TOX/2023/55

Committee on Toxicity of Chemicals in Food, Consumer Products, and the Environment

First Draft Statement on the Potential Risks from Arsenic in the Maternal Diet

Introduction

1. The Scientific Advisory Committee on Nutrition (SACN) last considered maternal diet and nutrition concerning offspring health in its reports on 'The influence of maternal, fetal and child nutrition on the development of chronic disease in later life' (SACN, 2011) and on 'Feeding in the first year of life' (SACN, 2018). In the latter report, the impact of breastfeeding on maternal health was also considered.

2. In 2019, SACN agreed to conduct a risk assessment on nutrition and maternal health focusing on maternal outcomes during pregnancy, childbirth, and up to 24 months after delivery; this would include the effects of chemical contaminants and excess nutrients in the diet.

3. SACN agreed that, where appropriate, other expert Committees would be consulted and asked to complete relevant risk assessments e.g., in the area of food safety advice. This subject was initially discussed during the horizon scanning item at the January 2020 meeting with a scoping paper being presented to the Committee in July 2020. This included background information on a provisional list of chemicals proposed by SACN. It was noted that the provisional list of chemicals was subject to change following discussion by the Committee on Toxicity of Chemicals in Food, Consumer Products, and the Environment (COT) which would be guiding the toxicological risk assessment process: candidate chemicals or chemical classes can be added or removed as the COT considered appropriate. The list was brought back to the COT with additional information in September 2020. Following discussion at

the meeting, it was agreed that papers on several components should be prioritised and to this end, papers on iodine, vitamin D, and dietary supplements have been or will be presented to the Committee. The remaining list of compounds was to be triaged based on toxicity and exposure.

4.   Following the discussion of the first prioritisation paper on substances to be considered for risk assessment by the COT, the Committee decided that each of the heavy metals (lead, mercury, cadmium, and arsenic (As)) should be considered in separate papers.

5.   A discussion paper (TOX-2023-20) was presented to the Committee at the March 2023 meeting, providing information on the toxicokinetics, toxicity, benchmark dose modelling and estimated exposure for total arsenic (tAs) and inorganic arsenic (iAs). The Committee highlighted that more detail was required regarding the potential epigenetic effects of As and that the aggregate exposure assessment required refinement to provide clarification of exposure estimates for the average dietary consumer alongside the values for high end consumption.

6.   Annex A is a first draft statement discussing the risks posed to maternal health by arsenic in the diet and the environment, summarising the key discussions and conclusions of the Committee. Annex A also includes an updated exposure assessment requested by the Committee. Additional information on epigenetic effects can be found in TOX/2023/54. The main information/data from this paper have also been included in the statement in Annex A.

7.   Additional information not yet considered by the Committee has been highlighted in yellow.

This is a draft statement for discussion. It does not reflect the final views of the Committee and should not be cited.

Questions for the Committee

The Committee are asked to consider:

i. Does the Committee have any comments on the structure or content of the statement?

ii. Does the Committee have any comments on the revised aggregate exposure assessment and subsequent conclusions?

iii. Taking into consideration that EFSA are in the process of updating their assessment on arsenic, do Members want to wait until this opinion is published and incorporate this in the next version of this statement?

iv. Does the Committee have any other comments?

Secretariat

October 2023

TOX/2023/55 Annex A

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Background

5.   Arsenic is a metalloid that occurs in the environment in a variety of forms and as a result of both natural and anthropogenic activity. Inorganic As (iAs) present in the environment occurs primarily in the trivalent or pentavalent oxidation states. These species are comprised mainly of complexes, such as dimethylmonoarsenate (DMA), or as arsenite (As(III)) and arsenate (As(V)) oxoanions. In food samples, iAs is often reported as As(III) and As(V), or as the sum of these as total As (tAs), even though iAs is likely bound to peptides or proteins in the food itself (EFSA, 2009). The key As species discussed in this paper are summarised in Table 1 in Appendix 1.

6.   It is generally accepted that iAs compounds are more toxic than the organic As compounds (arsenobetaine (AB), arsenosugars, and arsenolipids) that are commonly found in fish, seafood, and other marine organisms.

