which was necessary for the study by Leonardi et al. (2012). The US population used for the study of skin cancer was considered comparable with the European population in terms of nutrition and socioeconomic factors.

The results when modelling the Gilbert-Diamond study using a BMR of 1% or 10% (relative increase of the background incidence after adjustment for confounders) showed lower and higher BMDs and BMDLs, respectively, but differences were, however, not very large, which further strengthens the validity of the RP. Finally, squamous cell carcinoma is a more serious type of skin cancer than basal cell carcinoma. In addition, the $BMDL_{05}$ when modelling the study by Leonardi et al. (2012) was about 10 times lower than the median dose in the lowest dose category, and the BMD was below the dose in the reference category, which makes the estimate uncertain. However, the results from the study by Leonardi et al. (2012) support the choice of skin cancer as a RP for hazard assessment and the relatively low $BMDL_{05}$ calculated when modelling the study by Gilbert-Diamond et al. (2013).

The $BMDL_{05}$ values for the lung outcomes in the cross-sectional study in the US by Powers et al. (2019) were also low, one of them as low as 0.04 μg/kg bw per day. This outcome was based on self-reporting (if a medical person ever told them they had emphysema). The BMDLs for impaired lung function showed BMDLs of 0.07 and 0.1 μg/kg bw per day. Overall, an RP of 0.06 μg/kg bw per day should therefore be also considered to cover lung outcomes other than lung cancer which is is described separately below.

The BMDLs for some of the studies on lung cancer (Steinmaus et al., 2014a), bladder cancer (Chen et al., 2010b), ischemic heart disease (Moon et al., 2013) and chronic kidney disease (Hsueh et al., 2009) were in the range 0.12–0.17 μg/kg bw per day. An RP of 0.06 μg/kg bw per day should therefore also to cover those outcomes. For lung cancer, a common and very serious disease, the CONTAM Panel discussed whether a 5% relative increase in incidence was too high to use as a BMR. However, the CONTAM Panel notes that the BMDL when modelling the study by Steinmaus et al. (2014a) with a BMR of 1% relative increase in incidence is 0.06 μg/kg bw per day (see Annex E).

Some of the other studies listed in Table 33 also showed low BMDLs. This was the case for one of the studies on skin lesions (Ahsan et al., 2006), a cross-sectional study in Bangladesh. However, the study by Pierce et al. (2011) on the same population used a longitudinal design and was therefore considered more valid. In addition, the BMD for the study by Ahsan et al. (2006) was lower than the dose in the reference group. Another example is the longitudinal study on CKD by Zheng et al. (2015). This outcome was based on an estimated GFR of < 60 mL/min per 1.73 m^2. The study by Hsueh et al. (2009) had stronger criteria for CKD (reduced eGFR for at least 3 months) and low eGFR (mean 28 mL/min per 1.73 m^2) and is likely to be more valid.

For other outcomes listed in Table 33, the BMDLs were considerably higher and a RP of 0.06 μg/kg bw per day is therefore considered to cover these outcomes as well.

3.3 | Consideration of the approach to risk characterisation

iAs is a human carcinogen, being causally associated with cancers of the skin, lung and bladder, with lesser evidence for various other types of cancer. iAs does not interact directly with DNA but induces DNA base oxidation and both DNA single and double strand breaks. Clastogenic and aneugenic effects have been demonstrated both *in vitro* and *in vivo* as measured by a dose-dependent increase of chromosomal aberrations, micronuclei and aneuploidy. In addition, iAs effectively inhibits DNA repair both *in vitro* and *in vivo* thus enhancing its own genotoxic potential and acting as a co-mutagen. iAs

induces clastogenic events in humans in a range of low to moderate exposure levels. These effects have also been reported when exposure occurs in the pre-natal and early stages of life. Moreover, cross-generational effects of iAs on genotoxicity, DNA methylation and reproduction (Nava-Rivera et al., 2021; Yin et al., 2022) have been described in rodent models. Based on the evidence that iAs exerts its genotoxic effects, at least in part, by inducing oxidative DNA base modifications and DNA strand breaks, it has been proposed that iAs has an indirect genotoxic mode of action via production of oxidative stress, which could be thresholded.

However, there is clear evidence that iAs induces DNA double strand breaks, both *in vitro* and *in vivo* (including humans) at low levels of exposure. These lesions have been shown to arise by both replication-dependent and replication-independent mechanisms, suggesting that genotoxic clustered DNA lesions may also arise due to the presence of radical species in the close vicinity of DNA. On the other side, the aneugenic effects of iAs are likely to be thresholded, probably involving proteins of the spindle apparatus. Determining whether a threshold dose-effect relationship exists for the clastogenic effects remains challenging (Elhajouji et al., 2011) No threshold has been reported for chromosomal damage after exposure of human cells to low doses of ionising radiation (Boei et al., 2012) likely due to unrepaired DSB. Since DSB have been observed after iAs exposure it remains possible that iAs-induced clastogenic effects are not thresholded.

In addition, iAs is a potent inhibitor of DNA repair, which is the underlying mechanism for its co-mutagenic effects. The interactions with the DNA repair/DDR system are based on protein interactions, again indicating the possibility of thresholded mechanisms. However, the inhibition of DNA repair impacts on the main self-defence mechanisms that play a crucial role in genotoxicity thus potentially affecting the shape of the dose–response curves at low doses. iAs is also involved in multiple effects by altering signalling pathways and the epigenetic landscape. Changes in DNA methylation are reported in populations exposed to low to moderate levels of iAs. Major epigenetic alterations, DNA methylation and histone modifications, are regulated by various enzymes and thus are likely to be thresholded. The epigenome may act as a modifier of exposure effects at low doses and of risk for long-lasting effects.

All the effects described above are associated with carcinogenesis. Thus, it can be envisaged that both thresholded and non-thresholded mechanisms could apply to the genotoxic effects of iAs. In addition, the methylation of iAs, particularly to trivalent methylated as well as pentavalent methylated thiolated species, should be regarded as an activation process that forms reactive species, which might exert even stronger genotoxic effects, inhibit DNA damage response including DNA repair pathways, promote ROS generation and induce cell transformation. It has been shown *in vitro* that inorganic arsenic metabolites are genotoxic and disturb various targets of the cellular DNA damage response. Genomic stability is likely to be affected by iAs and its metabolites in parallel by different pathways. Given the combination of different actions, there are considerable uncertainties regarding the shape of the dose–response curves for carcinogenicity at low levels of exposure.

Therefore, it is not appropriate to establish a health-based guidance value (HBGV) and a margin of exposure (MOE) approach has been applied in the risk characterisation (see Section 3.6). There are no precedents in EFSA for identification of an MOE of low concern, when using a BMDL derived from human cancer data. Therefore, the Panel decided not to determine a value for an MOE of low concern.

3.4 | Occurrence data

3.4.1 | Occurrence data used in the present assessment

Following the ToR, the present risk assessment should take into account the updated dietary exposure assessment endorsed by the CONTAM Panel in November 2020 (EFSA, 2021). This Section provides a summary of the occurrence data used for that exposure assessment; detailed information can be found in the corresponding EFSA scientific report (EFSA, 2021).

After data cleaning and analysis of the submitted occurrence data, the 2020 EFSA scientific report initially considered a total of 13,608 analytical results on iAs from samples collected between 2013 and 2018 in 23 different European countries. Out of them 7623 analytical results corresponded to drinking water[19] and 5985 to different types of food. Overall, most of the samples were detected using ICP–MS, although for the samples of drinking water the preferred detection method was Atomic Emission Spectrometry (AES). Among the samples of drinking water, the highest mean levels of arsenic were reported for unspecified drinking water (mean = 2.0–2.4 μg/kg, LB–UB) while the lowest levels were for carbonated mineral water (mean = 0.8–1.7 μg/kg, LB–UB). A total of 356 samples of different types of drinking water were reported with iAs levels above 10 μg/L;[20] they were excluded to avoid introducing a bias when estimating dietary exposure to iAs.

The most represented food category was 'Grains and grain-based products' with a total of 2928 analytical data submitted on iAs; within this food category close to 1800 samples of different types of rice were included together with rice-based commodities known to contain relatively high levels of iAs. Rice samples and rice-based products were reported with the highest levels of iAs, with mean values of 233 μg/kg in red rice (LB = UB) and 128–131 μg/kg (LB–UB) in brown rice among the rice samples. It is also important to note the relatively high levels of iAs reported for few samples codified as

[19]Almost all samples reported as drinking water were analysed for total arsenic (7560 out of 7623). It was assumed that the reported levels on tAs correspond to iAs as it is well established that almost all arsenic in drinking water is inorganic, either As(III) or As(V) (US EPA, 2001; FAO/WHO, 2011).

[20]Parametric value established by the Council Directive 98/83/EC for water intended for human consumption and ML established for natural mineral waters by Commission Directive 2003/40/EC.

'Rice cakes/Rice waffles/Rice crackers', with mean levels of 146–148 µg/kg (LB-UB). The relatively high presence of iAs in this type of product was already identified in the 2014 EFSA scientific report (EFSA, 2014) and is also profusely described in the literature (Dominguez-Gonzalez et al., 2020; Islam et al., 2017).