7.   In 2015, the European Commission (EC) set maximum levels (MLs) for iAs in rice and rice-based products. Following the European Food Safety Authority's (EFSA) updated exposure assessment in 2021, the EC established new MLs, for the commodities that contribute to As exposure, and lowered existing levels, where practical, based on occurrence data (Commission Directive 2006/125/EC of 5th December 2006) (European Commission, 2023). The EC stated that the MLs were set specifically for rice and rice-based products as the analysis of iAs in these foods is reliable (Commission Regulation (EU) 2023/465).

Previous Evaluations

8.   Expert opinions on exposure to As in food have been published by EFSA's Panel on Contaminants in the Food Chain (CONTAM) in 2009 and most recently in a draft opinion in 2023, which was considered and commented on by the COT at their September 2023 meeting (TOX/2023/46) and the associated minutes). Some information from the draft EFSA opinion has been included in this statement but it will not be considered further until it has been published by EFSA as a final opinion. The Joint Food and Agriculture Organization (FAO)/ World Health Organization (WHO) Expert Committee on Food Additives (JECFA) have published monographs on As in 1983 and most recently in 2011 (FAO/WHO, 1983; FAO/WHO, 2011). The WHO has also reviewed exposure to As via drinking water as part of the development of their 'Guidelines for Drinking Water Quality' (WHO, 2022). The International Agency for Research on Cancer (IARC) had published an evaluation of the carcinogenicity of As and As compounds in 2018, and the COT has published statements on As in response to the total dietary survey in 1999 (COT, 2003) and on As in the diet of infants and young children (COT, 2016).

9.   The COT concluded, based on the available data, that dietary exposure to organic As was unlikely to constitute a risk to health, but that dietary exposure to iAs should be as low as reasonably practicable (ALARP) since it is genotoxic and a known human carcinogen (COT, 2003).

10.   In the evaluation of As in the diet of infants and young children, the COT concluded that the benchmark dose lower limit (BMDL) (the lower 95% confidence limit of the BMD) as established by JECFA in 2011, should be used to characterise the potential risks from exposure to iAs. Therefore, exposures should be compared to the $BMDL_{0.5}$ of 3.0 µg/kg bw/day (identified for a 0.5% increased incidence of lung cancer above background) (FAO/WHO, 2011). The JECFA assessment was based on more robust and recent evidence than the EFSA evaluation from 2009. The COT agreed with the Food Standards Agency (FSA) advice for toddlers and young children (aged 1 - 4.5 years), that they should not be given rice drinks as a substitute for breast milk, infant formula, or cows' milk, and reiterated their previous conclusion

that efforts to reduce the levels of iAs in food and water should continue (COT, 2016).

11.   The most recent review on As in food was completed by the COT following a re-evaluation of the risk to public health from inorganic arsenic in food (TOX/2023/46) by EFSA due to the availability of new studies detailing the toxic effects of iAs, new information on adverse health effects and additional occurrence data/ estimate exposures.

12.   From the analysis, EFSA determined that the probability of the mean exposures exceeding the associated BMDs range from unlikely to likely (~ 0.17 to ~0.86 respectively) considering the conditional uncertainty analysis and the two skin cancer studies. EFSA further concluded that the based on the available data, an MOE of 1 describes the exposure level that could be associated with a 5% increase in incidence for skin cancer and found that the calculated MOEs raised concern for incidence of skin cancer. It was also concluded that although MOEs calculated for children are higher, this does not necessarily indicate more risk and that children would be covered by EFSAs risk characterisation. However, EFSA did note that exposure of susceptible individuals would be of greater concern due to inadequate representation of these groups in epidemiological studies.

13.   EFSA determined that guidance is needed on the use of human data for risk assessments, especially for BMDL modelling and assessment of substances that are genotoxic carcinogens based on human data. Several recommendations were also made regarding demand for evidence surrounding epigenetic alterations, mode of interaction of As with DNA, mechanisms related to genomic instability, effects of pre- and perinatal exposure, effects of early life exposure on disease progression in adult life and the role of inter-individual variation in susceptibility.

14.   The Committee acknowledged that the relationship between As and skin lesion was well established, though the mechanism was unclear, and further information was needed in this area. The Committee also stated that the output of EFSA's BMD modelling did not comply with EFSA Scientific Committee recommendations so may not be appropriate.

15.   The Committee noted that iAs is genotoxic and carcinogenic but may not necessarily be a genotoxic carcinogen. The COT stated that based on animal data an MOE of ≥10,000 would be of low concern for a genotoxic carcinogen but may be mechanistically inappropriate in this case and hence remained with a view of MOEs of <10 being an appropriate level of concern as decided previously. The Committee decided that they did not accept EFSA's view that they were unable to identify a MOE of low concern as there was no precedent for using human epidemiology data.

Absorption, Distribution, Metabolism, and Excretion (ADME)

16.   Inorganic As that has been ingested is absorbed differently depending on the solubility of the As compound, the food matrix, and the presence of other compounds in the gastrointestinal (GI) tract. Water-soluble As species are found to be more easily absorbed than fat-soluble As species (EFSA, 2009). In humans, iAs is rapidly cleared from the blood and is widely distributed to almost all organs (FAO/WHO, 2011).

17.   Bolan et al. (2021) reviewed the intestinal permeability of iAs as influenced by chelating agents and gut microbes using an in vitro GI/Caco-2 cell intestinal epithelium model. The study showed a significant decrease in the permeability of iAs (as arsenic oxide – As(III)), by 7.5% as measured by the apparent permeability coefficient value (P_{app}). Both the chelating agents and gut microbes decreased the intestinal permeability of As and hence mitigate As toxicity. Several routes of metabolism and methylation have been shown for iAs, where inter-individual differences in the capacity to metabolise As causes variation from person to person in the extent of toxicity seen (Luo et al., 2018; Paul, Majumdar and Giri, 2015; Hsu et al., 2015).

18.   Ingested iAs is excreted as As(V) and As(III), and as the pentavalent metabolites methylarsonic acid (MMA(V)) and dimethylarsinic acid (DMA(V)), with lesser amounts of the trivalent metabolites' methylarsonous acid (MMA(III)), dimethylarsinous acid (DMAA(III)), and thioarsenical metabolites. It was assumed

that methylation of iAs was a detoxification route (Gebel, 2002), however, some data suggested that the simple organic As species MMA(III) and DMA(III) appear to be more toxic than iAs (As(III) and As(V)), and have high affinity for thiols and cellular proteins indicative of their chemical reactivity (FAO/WHO, 2011).

19.   Inorganic As and its metabolites are readily excreted in the urine and bile. In humans, urinary excretion is the predominant route. The composition of urinary iAs metabolites varies from person to person and has been interpreted to reflect iAs methylation efficiency. However, the primary form of iAs excreted in human urine has been shown to be DMA(III) (Vahter, 1999).

20.   There are currently limited data on the ADME of organic As species in humans. AB, one of the main organoarsenicals found in seafood, particularly crustaceans, is not metabolised by humans and passes through the body rapidly, and is excreted unchanged (Le, Cullen and Reimer, 1994). Taylor et al. (2017) reviewed human exposure to organic As from seafood and suggested that other organic compounds, i.e. arsenolipids and arsenosugars, were shown to break down to form the major metabolite, DMA, which is excreted in urine (Raml et al., 2009).

21.   In a study performed by Buchet et al. (1981, abstract only), volunteers ingested a single oral dose of organic As (500 µg As) either as methylarsonate (MA(V)), or DMA(V). The amount of As excreted in urine after four days was 78% and 75% of the ingested dose respectively. This suggested a GI absorption of greater than 75% for pentavalent organoarsenicals. However, more recent data, suggested considerable individual variability in the absorption of arsenosugars (Raml et al., 2009).