Another food category with a high number of samples was 'Fish and other seafood' ($n = 938$), with almost half of the samples codified as 'Fish meat' ($n = 451$). The reported levels of iAs for 'Fish meat' were relatively low (mean LB = 4 µg/kg) while higher levels were reported for crustaceans (mean LB = 15 µg/kg) and for molluscs, in particular in clams (mean LB = 108 µg/kg). The food group 'Vegetables and vegetable products (including fungi)' was also well represented with 589 samples. Particular attention was given to mushrooms as they are well known to accumulate different arsenic species, including iAs, depending on the substrate and the fungal species. Overall, iAs was more often quantified in samples of wildly growing mushrooms as compared to those cultivated; mean levels up to 16.9 µg/kg (LB) were reported for samples of Cantharelle (*Cantharellus cibarius*) and up to 17.2 µg /kg (mean LB) for few samples of the genus Boletus. Seaweed samples accounted for almost half of the samples ($n = 279$) reported as 'Vegetables and vegetable products (including fungi)'. Although arsenic in seaweeds is primarily found in the form of arsenosugars, some brown alga in particular the seaweed Hiziki or Hijiki (*Sargassum fusiforme*, syn. *Hizikia fusiformis*) but also Kombu (*Laminaria* spp.) reported levels of iAs close to 100 mg/kg and high iAs/tAs ratios (75%–85%).

For the assessment of the exposure in the young population, a total of 482 samples of 'Food for infants and young children' with data on iAs were available. Among the samples codified as 'Cereal-based food for infants and young children' ($n = 224$), the highest levels of iAs were reported for samples containing rice as ingredient (mean levels = 77–79 µg/kg, LB-UB). To mention a group of samples codified as 'Biscuits, rusks and cookies for children' with relatively high levels of iAs (mean levels = 83–94 µg/kg, LB-UB); under this category are included typical snacks (rice cakes, rice crackers, rice biscuits) that are widely used to feed infants and young children. On the other hand, very low levels of iAs were reported for both 'Follow-on formula, milk-based' and 'Infant formula, milk-based', with mean values of 0.08–2.1 µg/kg (LB–UB) and 0.02–4.0 µg/kg (LB–UB), respectively. This is in line with data reported in the literature, although the contribution of infant and follow-on formulae might drastically increase in certain areas due to the use of drinking water with relatively high levels of iAs to reconstitute the formulae. Additionally, for infants and children who suffer from milk intolerance (e.g. lactose) and/or milk allergies (e.g. proteins) milk-based infant and follow-on formulae are replaced by the so-called 'Foods for special medical purposes' (FSMPs). Among them, rice-based formulae are gaining acceptance (Bocquet et al., 2019) and although no occurrence data were available for this particular food group, a dedicated exposure scenario was conducted in infants based on its consumption using occurrence data from the literature (see EFSA, 2021 for further details). During the preparation of the 2021 EFSA scientific report several uncertainties were identified linked to the occurrence data used in dietary exposure assessment. A more detailed analysis of these uncertainties is provided in the Uncertainty analysis.

3.5 | Exposure assessment

3.5.1 | Exposure assessment used for the present opinion

Following the ToR, the present risk assessment should take into account the updated dietary exposure assessment endorsed by the CONTAM Panel in November 2020 (EFSA, 2021). This Section provides an overview of that assessment, including the exposure estimates across different age classes in Europe and the main foods contributing to the dietary exposure to iAs; detailed information can be found in the corresponding EFSA scientific report (EFSA, 2021).

The 2021 EFSA scientific report considered consumption data from 23 different European countries and a total of 44 different dietary surveys (87,945 subjects) to estimate the chronic dietary exposure to iAs. In addition to the different age classes considered (Infants, Toddlers, Other children, Adolescents, Adults, Elderly and Very elderly), seven surveys were also used providing consumption data on specific population groups: 'Pregnant women' (five dietary surveys) and 'Lactating women' (two dietary surveys). The highest dietary exposure to iAs[21] was estimated in the young population (infants, toddlers and other children). The highest mean dietary exposure estimates at the lower bound (LB) were in toddlers (0.30 µg/kg bw per day), and in both infants and toddlers (0.61 µg/kg bw per day) at the upper bound (UB). At the 95th percentile, the highest exposure estimates (LB–UB) were 0.58 and 1.20 µg/kg bw per day for toddlers and infants, respectively. In general, UB estimates were two to three times higher than LB estimates (EFSA, 2021). Table 34 shows a summary of the chronic dietary exposure estimates to iAs across 44 different dietary surveys carried out in 23 different European countries.

[21] As indicated in Section '3.4. Occurrence data', the analytical data used in this exposure assessment are on iAs. For the data on 'Drinking water' the inmense majority of the data were reported as total arsenic but they are considered as iAs (US EPA, 2001; FAO/WHO, 2011).

TABLE 34 Summary statistics of the dietary chronic mean and P95 exposure assessment (μg/kg bw per day) to iAs across European dietary surveys. Estimates were rounded to two decimal places.

	Mean dietary exposure (μg/kg bw per day)						
		Lower bound (LB)			Upper bound (UB)		
	N	Min	Median	Max	Min	Median	Max
Infants	13	0.09	0.15	0.22	0.26	0.42	0.61
Toddlers	16	0.12	0.17	0.30	0.34	0.44	0.61
Other children	19	0.07	0.11	0.17	0.19	0.30	0.37
Adolescents	20	0.04	0.06	0.11	0.10	0.16	0.23
Adults	22	0.03	0.04	0.07	0.08	0.11	0.15
Elderly	20	0.03	0.03	0.06	0.06	0.10	0.14
Very elderly	15	0.03	0.03	0.05	0.08	0.10	0.14
Pregnant women	5	0.04	0.06	0.07	0.10	0.13	0.14
Lactating women	2	0.03	–	0.06	0.09	–	0.14
	95th percentile dietary exposure (μg/kg bw per day)						
		Lower bound (LB)			Upper bound (UB)		
	N	Min	Median	Max	Min	Median	Max
Infants	13	0.21	0.36	0.52	0.76	0.84	1.20
Toddlers	16	0.24	0.37	0.58	0.62	0.75	0.99
Other children	19	0.17	0.26	0.37	0.41	0.54	0.67
Adolescents	20	0.10	0.14	0.26	0.21	0.30	0.44
Adults	22	0.07	0.10	0.19	0.16	0.21	0.33
Elderly	20	0.06	0.08	0.14	0.13	0.18	0.25
Very elderly	15	0.07	0.08	0.14	0.14	0.17	0.23
Pregnant women	5	0.09	0.12	0.19	0.17	0.22	0.28
Lactating women	2	0.08	–	0.14	0.16	–	0.25

Abbreviations: bw, body weight; LB, lower bound; *N*, number; UB, upper bound.

The main contributors to these differences between LB and UB exposure were some food categories (e.g. 'Milk and dairy products', 'Grains and grain-based products (no rice)' and 'Fruit and vegetable juices', among others) with low LB values, a relatively high number of left-censored data and relatively high consumption in different age classes. Across the different age classes, the main contributors to the dietary exposure to iAs (LB) were 'Rice', 'Rice-based products', 'Grains and grain-based products (no rice)' and 'Drinking water'. Particular foodstuffs indicated for the young population (e.g. 'Cereal-based food for infants and young children' and 'Biscuits, rusks and cookies for children') made a relevant contribution in the dietary exposure to iAs in this age group. Overall, the contribution of milk-based infant and follow-on formulae to the intake of iAs was rather low due to its relatively low iAs levels, although the final levels could be strongly affected by the iAs present in the drinking water used for reconstitution. In the adult population, food groups such as 'Vegetables and vegetable products' and 'Fish and other seafood' were also apparent sources of iAs in certain countries.

Different ad hoc dietary exposure scenarios were conducted to complement the general exposure scenario (EFSA, 2021). As an example, in infants, exposure to iAs was estimated considering the consumption of rice-based formula. A mean level of iAs of 12 μg/kg ($n = 7$, range 9–20 μg /kg) as reported by Meyer et al. (2018) for this type of samples, and consumption values of 200 and 260 mL/kg bw per day (mean and high-level consumption) as recommended by the EFSA Scientific Committee for infants below 16 weeks of age (EFSA Scientific Committee, 2017) were used. Dietary exposure to iAs was estimated as 0.30 and 0.39 μg/kg bw per day in mean and high consumers, respectively. Another ad hoc scenario was carried out using the reported consumption of 'Cereal-based food for infants and young children', and the occurrence data from the 93 samples codified under this group identified as having rice as an ingredient. The consumption of this type of food with rice as ingredient is becoming more and more popular among young children affected by either celiac disease or gluten intolerance that must follow a gluten-free diet. Dietary exposure estimates to iAs at the P95 as high as 0.62 μg/kg bw day and 0.70 μg/kg bw day were calculated for toddlers and infants, respectively. These values correspond to exposure estimates considering high consumption of cereal-based food of 45 g/day and 50 g/day for infants and toddlers respectively with relatively high levels of iAs (P95 occurrence (LB) of 130 μg/kg). As compared to the previous 2014 EFSA scientific report on dietary exposure to iAs, the estimates were noticeably lower, with the maximum means and 95th percentile estimates across the different age classes around 1.5–3 times lower. These differences were explained by the different occurrence/consumption data and/or the different methodology used in both reports; dietary exposure estimates in the 2021 EFSA scientific report were in good agreement with recently published scientific literature that also made use of measured iAs to estimate dietary exposure to iAs.

Several recommendations regarding the exposure assessment for iAs which are still valid were made in the 2021 EFSA scientific report. They are therefore not described in the present Opinion.

3.6 | Risk characterisation

There are no precedents in EFSA for identification of an MOE of low concern, when using a BMDL derived from human cancer data. Therefore, the Panel decided not to determine a value for an MOE of low concern.

The Reference Point (0.06 μg/kg bw per day) identified by the CONTAM Panel for skin cancer is within the range of the dietary exposure estimates for iAs for average (0.03–0.15 μg/kg bw per day) and slightly below the range of high-level adult consumers (0.07–0.33 μg/kg bw per day) in Europe (see Table 34). Therefore, in adults, the MOEs range between 2 and 0.4 for mean consumers and between 0.9 and 0.2 at the 95th percentile exposure, respectively. An MOE of 1 describes the exposure level that could be associated with a 5% increase relative to the background incidence for skin cancer, based on the available data. Despite the uncertainties, the CONTAM Panel concludes that these MOEs raise a health concern for skin cancer. The CONTAM Panel noted that the BMDLs for some of the studies on lung cancer, bladder cancer, ischemic heart disease and chronic kidney disease were in the range 0.12–0.17 μg/kg bw per day, which is also within the range of dietary exposure estimates. Therefore, there is a possible concern also for these endpoints.