22.   Inorganic As has been shown to readily pass through the placenta, along with its metabolites, in mammals (Lindgren et al., 1984; Willhite and Ferm, 1984) including humans with similar exposure levels in mother and foetus (Concha et al., 1998; Hall et al., 2007). Arsenic metabolism was also found to increase during pregnancy resulting in increased exposure of iAs and its metabolites to the foetus in early gestation (Concha et al., 1998; Hopenhayn et al., 2003). Data indicate that

pregnancy increases iAs metabolism independent of genotype (Gardner et al., 2012, abstract only). In contrast to the rapid transfer of iAs to the foetus, very little iAs was excreted in breast milk despite high iAs exposure from drinking water in a cohort of mothers in Bangladesh (Concha et al., 1998). As the small amounts of As passing to milk were almost entirely in the inorganic form it has been suggested that efficient maternal methylation of As protects against excretion in breast milk (Fängström et al., 2008).

Toxicity

Inorganic Arsenic

23.   Acute exposure to iAs results in clinical symptoms such as nausea, vomiting, colicky abdominal pain, and diarrhoea, with symptoms resolving within 12 hours without treatment or intervention for recovery. Other acute effects include psychosis, skin lesions, seizures, and cardiomyopathy along with effects such as respiratory failure, encephalopathy, and pulmonary oedema (Ratnaike, 2003).

24.   Chronic iAs exposure resulted in symptoms such as multisystem disease and malignancy. Health outcomes resulting from iAs toxicity varies between individuals and different geographical areas. The onset symptoms of chronic iAs poisoning are non-specific and include abdominal pain, diarrhoea, and sore throat, followed by a large range of other clinical features affecting the skin, GI, cardiovascular, neurological, genitourinary, respiratory, endocrine, and haematological systems (Ratnaike, 2003).

25.   Arsenic exposure in utero and early childhood is associated with increased mortality due to cancers, lung disease, heart attacks, kidney failure, as well as impairment of cognitive development, intelligence, and memory (WHO, 2023). Alongside these effects, there is evidence indicating neurobehavioral effects as a result of iAs exposure during childhood from exposure in areas with elevated concentrations of As in drinking water.

26.   Arsenic and associated compounds have been considered by IARC, with the most recent evaluation concluding that As and iAs compounds are carcinogenic to humans (Group 1) with sufficient evidence for carcinogenicity in particular for kidney, liver, and prostate. The iAs complexes dimethylarsinic acid (DMAA(V)) and MMA(V) are possibly carcinogenic to humans (Group 2B). Arsenobetaine and other organic As compounds not metabolized in humans were not classifiable as to their carcinogenicity to humans (Group 3). IARC concluded that trivalent iAs is carcinogenic in utero by, including but not limited to, disrupting the oestrogen receptor, glucocorticoid receptor, and other steroid signalling, altered expression of genes and acquired resistance to apoptosis allowing survival of cells with deoxyribonucleic acid (DNA) damage (IARC, 2018).

27.   A review of the mechanisms of iAs toxicity (Ratnaike et al., 2003) found that iAs can inactivate up to 200 enzymes, that are notably involved in DNA replication/repair and cellular energy pathways. Arsenic was found to be substituted for phosphate in compounds like adenosine triphosphate (ATP) and free As has been shown to exhibit toxicity via reactive oxygen species (ROS) causing DNA damage and lipid peroxidation (Cobo and Castiñeira, 1997). Reactive oxygen intermediates can enter redox cycling and disrupt metabolic activation processes.

Organic Arsenic

28.   A review of the toxicity of organoarsenicals and their potential adverse effects showed that in general, the lower the oxidation state of the organic compound the higher the toxicity and hence the higher the rate of methylation to produce arsenic species with lower toxicity (Luvonga et al., 2020).