The CONTAM Panel notes that dietary exposure is higher in the younger age groups and therefore the respective MOEs are smaller. However, this does not necessarily indicate that children are at greater risk, because the effects are due to long-term exposure and most of the epidemiological studies are conducted in adults who would also have had higher dietary exposure during early life. Therefore, the CONTAM Panel concludes that children are covered by this risk characterisation.

Arsenic is known to impair DNA damage response and DNA repair and individuals with genetic variants in these pathways have increased cancer susceptibility (see Section 3.3). Although risk characterisation is based on the results of relatively large epidemiological studies, susceptible individuals of higher genetic risk may not be adequately represented in these studies. Therefore, dietary exposure to arsenic may be of greater concern for such individuals than for the general population.

3.7 | Uncertainty analysis

The evaluation of the uncertainties in the present assessment was performed following the principles laid down in the Guidance on uncertainty analysis in scientific assessments (EFSA Scientific Committee, 2018). The purpose of the uncertainty analysis is to identify and quantify the major uncertainties of the specific risk assessment and combine them to assess the overall certainty of the final conclusion.

To harmonise uncertainty analyses, the CONTAM Panel has developed a road map that structures the risk assessment process in broader groupings, as well as subgroupings. Sets of questions have also been defined to help the collection of uncertainties. There are four overarching elements of the road map: (i) chemical characterisation and analytical methods, (ii) exposure assessment, (iii) hazard identification and characterisation and (iv) risk characterisation. Based on the available time and resources, the CONTAM Panel decided to mainly focus on (i), (iii) and (iv), rather than (ii). The exposure assessment was carried out earlier and it has also been published as a standalone document (EFSA, 2021). The uncertainties identified for (i) and (iii) are described in Table 35. As an extension of (iii) a quantitative assessment of BMD uncertainty depending on the BMR is also performed separately.

At the level of the risk characterisation (iv), a quantification of overall uncertainty in the margin of exposure is performed. This data-driven analysis (section 3.7.3) is based on information of uncertainty described by the exposure and BMD estimates in the Opinion, i.e. LB and UB scenarios for the exposure and estimated BMD credible intervals. This assessment is therefore conditional on the assumption that identified uncertainties below (Section 3.7.1) that may not be covered by the exposure and BMD estimates used, or the sensitivity analyses performed (Sections 3.7.3.3 and 3.7.3.4), is relatively low. The overall conclusion in section 3.7.4 is therefore based on the quantitative analysis (3.7.3) in combination with qualitative consideration of remaining uncertainty.

3.7.1 | Identification and prioritisation of uncertainties

No major uncertainties were identified with respect to chemical characterisation and analytical methods, but several uncertainties were identified related to hazard and risk characterisation (Table 35). At the level of the risk characterisation metric (the margin of exposure, MOE) the impact of identified uncertainties related to epigenetics, genotoxicity, ADME, as well as biomarkers of exposure were regarded to be of low priority (see Table 35). Also, uncertainties related to the validity of the epidemiological studies used for dose–response analysis were of low priority, considering the assessment of risk of bias (Section 3.2.4.2 and Table 33). However, other uncertainties related to the epidemiological studies, dose–response analysis of critical endpoints and selection of an RP were generally of medium priority. This includes uncertainties related to the exposure assessments in all the studies; e.g. the uncertainty in the intake (L/day) of As-contaminated water and the assumed dietary intake of iAs. Default values for water intake have been used as described in Section 3.2.4.2, i.e. they

ranged from 1.5 to 4 L/day across critical studies (see Table 33). This intake was rarely quantified by interviews (except in Steinmaus et al., 2014a). The intake of iAs from other food had to be estimated from the literature, i.e. assumed intakes ranged from 7.7 to 60 μg/kg bw per day across critical studies (see Table 33). For the studies using u-tiAs (e.g. the critical study, Gilbert-Diamond et al., 2013), this source of uncertainty was not present, but there is uncertainty in the transformation from urinary iAs to dietary iAs. Also, related to the epidemiological studies residual confounding is always possible. Some studies have probably over-adjusted for covariates in the causal chain. With respect to the dose–response analysis of critical endpoints, the small sample sizes of some of the individual studies were regarded to be of medium priority. In some cases, despite significant dose–response associations reported in the studies, the odds ratios (ORs) in separate exposure categories were not always statistically significant.

All these uncertainties may not be covered by the estimated BMD credible interval. Also, while covered by the BMD credible interval, it was considered that the relatively low BMR selected may have an impact on the uncertainty in the RP. Therefore, a more detailed quantitative analysis of BMD uncertainty was performed (see Section 3.7.2). Also, a broad quantification of the uncertainty in the margin of exposure across critical endpoints was accomplished (see Section 3.7.3). To further address identified uncertainties related to the epidemiological studies this quantification of uncertainty included sensitivity analyses related to the selected exposure categories and the midpoints in the exposure categories (see Section 3.7.3.3), and the estimated sizes of the source populations for case–control studies (see Section 3.7.3.4). Also, studies selected for the quantitative analysis in Section 3.7.3 cover most of the assumptions on daily water and dietary intakes noted in Table 33.

Uncertainties related to the exposure assessment are presented in EFSA (2021). They concerned both the occurrence and consumption data, as well as the linkage of that data and use of a factor for preparation of foods as consumed. As for uncertainties in Table 35 the uncertainties related to the exposure were regarded to have the potential to cause both over- and underestimation, but they were not prioritised.

TABLE 35 Elements of the CONTAM road map and relevance for the uncertainty analysis - hazard identification and characterisation and risk characterisation.

Main group	Sub-group	Overarching questions	Description of uncertainty	Uncertainty[a]	Priority ranking[b]
Chemical characterisation and analytical methods	**Chemical characterisation**	Is there uncertainty in the chemical composition of the compound administered to experimental animals and in *in vitro* studies?	Uncertainty in the applied dose	**No**	—
			Exact composition of the tested compounds	**No**	—
	Analytical methods	Is there uncertainty in the analytical process?	Lack of certified reference materials and proficiency tests	**No**	—
Hazard identification and characterisation	**Epigenetics**	Is there uncertainty in the growing body of evidence regarding epigenetic effects?	Relevance of the data to human health effects	**Yes**	**1**
	Genotoxicity	Is there uncertainty on the genotoxicity of the substance	Uncertainty regarding mode of action for both iAs and its human metabolites	**Yes**	**1**
	ADME	Is there uncertainty in any aspect of human ADME? This may include insufficient information on absorption, distribution, metabolism or excretion of iAs	Absorption	**Yes**	1
			Distribution	**Yes**	1
			Metabolism	**Yes**	1
			Excretion	**Yes**	1
	Biomarkers of exposure	Is there uncertainty in the studies of biomarkers of exposure?	Variability of urinary As excretion.	**Yes**	1
	Epidemiological studies	Is there U in the validity of the studies causing a risk of bias?	Study design	**Yes. Differs between studies, for details, see risk of bias assessment. The overall risk of bias for modelled studies was considered to be low**	1–2. A few of the studies were cross-sectional
			Selection bi		1–2 Some case–control studies used hospital controls
			Exposure assessment		2. Exposure assessment is uncertain in all the studies. For example, arsenic in drinking water may vary, and water intake and intake of iAs from other food vary between individuals. The untertainty is assumed to be less in studies using u-tiAs, but u-tiAs mirrors variability in exposure. In most cases the misclassification will be non-differential causing an underestimation of a true risk
			Outcome assessment		1–2. A few studies used self-reported outcomes.
			Confounding		2. Residual confounding is always possible. Some studies have probably over-adjusted for covariates in the causal chain

(Continues)

TABLE 35 (Continued)

Main group	Sub-group	Overarching questions	Description of uncertainty	Uncertainty[a]	Priority ranking[b]
	Dose–response analysis of critical end points	Is there uncertainty regarding the dose response analysis e.g. trend occurrence, large data variation, possible covariates?	Small number of cases in some of the studies	**Yes**	2
			Geographical representativeness and consistency and human variability due to genetic differences	**Yes**	1
			Human variability due to genetic differences	**Yes**	2
	Selection of RP	Are there uncertainties in the selection of the RP that are not covered by the BMD confidence interval e.g. is model uncertainty covered?	May not cover all uncertainties related to epidemiological studies, and dose–response analysis of critical endpoint(s) Variation	**Yes**	2
		Is there uncertainty on the relevance of the selected BMR and (how) will this affect the results from BMD analysis?	Selection of a relatively low BMR may increase uncertainty of the BMD and BMDL at the BMR	**Yes**	2
Risk characterisation	**Risk metric**		Uncertainty due to uncertainty in exposure estimates and RP/BMDs	**Yes**	2

Abbreviations: ADME, absorption, distribution, metabolism, excretion; As, arsenic; bi, bias; BMD, benchmark dose, BMDL, benchmark dose lower confidence limit; BMR, benchmark response, CONTAM, Panel on Contaminants in the Food Chain; iAs, inorganic arsenic; RP, reference point; U, uncertainty, u-tiAs, total urinary inorganic arsenic (sum of iAs and its methylated metabolites MMA and DMA).

[a]Yes, No or NA (not applicable).

[b]0 - negligible, 1 – low, 2 – medium, 3 – high.