29.   No acute toxicity has been reported for organic compounds such as arsenolipids and arsenosugars, and their potential mechanisms of action (MoA) and toxicity are yet to be fully elucidated. It has been suggested that the toxicity of these compounds arises from the formation of more toxic metabolites. Arsenocholine (AC) is a known precursor for AB synthesis and does not break down to iAs, MMA, or DMA, and hence, was considered benign. Similarly, AB was found to be a stable

non-toxic As species, resisting hydrolysis and metabolism in humans, and being eliminated from the body unchanged. Arsenosugars on the other hand were more susceptible to degradation/metabolism in the body where some arsenosugars, primarily in the trivalent oxidation state, have shown toxicity to the cell. However, these species have never been detected in biological systems. Arsenolipids showed similarities in their metabolites with iAs(III) which is a defined carcinogen and hence are an organic As species of toxicological concern (Luvonga et al., 2020).

Maternal/ Pregnancy Effects

30.   Of the 489 births recorded in a cohort selected from a population in rural Bangladesh, 109 adverse pregnancy outcomes were recorded (18.3%) including 23 stillbirths (3.9%) and 60 spontaneous abortions (10.0%). Higher prenatal urinary tAs concentrations were associated with an increased risk of adverse pregnancy outcomes (Shih et al., 2017). These data agreed with a previous meta-analysis (Quansah et al., 2015), and other studies, and reviews (Ahmad et al., 2001; Cherry, 2008; Hopenhayn-Rich et al., 2000; Milton et al., 2005; von Ehrenstein et al., 2006). However, some studies have not demonstrated an association between stillbirth (Myers et al., 2010; Rahman et al., 2010) or spontaneous miscarriage (Bloom et al., 2014) following elevated levels of tAs exposure above background concentrations.

31.   Attreed et al. (2017) performed a systematic review on the association between in utero exposure to As (species not given) and immunotoxicity, through cell-mediated and humoral immunity. The review identified several studies reporting As exposure to affect the humoral immune response and increased total immunoglobin G (IgG) levels in both mothers and non-mothers. However, in pregnant women As exposure has been shown to impair transplacental transport of IgG, reducing the number of antibodies received by the foetus. Exposure to As has also been reported to increase susceptibility to viruses.

32.   Richter et al. (2022) described associations between prenatal As exposure and the risk of congenital heart disease (CHD). CHD was found to be more prevalent in infants where prenatal exposure in drinking water was ≥ 5 µg/L compared to exposure at < 5 µg/L, with 12.3 and 9.2 cases of CHD per 1,000 births respectively.

For severe CHD, infants with high maternal exposure (≥ 5.0 μg/L) had a 0.5 case increase per 1,000 births compared to exposure at lower levels. The study found that overall, even at low concentrations (0.5-0.9 μg/L), maternal exposure to iAs increases the risk of CHD in infants.

33.   A study by Ahmed et al. (2019) found no significant association between maternal tAs exposure via drinking water and offspring loss but time-varying associations with mortality. The authors concluded that the non-linear association suggested that As toxicity may vary depending on the gestational age of the foetus and that exposure to As during early gestation could invoke survival pressure of the developing foetus and hence contribute to survival bias.

34.   Susko et al. (2017) found a moderately lower probability of conception in women that experienced longer time to pregnancy (TTP) after low-level iAs exposure compared to women with shorter TTPs, and further compared to unexposed (average drinking water As level of 0 μg/L) women. When consuming an average of 1 μg/L of iAs in drinking water, the 6th, 9th, and 12th menstrual cycles showed a 5%, 8%, and 10% lower probability of pregnancy respectively.

35.   A review by Ishfaq Ahmad et al., (2021) found that As exposure had links with inhibition of oestrogen receptors, endometriosis, angiogenesis in the endometrium, sterility, and subfertility among other effects.

36.   Other toxicological effects of As including changes to neonatal gene expression, impaired neurodevelopment, increased incident of adverse birth outcomes, decreased birthweight and gestational age, immunotoxicity, increased cardiac and non-cardiac birth defects, DNA and micronuclei damage and incidence of maternal proteinuria, fecundity, changes in thyroid hormone parameters, and reproductive toxicity have been previously reviewed by; Stone et al., (2021), Wang et al., (2018), Smeester et al. (2017), Zaw and Taneepanichskul (2019), Suhl et al. (2022), Navasumrit et al., (2019), de Assis Araujo et al. (2022), Devick et al. (2022), Wang et al., (2018), (Winterbottom, Moroishi, et al., 2019), Deyssenroth et al., (2022), Wei et al., (2017), Kile et al. (2015), Abdel Hameed (2020), Chen et al. (2011), Liang et al., (2020), Liu et al. (2022), and Zargari et al., (2022).

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Epigenetic Effects

37.   Arsenic's contribution to epigenetic changes in pregnancy and maternal health are discussed in TOX/2023/54. This section will be updated to take account of the Committee's discussion of that paper.

38.   Epigenetic effects have been shown following periods of exposure to iAs/tAs and include, but are not limited to, histone modifications, non-coding ribonucleic acid (RNA) regulation and changes to DNA methylation (Chakraborty et al., 2022).

39.   Increased levels of As in amniotic fluid showed to increase expression of several genes, all associated with adverse birth outcomes and reproductive effects (Smeester et al., 2011). Exposure to tAs was also shown to affect multiple biological mechanisms in the placenta and induce sex-dependent gene expression (Winterbottom, Ban, et al., 2019) along with changes to in placental gene expression resulting in reduced foetal growth (Deyssenroth et al., 2022). Prenatal As exposure has shown to perturbate major general genes, causing epigenetic changes including CpG methylation (Laine and Fry, 2016) which have been linked with inflammatory and immune response pathways.

40.   Further review of epigenetic modifications by Chakraborty et al., (2022) found that As can strongly influence DNA methyltransferase activity (Khan et al., 2017; Rea et al., 2017; Du et al., 2018) and cause decreased hypermethylation in peripheral blood and a decrease in expression of genes and six individual CpG sites (Ameer et al., 2017). Arsenic exposure further showed to dysregulate and alter the pattern of microRNA expression in several studies (Gonzales, 2012; Gonzalez et al., 2015; Michailidi et al., 2015; Banerjee et al., 2017; Chen et al., 2017) influencing multiple microRNAs (including miR-191, miR-155, miR-21 and miR-145) that have been linked with multiorgan damage (Zeng et al., 2019). MicroRNA changes were also linked to poor outcomes for mother and neonate during gestation, where prenatal exposure was associated with silencing of key genes involved in infant immune response (Rager et al., 2014).

41.   Arsenic has also been shown to cause cancerous effects by disruption of microRNA pathways. Upregulation of miR-21 (Luo et al., 2015) and overexpression of miR-301 (Zhong et al., 2018) has been linked with lung cancer formation. Several studies have concluded that As exposure can downregulate microRNAs (Wang et al., 2014; Michailidi et al., 2015; Ngalame et al., 2016; Liu and Bain, 2018) including miR-200b, an inhibitor of cancer metastasis and tumour suppressor (Wang et al., 2011; Michailidi et al., 2015). Other studies found that As can downregulate miR-31 leading to malignant cell formation (Chen et al., 2018) and overexpression of miR-143 expression resulting in increased cell proliferation and apoptotic resistance (Ngalame et al., 2016). Histone modifications were also linked to carcinogenesis through induced structural perturbations (Martinez-Zamudio and Ha, 2011). Methyltransferases, demethylases, acetyl transferases, deiminases and kinases have all shown direct interaction with arsenicals and result in different post translational modifications of histones depending on the enzyme targeted (Bannister and Kouzarides, 2011). Phosphorylation of histones has proven to be affected by chronic As exposure in several ways, with an ultimate endpoint of DNA damage by interfering with chromosome condensation during the cell cycle (Prigent and Dimitrov, 2003; Rossetto, Avvakumov and Côté, 2012). Further cell phases have shown to be disrupted by As exposure including prometaphase and interphase (Prigent and Dimitrov, 2003; Suzuki et al., 2009) along with changes during transcriptional initiation (Lo et al., 2000; Zhang, 2003).