3.7.2 | Assessment of BMD uncertainty

Estimating BMDs associated with low response levels, regarded to be relevant for public health, may introduce extra uncertainty compared to using higher BMRs. This includes the impact of the estimated exposure from food. While the use of a BMR of 5% (relative increase) was compatible with the BMD uncertainty criteria in EFSA (EFSA Scientific Committee, 2022) this issue is addressed in more detail by evaluating how the BMD credible interval depends on the BMR and affects the BMDLs. Also, the approach taken to modelling total exposure compared to iAs water concentrations is discussed in this section.

3.7.2.1 | *Comparison of relative BMRs of 1%–10%*

As one part, BMD uncertainty quantified by the ratio between the BMDU and BMDL was assessed across the relevant response region, i.e. at BMRs of 1, 5 and 10% (see Table 36). As expected, the BMDU to BMDL ratio increases as the BMR becomes lower. When reducing the BMR from 10% to 5%, the BMDU to BMDL ratio increases by less than a factor of 2, in all data sets. However, when further reducing the BMR from 5% to 1% the BMDU to BMDL ratio increases by more than a factor of 2 for several data sets. Also, in two instances the uncertainty at a BMR of 5% is the lowest, but in one instance it is the highest.

Considering the BMDU to BMDL ratios in combination with the BMD to BMDL ratios presented in Table 36, it can be concluded that the BMD distribution is mostly left skewed (negatively skewed) so that the BMD to BMDL ratio is larger than the corresponding BMDU to BMD ratio. Generally, this is also more pronounced as the BMR becomes lower. Overall, using a BMR of 5% is compatible with respect to uncertainty criteria in the EFSA BMD guidance (EFSA Scientific Committee, 2022). In Table 36, these criteria are violated for three data sets in the case of a BMR of 1%, considering all critical data sets adequate for modelling.

Results are herein presented and discussed for the cancer endpoints. Consideration of all critical effects (data not shown) provided a similar picture to that described above.

3.7.2.2 | *Comparison of relative BMRs of 5% and 50%*

As an extension, a substantially higher BMR of 50% (relative increase of the background incidence after adjustment for confounders) was applied for comparative purposes. This was done for bladder cancer (Chen et al., 2010b; Steinmaus et al., 2013) and lung cancer (Steinmaus et al., 2014a). These studies were deemed eligible for BMD modelling as discussed above and allowed the use of a BMR of 50%. For Gilbert-Diamond et al. (2013) a BMR of 50% is outside the response range making the BMD estimate highly unstable. Chen et al. (2010b) was selected since this data set shows the highest uncertainty in terms of the BMDU to BMDL ratio. In the case of Steinmaus et al. (2013) exposure estimates corresponding to lifetime average before 1971 were considered, and for Steinmaus et al. (2014a) exposure estimates corresponding to the 5 years of highest exposure were used. In Northern Chile the iAs levels in the drinking water decreased over the years and in the study by Steinmaus et al. (2013) the increased cancer incidences are, according to the authors, caused by the formerly much higher exposure, rather than the lower arsenic levels in water in recent decades. The background exposure from food is 0.65 and 0.3 μg/kg bw per day for the studies by Chen et al. (2010b), and Steinmaus et al. (2013, 2014a), respectively.

For Chen et al. (2010b) the $BMDU_{50}$ to $BMDL_{50}$ ratio was 6.9 (7.31/1.06), which is about a factor 5 smaller than at a BMR of 5% ($BMDU_{05}$:$BMDL_{05}$ = 5.46/0.15 = 36, Table 36). For Steinmaus et al. (2013) the $BMDU_{50}$ to $BMDL_{50}$ ratio was 2.1 (3.44/1.67). This is about three times lower than at a BMR of 5% ($BMDU_{05}$:$BMDL_{05}$ = 1.81/0.30 = 6.0, Table 36). For Steinmaus et al. (2014a) the $BMDU_{50}$ to $BMDL_{50}$ ratio was 1.9 (1.97/1.06). This is about five times smaller than at a BMR of 5% (Table 36, $BMDU_{05}$:$BMDL_{05}$ = 1.71/0.17 = 10.1, Table 36). The actual $BMDL_{50}$ for Chen et al. (2010b) and Steinmaus et al. (2013, 2014a) is about a factor 7, a factor 6 and a factor 6 higher than the $BMDL_{05}$, respectively. All BMD reports can be found in Annex E.

In conclusion, using the target BMR relevant for public health (BMR of 5%, relative increase of the background incidence after adjustment for confounders) is regarded as an approach which does not create undue uncertainty around the BMD.

3.7.2.3 | *Modelling total exposure versus water concentrations*

The BMD analysis was performed based on estimates of total exposure. The observed incidences relate to this exposure metric. An alternative is to use the water iAs concentrations as a basis for modelling. However, this will provide a dose–response shape that differs (to some degree) due to differences in relative dose spacing between the two approaches (see Appendix to Annex E5). Consequently, this may affect both the point estimate of the BMD and its uncertainty. Based on analyses of a sub-set of data for modelled outcomes, the point estimate of the BMD was generally not very different between the two approaches. However, the BMD uncertainty (BMDU to BMDL ratio) became higher (up to a factor 6) under the approach taken (total exposure) compared to first modelling the As concentrations and then adding exposure from food. The BMDLs were then also lower for the approach taken. The CONTAM panel considered that it is most appropriate to model the actual (total) dose–response relationship. The benchmark concentration (BMC) reports for the alternative modelling approach are shown in Annex E5.

3.7.3 | Quantification of uncertainty in the margin of exposure

Monte Carlo simulations were conducted to support the (data-driven) quantification of overall uncertainty. The uncertainties in estimated BMDs and exposures were characterised by probability distributions that were combined to a distribution for the margin for exposure. The probability of exceeding the BMD (i.e. probability of a MOE < 1) for each selected critical effect and exposure scenario (mean or 95th percentile of exposure for adults) was then estimated. Results of this analysis are shown in Table 36, where estimated probabilities are also classified according to the approximate probability scale recommended for harmonised use in the EFSA guidance on uncertainty analysis (EFSA Scientific Committee, 2018).

3.7.3.1 | *Technical description of the approach*

A generalised extreme value distribution was used to approximate the non-parametric BMD uncertainty distribution generated by the EFSA BMD software. The extreme value distribution was selected due to its flexibility to describe various forms of the BMD distribution, i.e. it can assume asymmetrical shapes in either direction (left or right skew), and it can also approximate a symmetrical case. The 5th percentile, the mode and 95th percentile of this distribution was first defined by the BMDL, the BMD and the BMDU, respectively. The three parameters of the generalised extreme value distribution were then estimated by using a non-linear system solver (fsolve) in Matlab. $N = 30{,}000$ BMD values were randomly generated from the estimated uncertainty distribution for each endpoint. For a number of selected critical effects (Chen, Chiou, Hsu, Hsueh, Wu, Wang, & Chen, 2010; Gilbert-Diamond et al., 2013; Steinmaus et al., 2014a) a more accurate approach was applied that uses the distribution generated by the BMD software (posterior BMD distribution) instead of a fitted generalised extreme value distribution.

The uncertainty distribution for the exposure was assumed to be uniformly distributed. The lower and upper limits of the distribution were estimated by consideration of MIN and MAX results across LB and UB scenarios for adults in Table 34. More specifically, a randomly generated value between MIN and MAX for the LB exposure scenario was combined with a randomly generated value between the MIN and MAX for the associated UB exposure scenario. From this resulting LB-UB interval, a new value was randomly generated representing one alternative exposure. As for the BMD, $N = 30{,}000$ exposure values were generated in this way (i.e. one value generated from 30,000 LB-UB intervals) with respect to the mean and the 95th percentile of exposure, respectively. The approach applied assumes that the MIN and MAX values for LB scenarios are correlated to the MIN and MAX values for associated UB scenarios. This ensures that the LB is smaller than the UB across simulated LB-UB intervals.

MOEs were estimated by Monte Carlo simulations, i.e. by randomly combining the $N = 30{,}000$ generated BMD and exposure values for each endpoint and exposure scenario. Probabilities in Table 36 correspond to the frequency of an MOE below 1.

3.7.3.2 | *General results*

Estimated probabilities of exceeding the BMD in Table 36 for the different critical effects are summarised below by consulting the approximate probability scale recommended for harmonised use in EFSA (EFSA Scientific Committee, 2018). Also, as noted in the previous section, the distribution generated by the BMD software (posterior BMD distribution) rather than a fitted extreme value distribution was used for Gilbert-Diamond et al. (2013), Chen et al. (2010b) and Steinmaus et al. (2014a) as part of the analysis. Based on these datasets, the difference in result depending on BMD distribution was small, i.e. probabilities differed by 0 to 0.03 units (see footnote in Table 36 for details).

Based on the most critical study on skin cancer it is unlikely (probability = 0.17) that the mean exposure exceeds the estimated BMD, while it is likely (probability = 0.7) that an exposure at the 95th percentile does exceed it. Considering the BMD from the other skin cancer study it is likely/very likely that both exposure scenarios exceed the estimated BMD. For both the mean and 95th percentile of exposure it is unlikely (probability = 0.16 or lower) that any of the estimated BMDs from the studies on bladder and lung cancer are exceeded. For lung cancer (Steinmaus et al., 2014a) this also applies if considering a BMD associated with a BMR of 1% instead of 5% (relative increase of the background incidence after adjustment for confounders, data not shown).

TABLE 36 Probability of exceeding the BMD (MOE < 1) associated with a BMR of 5% for adults, and information of BMD uncertainty for BMRs of 1%, 5% and 10% (relative increase of the background incidence after adjustment for confounders).