42.   It has been proposed that As can induce carcinogenesis via two possible mechanisms, modification of the epigenome via direct interaction with chromatin remodelers and indirectly through generation of ROS that interfere with chromatin remodelers (George et al., 2023). Another suggested mechanism is N^6-methyladenosine, a type of RNA epigenetic modification, can cause upregulation of ribosome biogenesis causing a cascade of events that can induce skin cancer (Zhao et al., 2023). Zhao et al., (2023) also discussed upregulation of RNA methyltransferase-like-3 (METTL3) as a result of is N^6-methyladenosine modifications. The authors concluded that METTL3 was associated with inflammatory homeostasis and skin lesions in exposed individuals and upregulation of this gene increased successive effects on cytokines and keratins.

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<mark>43.   Type-2 diabetes was shown to be a commonly measured outcome of As exposure where epigenetic changes and changes to miR-NA-146a, have been linked with decreased insulin secretion (Beck et al., 2019). Domingo-Relloso et al., (2022) also associated several differentially methylated positions following early life As exposure to incidence of diabetes.</mark>

Derivation of a Heath Based Guidance Value

44.   The assessments by EFSA (2009) and JECFA (2011), were reviewed by the COT in its 2016 statement for As in the infant diet. The COT concluded that the JECFA $BMDL_{0.5}$ of 3.0 µg/kg bw/day identified for lung cancer would be more appropriate to assess the potential risks from exposure to iAs (COT, 2016).

Benchmark Dose Modelling

45.   An association between As and lung cancer was observed in a cohort study in Taiwan and was the basis for the $BMDL_{0.5}$ determined by JECFA in 2011.

46.   Chen et al., (2010) evaluated cumulative exposure to iAs via drinking water from shallow wells (< 40 m in depth) over 11 years for 8,086 participants aged ≤ 40 years (4,586 households in 18 villages). All participants were interviewed via questionnaire and information such as cigarette smoking, demographic characteristics, habitual alcohol consumption status, and residential and well water consumption history were recorded. The incidence of lung cancer was determined by a review of national cancer registry profiles and newly diagnosed cases within the study period. Total dietary exposure (i.e., from food and water) was not evaluated in this study. (Chen et al, 2010).

47.   Results showed that participants drinking well water containing 10 µg/L or more of iAs at the time of enrolment or who drank well water from birth had an increased risk of lung cancer of approximately 30% (RR = 1.32, 95% CI: 0.87, 1.98 for drinking from birth; RR = 1.28, 95% CI: 0.90, 1.83 for still drinking). The authors concluded that there was a significant dose response between the risk of lung

cancer and increased iAs concentration. The dose-response relationship was less prevalent in those participants that stopped drinking well water (p = 0.115) when compared to those who still drank well water at enrolment (p = 0.002). The study found that there was approximately a 2-fold increase in risk for the highest cumulative exposure of > 10,000 μg/L. However, at iAs concentrations of 100 μg/L to 300 μg/L evidence of excess risk was displayed (RR 1.54, 0.97-2.46) and those drinking iAs concentrations above 300 μg/L showed a relative risk of 2.25 (95% CI: 1.43, 3.5) when compared to the reference group of <10 μg/L. (Chen et al., 2010)

48.   Cigarette smoking and high iAs exposure was associated with a large increase in the risk of lung cancer. Participants who had consumed water containing ≥ 100 μg/L iAs and smoked ≥ 25 packs of cigarettes per year (over the study period) showed to have a 7-fold increased risk than those participants that drank water containing iAs <10 μg/L and had never smoked cigarettes (RR = 6.97, 95% CI: 3.4, 14.3). Analysis of the combination of iAs concentration and the durations of exposure determined that participants that had been drinking high iAs concentrations (≥ 300 μg/L) for over 50 years at the time of the study resulted in a 10-fold increased risk of lung cancer (RR=9.71, 95% CI: 2.84, 33.2) than those who drank low concentrations (<10 μg/L) over 30 years or less. (Chen et al., 2010).