		BMDU:BMDL ratio			BMD:BMDL ratio			Probability of exceeding the BMD (BMR of 5%)[b]			
Critical effect	**Reference**	**BMR 1%**	**BMR 5%**	**BMR 10%**	**BMR 1%**	**BMR 5%**	**BMR 10%**	**Mean exposure**	**95th percentile**		
Skin cancer	Gilbert-Diamond et al. (2013)	6.4	3.4	2.6	3.7	2.4	1.8	0.17	Unlikely	0.69	Likely
	Leonardi et al. (2012)	–[a]	7.2	49	–[a]	4.3	3.2	0.86	Likely	1.0	Very likely
Bladder cancer	Chen et al. (2010b)	–[a]	37	23	–[a]	9.0	5.9	0.01	Very unlikely	0.08	Very unlikely
	Steinmaus et al. (2013)[c]	3.7	2.4	2.0	2.3	1.7	1.5	< 0.01	Very unlikely	< 0.01	Very unlikely
	Steinmaus et al. (2013)[d]	4.6	2.9	2.3	2.6	1.9	1.7	< 0.01	Very unlikely	< 0.01	Very unlikely
	Steinmaus et al. (2013)[e]	20	7.7	5.2	5.6	2.7	2.3	0.01	Very unlikely	0.10	Unlikely
	Steinmaus et al. (2013)[f]	13	6.0	4.3	5.5	3.2	2.5	< 0.01	Very unlikely	0.01	Very unlikely
Lung cancer	Chen et al. (2010a)	23	8.9	5.3	8.2	4.1	2.8	< 0.01	Very unlikely	< 0.01	Very unlikely
	Steinmaus et al. (2013)[c]	3.8	3.7	2.1	2.2	2.5	1.6	< 0.01	Very unlikely	< 0.01	Very unlikely
	Steinmaus et al. (2013)[d]	2.7	1.8	1.7	1.6	1.3	1.3	< 0.01	Very unlikely	< 0.01	Very unlikely
	Steinmaus et al. (2013)[e]	477[a]	6.6	6.3	5.7	3.4	2.6	< 0.01	Very unlikely	< 0.01	Very unlikely
	Steinmaus et al. (2013)[f]	3.5	2.3	1.9	2.2	1.7	1.5	< 0.01	Very unlikely	< 0.01	Very unlikely
	Steinmaus et al. (2014a)[g]	17	7.9	5.2	8.2	4.1	3.1	0.01	Very unlikely	0.07	Very unlikely
	Steinmaus et al. (2014a)[h]	29	10	6.6	12	4.6	3.3	0.01	Very unlikely	0.06	Very unlikely
	Steinmaus et al. (2014a)[i]	24	7.9	5.2	8.2	3.9	2.8	0.02	Very unlikely	0.16	Unlikely

Abbreviations: BMD, benchmark dose; BMDL, benchmark dose lower confidence limit, BMDU, benchmark dose upper confidence limit; BMR, benchmark response; MOE, margin of exposure.

[a]Results not compatible with criteria in EFSA guidance (EFSA Scientific Committee, 2022) related to BMD uncertainty (Best fitting model fits sufficiently well, BMDU/BMDL ≤ 50, The lowest non-zero dose/BMD ≤ 10 and BMD/BMDL ≤ 20).

[b]Estimated probabilities based on combination of uncertainty distributions for the BMD and the exposure. For Gilbert-Diamond et al. (2013), Chen et al. (2010b) and Steinmaus et al. (2014a) the posterior BMD distribution is used as part of these calculations, while the generalised extreme value distribution (parametric approach) is used for the other studies. In the latter case the BMD credible interval values were used to estimate the best parameter set for the extreme value distribution recovering the reported percentiles, and they were used to generate a parametric distribution resembling the BMD posterior distribution. In both cases a uniform uncertainty distribution is used for the exposure. Considering the mean exposure the parametric approach gives a probability of 0.14 (i.e. 0.03 units lower) for Gilbert-Diamond et al. (2013) and for Chen et al. (2010b) and Steinmaus et al. (2014a) results differ by less than 0.01 units. Considering the 95th percentile the parametric approach gives probabilities that are 0.01–0.02 units lower than the table values for Gilbert-Diamond et al. (2013), Chen et al. (2010b) and Steinmaus et al. (2014a). Estimated probabilities are classified (by terms) according to the approximate probability scale recommended for harmonised use in EFSA Scientific Committee (2018). The approximate scale has been simplified at the extremes so that all probabilities below 0.10 and above 0.90 classify as 'very unlikely' and 'very likely', respectively. Estimates below 1% are reported as < 0.01.

[c]Lifetime average, all years, based on concentrations of arsenic in water, and water intake of 1.9 L per person per day.

[d]Lifetime average, all years, based on arsenic daily intakes. The preferred exposure estimate for the study.

[e]Lifetime average before 1971, based on concentrations of arsenic in water, and water intake of 1.9 L per person per day.

[f]Lifetime average before 1971, based on arsenic daily intakes.

[g]Lifetime average, based on arsenic daily intakes.

[h]The highest 5-year average, based on arsenic daily intakes. The preferred exposure estimate for the study.

[i]The highest single year, based on arsenic daily intakes.

3.7.3.3 | *Sensitivity analyses related to exposure categories and midpoints used for dose–response modelling*

Some of the studies listed in Table 33 reported increased risk estimates for more than one way of characterising the exposure. The study by Steinmaus et al. (2014a) reported risk estimates for time-weighted average over the lifetime as well as the average for the 5 years with highest exposure and the year with the highest exposure. All three alternatives only considered exposure > 40 years back in time, so exposure at young age. The CONTAM Panel considered the average for the 5 years with highest exposure being the most relevant metric, but due to the uncertainty on this choice, sensitivity analyses were performed using also the other two metrics. As can be seen in Table 36 the results for Steinmaus et al. (2014a) for these metrics are similar. Also, it can be noted in Table 36 that probability results for the different exposure metrics in Steinmaus et al. (2013) are similar.

In some of the studies the reference category was reported as '< X μg/L' As in water (or similar when expressed for u-tiAs) and the highest exposure category was reported as '> Y μg/L'. In such cases the calculated doses used half the value of X for the reference category and the value of Y for the highest dose, but a sensitivity analysis 2 × Y was also tested for the highest dose. See Annex F for more details. For intermediate categories, the mean of the cut-offs was used as midpoint. For some key studies, such as Gilbert-Diamond et al. (2013) and Steinmaus et al. (2014a), the exact midpoints were obtained from the authors (personal communication Diane Gilbert-Diamond and Craig M. Steinmaus). Results from the sensitivity analysis are presented in Table 37 for Steinmaus et al. (2013) and Chen et al. (2010b). It is shown that doubling of Y has an effect on the BMDL, BMD and BMDU estimates. For the considered data this has no practical impact on the probability of exceeding the BMD for the mean exposure scenario. For the 95th percentile of exposure the probability changes classification from 'very unlikely' to 'unlikely' in two of the three cases.

3.7.3.4 | *Sensitivity analysis related to estimation of population size*

As mentioned in Section 3.2.4.2 (Transformations of relative risk estimates to quantal data), the source population size is one of model inputs. This parameter was occasionally not provided in the respective publications and relevant estimates were then calculated based on national statistics. Although national statistics provide the most valid source population estimates, some loss of accuracy may occur. Hence, sensitivity analyses were performed repeating the BMD modelling after increasing or decreasing the estimated source population sizes by 10 or 20% for the critical study (Gilbert-Diamond et al., 2013) and for the study by Steinmaus et al., 2014a).

When interpreting the results of this analysis, the following points are relevant:

1. For case–control studies, an estimation of the source population size must be performed since incidence rates cannot be calculated based on the cases and (sample of) controls alone.
2. Incidence rates would decrease across all exposure groups as the source population size increases.
3. Using a relative increase of the background incidence (after adjustment for confounders) as the model input, the impact on the BMD point estimate can be expected to be negligible.
4. It is the precision of the BMD estimate (and thereby the BMDL and BMDU) that is expected to be more affected by variation in the source population size.
5. No sensitivity analysis was deemed necessary regarding the case estimates since the case ascertainment and capture in the critical study was considered of low risk of bias.

Results in Table 37 show that for both studies (Gilbert-Diamond et al., 2013; Steinmaus et al., 2014a) the assessed decreases or increases in population size have negligible effects on BMD estimates and the probability of exceeding these BMDs. It should also be noted that since the case–control study uses a sample of controls from the source population to assess the distribution of exposure, the risk estimate is less precise than it is when the whole source population is used. However, the loss of precision is small if the number of controls is large (Rothman et al., 2008). For the case–control study by Gilbert-Diamond et al. (2013), the use of a sample of controls instead of the entire population decreases the lower confidence limit in the risk estimate by about 20%.

TABLE 37 Sensitivity analysis related to estimation of population size with respect to the BMD associated with a relative BMR of 5%, and the probability of exceeding this BMD for adults.

Reference	Scenario	BMDL	BMD	BMDU	Probability of exceeding the BMD[b]			
					Mean exposure	95th percentile		
Gilbert-Diamond et al. (2013), skin cancer	Reference scenario	0.062	0.15	0.21	0.14	Unlikely	0.70	Likely
	10% decrease	0.056	0.14	0.21	0.16	Unlikely	0.72	Likely
	20% decrease	0.061	0.15	0.21	0.14	Unlikely	0.70	Likely
	10% increase	0.061	0.15	0.21	0.14	Unlikely	0.70	Likely
	20% increase	0.060	0.15	0.21	0.15	Unlikely	0.71	Likely
Steinmaus et al. (2014a), lung cancer	Reference scenario[a]	0.19	0.76	1.5	< 0.01	Very unlikely	0.05	Very unlikely
	10% decrease	0.18	0.78	1.4	0.01	Very unlikely	0.05	Very unlikely
	20% decrease	0.18	0.78	1.5	0.01	Very unlikely	0.05	Very unlikely
	10% increase	0.15	0.72	1.4	0.01	Very unlikely	0.07	Very unlikely
	20% increase	0.16	0.70	1.4	0.01	Very unlikely	0.06	Very unlikely
Steinmaus et al. (2013), bladder cancer	Reference scenario[a]	0.57	1.1	1.6	< 0.01	Very unlikely	< 0.01	Very unlikely
	Highest exposure point estimate doubled	0.12	0.26	0.57	0.01	Very unlikely	0.21	Unlikely
Chen et al. (2010b), bladder cancer	Reference scenario	0.15	1.3	5.5	0.02	Very unlikely	0.06	Very unlikely
	Highest exposure point estimate doubled	0.12	0.36	2.8	0.02	Very unlikely	0.14	Unlikely
Steinmaus et al. (2013), lung cancer	Reference scenario[a]	2.1	2.8	3.8	< 0.01	Very unlikely	< 0.01	Very unlikely
	Highest exposure point estimate doubled	1.1	3.1	7.8	< 0.01	Very unlikely	< 0.01	Very unlikely

Abbreviations: BMD, benchmark dose; BMDL, benchmark dose lower confidence limit; BMDU, benchmark dose upper confidence limit.

[a]Lifetime average, based on arsenic daily intakes.

[b]Estimated probabilities based on combination of a generalised extreme value distribution for the BMD, and a uniform distribution for the exposure. For comparability the generalised extreme value distribution is used across all datasets in Table 37 while probabilities in Table 36 for datasets corresponding to reference scenarios for Gilbert-Diamond et al. (2013), Chen et al. (2010b) and Steinmaus et al. (2014a) are based on using the posterior BMD distribution as part of the analysis. Estimated probabilities are classified (by terms) according to the approximate probability scale recommended for harmonised use in EFSA (EFSA Scientific Committee, 2018). The approximate scale has been simplified at the extremes so that all probabilities below 0.10 and above 0.90 classify as 'very unlikely' and 'very likely', respectively. Estimates below 1% are reported as < 0.01.

3.7.4 | Summary on uncertainties

It is likely that the 95th percentile of exposure exceeds the estimated BMD based on Gilbert-Diamond et al. (2013). Considering the mean exposure, the quantitative analysis suggests that it is unlikely that the estimated BMD is exceeded. The other study on skin cancer suggests the BMD is likely to be exceeded (Leonardi et al., 2012). Accounting for sensitivity analyses and qualitative consideration of the impact of remaining uncertainty, the CONTAM Panel considers that conclusions based on the approximate probability scale are relevant with respect to the general population.

4 | CONCLUSIONS

4.1 | General information

The metalloid arsenic is widely present as an environmental contaminant both from natural occurrence and anthropogenic activity. Arsenic occurs in various organic and inorganic forms. In food and feed iAs species are predominantly in the +3 or +5 oxidation state, present as thio complexes or, as the oxo anions arsenite and arsenate. During sample preparation and analysis iAs bound to thio groups in peptides or proteins in food is converted to arsenite and arsenate and hence data on occurrence are nearly exclusively recorded as these two species. The sum of the quantified arsenite and arsenate in food (in mg As/kg wet weight) is often referred to as iAs. Determination of iAs consists of three main aspects: extraction, separation and element-specific detection.

4.2 | Toxicokinetics

- In humans, iAs is rapidly and to a large extent (45%–80%) absorbed after ingestion. It is widely distributed in the body in almost all organs and readily crosses the placental barrier. Little is transferred to human milk. It is metabolised in humans by reduction, oxidative methylation, thiolation and glutathiolation. The degree of methylation is crucial for its toxic effects. It is eliminated via the urine in the form of iAs and its methylated metabolites, with a half-life of around 2–3 days.
- The toxicokinetics of laboratory animals differ considerably from those of humans in particular with regard to their methylation capacity and thus results from animal experiments are not a suitable basis for human health risk assessment.

4.3 | Biomarkers of exposure

- There is no universally accepted biomarker for chronic iAs exposure.
- Measurements of total arsenic in blood or urine represent not only iAs but also organic arsenic species (e.g. originating from seafood consumption) and are thus of limited value.
- Specific measurements of iAs, and its methylated metabolites, or the sum of iAs and its methylated metabolites, also named total urinary iAs (u-tiAs), provide more appropriate estimates of iAs exposure. If continuous iAs exposure is stable over time, urinary arsenic may be used as a biomarker provided that arsenic species or u-tiAs are analysed.
- Inorganic arsenic accumulates in hair and nails. Thus, arsenic in hair and nails may also be used as biomarker for chronic iAs exposure.

4.4 | Markers of genotoxicity

- Chronic exposure to iAs via contaminated water in adulthood as well as in early life is associated with increased DNA damage (DNA breaks and oxidatively induced DNA base modifications) and clastogenic events in somatic cells from exposed individuals.

4.5 | Markers of epigenetic effects

- In utero or adult life chronic exposure to low levels of arsenic in drinking water is significantly associated with epigenetic alteration of DNA methylation levels in blood cells.

4.6 | *In vitro* and *in vivo* genotoxicity

- Although iAs does not directly interact with DNA, it induces oxidative stress, which can play a role in the formation of DNA base oxidation as well as both DNA single and double strand breaks. The production of oxidative clustered DNA lesions is likely responsible for the occurrence of double strand breaks.

- Arsenic interferes with DNA damage response at two levels: by inhibition of DNA repair and by interference with cell cycle control and apoptotic pathways. This is likely to account for the co-mutagenic effects of iAs when combined with exposure to DNA-damaging agents (e.g. UV radiation or benzo(a)pyrene).
- Inorganic arsenic is a weak mutagen but effectively induces clastogenic and aneugenic effects both *in vitro* and *in vivo* as measured by the occurrence of chromosomal aberrations, micronuclei and aneuploidy.

The methylation of iAs, particularly to trivalent methylated species, should be regarded as an activation process that forms more reactive species, which exert stronger cyto- and genotoxic effects.

4.7 | Carcinogenicity in studies with animals

- Although some studies have shown increased tumour incidence following oral (drinking water) administration of iAs, the results of different studies with respect to tumour sites and doses are inconsistent and do not provide a robust basis for use in risk assessment.

4.8 | Observations in humans and selection of critical studies

- The CONTAM Panel only considered studies including study subjects with exposure to long-term low to moderate levels of arsenic, defined as concentrations of arsenic in water of less than ~ 150 μg/L, or biomarker concentrations estimated to result from equivalent doses.
- The CONTAM Panel considers the association between low to moderate exposure to iAs and cancers of the skin, bladder and lung to be sufficient and causal.
- The CONTAM Panel considers the association between low to moderate exposure to iAs and an increased risk for spontaneous abortion, stillbirth, infant mortality, congenital heart disease, neurodevelopmental effects, ischemic heart disease, respiratory disease, chronic kidney disease and atherosclerosis to be sufficient and causal.
- The CONTAM Panel considers the evidence from epidemiological studies sufficient and causal for an association between low to moderate exposure to iAs and increased risk of skin lesions, i.e. pigmentation changes and hyperkeratosis. However, since the respective epidemiological studies were performed in low and medium income regions (Bangladesh, China) and nutrition and health status are important modifying factors, it is difficult to translate these risks to populations with more adequate nutrition, such as in Europe.
- The evidence from epidemiological studies performed in Bangladesh is sufficient to assume a causal association between low to moderate exposure to iAs and decreased birth weight. Results from other countries (Chile, Taiwan, Mongolia, Mexico, US) are mixed and thus the overall evidence is therefore insufficient. The average birth weight in Europe is much higher and undernutrition is less common. Therefore, the relevance of the evidence from Bangladesh in a European setting is unclear.
- There is insufficient evidence for an association between low to moderate exposure to iAs and breast, prostate, kidney, liver, pancreatic and gallbladder cancer, male fertility, neurotoxicity, stroke and hypertension, glucose metabolism, diabetes and metabolic syndrome.

4.9 | Dose response analysis approach

- Data from studies that were considered for dose–response modelling had to meet three criteria: (i) the overall risk of bias was considered low, (ii) the statistical analysis on the association between iAs exposure and the risk of the outcome reported by the authors had to show a statistically significant association with iAs as a continuous variable, a statistically significant trend test and/or a statistically significant increase of risk in the upper exposure category, (iii) results for at least three exposure categories (including the reference category) had to be reported.
- In the studies selected for dose–response modelling the CONTAM Panel first transformed *iAs concentrations in drinking water* (applying region specific exposure estimates from food) or urine (u-tiAs) to daily total iAs dietary exposures per kg bw per day for use in BMD calculations.
- The data analysed are adjusted incidences and resulting number of cases based on the risk ratios reported in these studies and the provided (cohort studies) or estimated (case–control studies) source population sizes.
- As BMR, a relative increase of the background incidence after adjustment for confounders by 5% was used.
- Overall, 20 of the identified potentially critical studies fulfilled all the above criteria and the respective BMD modellings that met the criteria specified in the EFSA BMD guidance (EFSA Scientific Committee, 2022) were used as the basis for the selection of an appropriate RP.

4.10 | Identification of a reference point

- The lowest BMDLs (< 0.1 μg/kg bw per day) based on a BMR of 5% (relative increase of the background incidence after adjustment for confounders) were calculated for skin cancer, skin lesions, respiratory disease and chronic kidney disease.
- Low BMDLs (≤ 0.17 μg/kg per day) were also calculated for lung cancer, bladder cancer and ischemic heart disease.
- The CONTAM Panel decided to use the $BMDL_{05}$ (0.06 μg/kg bw per day) from a case–control study on skin cancer (type: squamous cell carcinoma) in the US, as a Reference Point (RP). The results from a second skin cancer study (type: basal cell carcinomas) performed in Hungary, Romania and Slovakia support the choice for an RP for skin cancer for hazard assessment.
- The CONTAM Panel concluded that an RP of 0.06 μg iAs/kg bw per day should be considered also to cover lung cancer, bladder cancer, skin lesions, ischemic heart disease, chronic kidney disease, respiratory disease, spontaneous abortion, stillbirth, infant mortality and neurodevelopmental effects.

4.11 | Consideration of the approach to risk characterisation

- Inorganic arsenic is a genotoxic carcinogen. Both thresholded and non-thresholded mechanisms could apply to the different genotoxic effects of iAs and its trivalent and pentavalent methylated metabolites. Therefore, the CONTAM Panel concluded that it is not appropriate to establish a health-based guidance value (HBGV) and a MOE approach has been applied in the risk characterisation.

4.12 | Risk characterisation

- There are no precedents in EFSA for identification of an MOE of low concern, when using a BMDL derived from human cancer data. Therefore, the Panel decided not to determine a value for an MOE of low concern.
- The Reference Point (0.06 μg iAs/kg bw per day) identified by the CONTAM Panel for skin cancer is within the range of mean dietary exposure estimates for iAs in adults (0.03–0.15 μg/kg bw per day) and below any of the 95th percentile exposure estimates in adults (range = 0.07–0.33 μg iAs/kg bw per day). in Europe. Therefore, in adults, the MOEs range between 2 and 0.4 for mean consumers and between 0.9 and 0.2 at the 95th percentile exposure, respectively. An MOE of 1 describes the exposure level that could be associated with a 5% increase relative to the background incidence for skin cancer, based on the available data. Despite the uncertainties, the CONTAM Panel concludes that these MOEs raise a health concern.
- The CONTAM Panel notes that dietary exposure is higher in the younger age groups and therefore the respective MOEs are smaller. However, this does not necessarily indicate that children are at greater risk, because the effects are due to long-term exposure and most of the epidemiological studies are conducted in adults who would also have had higher dietary exposure during early life. Therefore, the CONTAM Panel concludes that children are covered by this risk characterisation.
- Although risk characterisation is based on the results of relatively large epidemiological studies, susceptible individuals of higher genetic risk may not be adequately represented in these studies. Therefore, dietary exposure to arsenic may be is of greater concern for such individuals than for the general population.

4.13 | Overall uncertainty in the risk characterisation

- Based on the conditional uncertainty analysis, and considering both studies on skin cancer the probability that mean exposure scenario exceeds the associated BMDs range from unlikely (likelihood ≈ 0.17) to likely (likelihood ≈ 0.86).

5 | RECOMMENDATIONS

- The CONTAM Panel notes that an EFSA guidance on the use of human data for risk assessments is needed, and in particular on BMD modelling of epidemiological data and for a quantitative risk assessment for genotoxic carcinogens based on epidemiological data is needed.
- The relevance of arsenic-induced epigenetic alterations to disease risk in exposed populations needs to be investigated.
- The interplay between epigenetic and genetic alterations induced by iAs deserves to be further investigated.
- The mechanisms of induction of DNA double strand breaks by arsenic should be investigated to clarify its mode of interaction with DNA.
- Further investigation is needed to address the mechanisms responsible for the induction of genomic instability by iAs. The health effects of pre- and perinatal exposure to arsenic and how arsenic-induced alterations occurring during early life can impact the risk of disease in adult life should be further investigated.

- The role of inter-individual variations in the susceptibility to arsenic-related health conditions should be investigated with a focus on arsenic biotransformation and differences in DNA repair.
- Several recommendations regarding the dietary exposure assessment for iAs were made in the 2021 EFSA scientific report, which are still valid.

ABBREVIATIONS

γH2AX	serine139-phosphorylated histone H2AX
8-OHdG	8-Hydroxy-2'-Deoxyguanosine
8-oxodG	8-hydroxydeoxyguanosine
A	adenine
ABI	Ankle-Barchial Index
ADHD	attention deficit hyperactivity disorder
Adj	adjusted
ADME	absorption, distribution, metabolism and excretion
ADP	adenosine diphosphate
AES	atomic emission spectrometry
aHR	adjusted hazard ratio
Akt	protein kinase B
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AO	adverse outcome
AOP	adverse outcome pathway
aOR	adjusted odds ratio
AP	apurinic/apyrimidinic
APE1	apurinic/apyrimidinic endonuclease 1
APOE ε4	apolipoprotein E ε4-allele
As	arsenic
As(III)	arsenite
As(V)	arsenate
AsB	arsenobetaine
AsMat	Health Consequences of Arsenic in Matlab
As_2O_3	arsenic trioxide
AS3MT	arsenic(III)-methyltransferase
ASCVD	atherosclerotic cardiovascular disease
ASD	autism spectrum disorder
ASHRAM	Arsenic Health Risk Assessment and Molecular Epidemiology
AST	aspartate transaminase
ATG	arsenic triglutathione
ATPase	adenosine triphosphatase
AWHS	Aragon Workers' Health Study
BCC	basal cell carcinoma
BDNF	brain-derived neurotrophic factor
BEAS-2B	bronchial epithelial airway sensitive-2B (normal human bronchial epithelial cell line)
BER	base excision repair
BfR	German Bundesinstitut für Risikobewertung
B-Hg	blood mercury
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
$BMDL_x$	benchmark dose lower confidence limit for an extra/relative risk of X% (specified in the context)
BMDU	benchmark dose upper confidence limit
$BMDU_x$	benchmark dose upper confidence limit for an extra/relative risk of X% (specified in the context)
BMI	body mass index
BMR	benchmark response
BP	blood pressure
BSID-III	Bayley Scales of Infant and Toddler Development, Third Edition
bw	body weight
BW	birthweight
CA	chromosomal aberration
CAC	coronary artery calcium
CAE	cumulative arsenic exposure
CAK	CDK-activating kinase
CANTAB	Tests from Cambridge Neuropsychological Test Automated Battery

CARDIA	Coronary Artery Risk Development in Young Adults
CARS	Childhood Autism Rating Scale
CAT	catalase
CC16	clara cell secretory protein
CCA	common carotid artery
Cd	cadmium
CD4/CD8	types of T helper cells
CFA	colony-forming ability
CHD	coronary heart disease
CI	confidence interval
CKD	chronic kidney disease
CM-H_2DCFDA	chloromethyl derivative of H_2DCFDA
CNS	central nervous system
CNV	copy number variation
Codex	Codex Alimentarius Commission
conc.	concentration
cont	control
CONTAM	the Panel on Contaminants in the Food Chain
COT	UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment
CPD	cyclobutane pyrimidine dimer
CpG	cytosine-phosphate-guanine
Cr	creatinine
CRP	C-reactive protein
CT	computed tomography
Cu	copper
CVD	cardiovascular disease
DATA Unit	EFSA Evidence Management Unit
DBP	diastolic blood pressure
DCFH-DA	2′,7′ dichloro-dihydrofluorescein diacetate
DDR	DNA damage response
DL	detection level
DM	diabetes mellitus
DMA	sum of DMA(III) and DMA(V)
DMA(III)	dimethylarsinite, dimethylarsinous acid
DMA(V)	dimethylarsinate, dimethylarsinic acid
DMAG	dimethylarsinic glutathione
DMMTA	dimethylmonothioarsenate
DN	double negative
DNMT	deoxyribonucleic acid methyltransferase
DP	double positive
DSB	double strand break
ECA	external carotid artery
ECG	electrocardiogram
EC-HPLC	high-performance liquid chromatography with electrochemical detection
EEC	European Economic Community
eGFR	estimated glomerular filtration rate
EGR1	early growth response factor 1
ELISA	enzyme linked immunosorbent assay
EMT	epithelial-to-mesenchymal transition
EPIC	European Prospective Investigation into Cancer and Nutrition
ERCC2	excision repair cross-complementation group 2
ESRD	end-stage renal disease
ETS	environmental tobacco smoke
EWAS	epigenome-wide association study
F0,1,2,3	filial generation 0, 1, 2, 3
FANCD2	Fanconi anaemia complementation group D2
FANCL	Fanconi anaemia complementation group L
FAO	Food and Agriculture Organization
FD	fluorescence detection
FDA	Food and Drug Administration (United States)
FeNo	fractional exhaled nitric oxide
FEV	forced expiratory volume

FOX	Folate and Oxidative Stress
FPG	formamidopyrimidine DNA glycosylase
FSMP	food for special medical purpose
FVC	forced vital capacity
GA	gestational age
GC	gas chromatography
GCLC	glutamate-cysteine ligase catalytic subunit
GD	gestational diabetes
GDM	gestational diabetes mellitus
gH2AX	serine139-phosphorylated histone H2AX
GI	gastrointestinal
GIA	general intellectual abilities
GIS	geographic information system
GM	geometric mean
GSH	glutathione
GST	glutathione S-transferase
GSTO1	glutathione S-transferase omega 1
GTCC	Genetic Toxicology Technical Committee
Gy	Grey
GW	gestational week
H2AX	H2A histone family member X
H_2O_2	hydrogen peroxide
HaCaT	human epidermal keratinocyte line
HAV	hepatitis A virus
HAZ	height-for-age-z-score
HbA1c	glycolated haemoglobin A1c
HBGV	health-based guidance value
HBV	hepatitis B virus
HDL	high-density lipoprotein
HEALS	Health Effects of Arsenic Longitudinal Study
HeLa cells	human cell line named after Henrietta Lacks
HepG2	human hepatoblastoma cells
HESI	Health and Environmental Sciences Institute
HG-AAS	hydride generation atomic absorption spectrometry
hOGG1	human 8-oxoguanine DNA glycosylase 1
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
HOME	Home Observation Measurement of the Environment
HPLC	high-performance liquid chromatography
HPLC-ED	high-performance liquid chromatography with electrochemical detection
HR	hazard ratio
HR	homologous recombination
HT	hypertension
iAs	inorganic arsenic
iAs(III)	arsenite
iAs(V)	arsenate
IED	intra-dimensional/extra-dimensional shift task
IgE	immunoglobulin E
IFG	impaired fasting glucose
IgG	immunoglobulin G
IARC	International Agency for Research on Cancer
IC_{50}	inhibitory concentration 50%
ICA	internal carotid artery
ICL	inter-strand DNA cross-link
ICP–MS	inductively coupled plasma mass spectrometry
IHD	ischemic heart disease
IMR-90 cells	human lung fibroblasts
IMT	intima-media thickness
IOM	Institute of Medicine
IQR	interquartile range
IQ	intelligence quotient
IRR	incidence rate ratio
iSumAs	sum of inorganic and methylated arsenic

JECFA	Joint FAO/WHO Expert Committee on Food Additives
LB	lower bound
LBW	low birth weight
LC–FD	liquid chromatography coupled to fluorescence detector
LC–MS	liquid chromatography coupled to mass spectrometry
LC–MS/MS	liquid chromatography–tandem mass spectrometry
LD50	lethal dose killing 50% of the animals
LDL	low-density lipoprotein
LIG	DNA ligase
LINE-1	long interspersed nucleotide element-1
LLN	lower limit of normal
ln	natural logarithm
LOAEC	lowest-observed-adverse-effect-concentration
LOAEL	lowest-observed-adverse-effect-level
LOD	limit of detection
LOEL	lowest-observed-effect-level
log	logarithmic
LOQ	limit of quantification
LS-174T	human epithelial colorectal adenocarcinoma cells
MAT	Math Achievement Test
MEF	mouse embryonic fibroblasts
MESA	Multi-Ethnic Study of Atherosclerosis
MeSH	Medical Subject Headings
MetS	metabolic syndrome
MG	macroglobulin
MI	myocardial infarction
MINIMat	Maternal and Infant Nutrition Interventions in Matlab
miRNA	micro ribonucleic acid
ML	maximum level
MMA	sum of MMA(III) and MMA(V)
MMA(III)	methylarsonite, monomethylarsonous acid
MMA(V)	methylarsonate, monomethylarsonic acid
MMF	maximum mid-expiratory flow
MMAG	monomethylarsonic diglutathione
MMP9	matrix metalloproteinase 9
MMSE	Mini-Mental State Examination
MN	micronucleus
MoA	mode of action
MOE	margin of exposure
MSCA	McCarthy Scales of Children's Abilities
mRNA	messenger ribonucleic acid
MS	mass spectrometry
MS/MS	tandem mass spectrometry
MTS	3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide
N7-MeG	N7-methylguanine
NA	not applicable
NAC	*N*-acetyl-L-cysteine
NAFLD	non-alcoholic fatty liver disease
NAG	*N*-acetyl-b-D-glucosaminidase
NCEP	National Cholesterol Education Program
NER	nucleotide excision repair
NFG	normal fasting glucose
NHANES	National Health and Nutrition Examination Survey
NHBE	normal human bronchial epithelial cells
NHBF	normal human bronchial fibroblast cells
NHEJ	nonhomologous end-joining
NLM	the U.S. National Library of Medicine
NOAEL	no-observed-adverse-effect-level
NOEL	no-observed-effect-level
NS	not significant

NTD	neural tube defect
OECD	Organisation for Economic Co-operation and Development
OFC	orofacial cleft
OGG1	8-oxoguanine DNA glycosylase 1
OR	odds ratio
P95	95th percentile
PAH	polycyclic aromatic hydrocarbon
PARPzf	the first zinc finger of PARP-1
PARP-1	poly (adenosine diphosphate-ribose) polymerase 1
Pb	lead
PChE	plasma cholinesterase
PEF	peak expiratory flow rate
PERCH	Pneumonia Etiology Research for Child Health
PFGE	pulse field gel electrophoresis
PIR	Poverty Income Ratio
PLK1	polo-like kinase 1
PM	particulate matter
PMI	primary methylation index
PCR	polymerase chain reaction
Pol β/POLB	DNA polymerase beta
PP	photoproduct
ppb	parts per billion
ppm	parts per million
PPVT	Peabody Picture Vocabulary Test
PTB	preterm birth
PTM	post translational modification
PTWI	provisional tolerable weekly intake
Q	quantile
RA	risk assessment
RBC	red blood cells
RC	risk characterisation
RCC	relative cell count
REGARDS	the REasons for Geographic and Racial Differences in Stroke
RNS	reactive nitrogen species
RONS	reactive oxygen and nitrogen species
ROS	reactive oxygen species
RP	reference point
RR	relative risk or risk ratio
RT-PCR	reverse transcriptase-polymerase chain reaction
RWPE-1	immortalised normal prostate epithelial cells
SAM	S-adenosylmethionine
sBDNF	serum brain-derived neurotrophic factor
SBP	systolic blood pressure
SCC	squamous cell carcinoma
SD	standard deviation
Se	selenium
SE	standard error
SEM	standard error of the mean
SES	socioeconomic status
SG	specific gravity
SHFS	Strong Heart Family Study
SHS	Strong Heart Study
SLVDS	San Luis Valley Diabetes Study
SMI	secondary methylation index
SMR	standardised mortality ratio
SOC	Stockings of Cambridge
SOCS3	suppressor of cytokine signalling 3
SOD	superoxide dismutase
SSB	single strand break
SSP	Spatial Span
T	tertile
T2D	type 2 diabetes

tAs	total arsenic
TDI	tolerable daily intake
thio-DMA(V)	thiodimethylarsinic acid
TK	toxicokinetics
TMC	total motor composite score
TMICS	Taiwan Maternal and Infant Cohort Study
ToR	terms of reference
TWA	time-weighted average
TWI	tolerable weekly intake
U	uncertainty or enzyme unit
u-As	urinary arsenic
u-AsB	urinary arsenobetaine
UB	upper bound
u-creatinine	urinary creatinine
u-DMA	urinary DMA
UF	uncertainty factor
u-iAs	urinary inorganic arsenic
u-tiAs	total urinary inorganic arsenic (sum of iAs and its methylated metabolites MMA and DMA)
u-MMA	urinary MMA
UROtsa	immortalised human urothelial cells
UV	ultraviolet light
UVC	ultraviolet light C
UVR	ultraviolet radiation
VC	vital capacity
VH10hTert	tert-immortalised human diploid skin fibroblasts
VLBW	very low birth weight
w-As	water-arsenic
WG	working group
WHO	World Health Organization
WHR ratio	waist-to-hip ratio
WISC-IV	Wechsler Intelligence Scale for Children 4th edition
WISC-RM	Wechsler Intelligence Scale for Children Revised Mexican Version
WOSL	without skin lesions
WSL	with skin lesions
wt	wild-type
XPC	Xeroderma Pigmentosum Complementation Group C
XPE	Xeroderma Pigmentosum Complementation Group E
XRCC1	X-ray repair cross-complementing protein 1
Zn	zinc

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CONFLICT OF INTEREST

If you wish to access the declaration of interests of any expert contributing to an EFSA scientific assessment, please contact interestmanagement@efsa.europa.eu.

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PANEL MEMBERS

Margherita Bignami, Laurent Bodin, James Kevin Chipman, Jesús del Mazo, Bettina Grasl-Kraupp, Christer Hogstrand, Laurentius (Ron) Hoogenboom, Jean-Charles Leblanc, Carlo Stefano Nebbia, Elsa Nielsen, Evangelia Ntzani, Annette Petersen, Salomon Sand, Dieter Schrenk, Tanja Schwerdtle, Christiane Vleminckx, and Heather Wallace.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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Annexes

Annex A

Protocol for risk assessment

Annex A is provided as a separate pdf file containing the risk assessment protocol selected by the CONTAM Panel to update the previous risk assessments of inorganic arsenic.

Annex B

Literature searches

Annex B is provided as a separate pdf file, and it contains the details of the comprehensive literature searches conducted for the risk assessment of inorganic arsenic.

Annex C

Risk of bias analysis

Annex C is provided as a separate Excel file containing the harmonised outcome of the two independent analyses and is available on the EFSA Knowledge Junction community on Zenodo at: https://doi.org/10.5281/zenodo.10459723.

Annex D

Exposure estimates and transformations

Annex D is provided in form of two separate Excel files, Annexes D1 and Annex D2. It includes conversion of water and urine iAs concentrations to iAs exposures, as well as transformations of relative risk estimates to quantal data. The Annexes D1 and D2 are available on the EFSA Knowledge Junction community on Zenodo at the following links: https://doi.org/10.5281/zenodo.10459767 (D1) and https://doi.org/10.5281/zenodo.10460952 (D2).

Annex E

BMD reports

Annex E is provided as five separate pdf files for BMD reports (Annex E1: BMR of 5%, Annex E2: BMR of 1%, Annex E3: BMR of 10% and Annex E4: BMR of 50% (relative increase of the background incidence after adjustment for confounders). In addition, the BMC reports for the alternative modelling approach (used only for the uncertainty analysis) using BMR of 5% (relative increase of the background incidence after adjustment for confounders) are provided in Annex E5.

Annex F

BMD summary table

Annex F is provided as a separate Excel file that presents a summary of the BMD analyses (BMRs of 1%, 5%, 10% and 50% as relative increase of the background incidence after adjustment for confounders). It includes important modelling outcomes such as BMD, BMDL and BMDU values, and compares these results to the criteria specified in the EFSA BMD guidance (EFSA Scientific Committee, 2022). Study- specific details and BMD input parameters are also provided. The Annex is available on the EFSA Knowledge Junction community on Zenodo at: https://doi.org/10.5281/zenodo.10460959.

Annex G

Outcome of the public consultation

Annex G provides responses to the public consultation comments along with the original comments, all within a separate pdf file.

Annexes A, B, E and G can be found in the online version of this output (in the 'Supporting information' section).