49.   JECFA carried out a dose-response analysis using the United States Environmental Protection Agency (USEPA) BMD software (BMDS). Nine different dichotomous models were fitted to the adjusted lung cancer dose-response data from Chen et al. (2010). The models resulting in acceptable fits, based on statistical considerations, were selected to derive BMD and the lower limit on the BMD (BMDL) values for a benchmark response (BMR) at the low end of the observed range of the data. The BMR selected at the low end of the observed data range was for a 0.5 % increased incidence over background levels. Of the nine models used, the quantal-linear model generated (along with several other equivalent models) the lowest $BMDL_{0.5}$ of 3 μg/kg bw per day. (FAO/WHO, 2011).

50.   For a quantitative assessment of the risk, only concentrations of iAs from drinking water were used and converted to total dietary exposure. Average exposure

estimates were used for volumes of water and food consumed. Average exposure values were used due to the assumptions and uncertainties in converting As concentration in drinking water to total dietary exposure. Sensitivity analysis showed that the $BMDL_{0.5}$ was in the range of 2.0 – 7.0 µg/kg bw/day, assuming that iAs exposure through drinking water (including water used in cooking) has a greater impact than exposure through food (FAO/WHO, 2011).

51.   In their statement on arsenic in the diet of infants aged 0 to 12 months and children aged 1 to 5 years (COT, 2016), the COT concluded that potential risks from the exposure of infants and young children to inorganic arsenic were characterised by margins of exposure (MOEs), calculated as the ratio of the $BMDL_{0.5}$ value of 3.0 µg/kg bw/day, to estimated exposures from dietary and non-dietary sources.

52.   While there is a widely accepted precedent for the interpretation of MOEs that have been calculated based on a BMDL for a 10% increase in the incidence of tumours in experimental animals, there is no such precedent for the interpretation of MOEs based on epidemiological studies of human cancer, in which reliable estimates of cancer incidences appreciably less than 10% are often available for use as the BMR. The Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC) has advised that such MOEs should be considered on a case-by-case basis (COC, 2012).

53.   In interpreting the MOEs calculated for inorganic arsenic, the COT noted that the BMDL that had been used was for a 0.5% increased risk of lung cancer in humans, and was based on data from a recent, well-conducted, prospective cohort study (Chen et al., 2010). Chen et al (2010) reported that the cancer risk increased with duration of exposure, which was typically of the order of decades in their study. Furthermore, the Committee noted that inorganic arsenic does not appear to exhibit direct genotoxicity; it appears instead to exhibit genotoxicity as a secondary effect, potentially following primary effects such as oxidative damage, epigenetic effects and interference with DNA damage repair. For these reasons, the Committee agreed that in this case an MOE of 10 or above would be considered of low concern.

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Exposure Assessment

Exposure from Food

54.   The FSA Exposure Assessment Team provided dietary exposure data for iAs and tAs. Exposures were derived using food consumption data from the UK dietary survey - National Diet and Nutrition Survey (Bates et al., 2014, 2016, 2020; Roberts et al., 2018), and occurrence data from the UK Total Diet Study (TDS) (FERA, 2015). Estimates provided are for inorganic As (measurement of inorganic As species only) and total As (measurement of the sum of inorganic As species and non-specified organic species) for women of childbearing age (16 – 49 years).

55.   The food groups with the highest contribution of iAs only in the diet were miscellaneous cereals (which includes rice and rice products) and potatoes with a mean exposure of 0.027 and 0.016 µg/kg bw/day respectively and 97.5[th] percentile exposure of 0.076 and 0.048 µg/kg bw/day respectively.

56.   The total mean exposure of iAs only was estimated as 0.043-0.26 µg/kg bw/day (Lower bound (LB) – Upper bound (UB)) and 97.5[th] percentile exposure 0.098 - 0.51 µg/kg bw/day (LB – UB).

57.   The food groups with the highest contribution of tAs in the diet were from the food groups fish and seafood, miscellaneous cereals, and poultry with a mean exposure of 0.74, 0.018 and 0.0062 µg/kg bw/day respectively, and 97.5[th] percentile exposure of 3.6, 0.053 and 0.022 µg/kg bw/day respectively.

58.   The total mean exposure of tAs was estimated as 0.77-0.89 µg/kg bw/day (LB – UB) and P97.5 of 3.6-3.8 µg/kg bw/day (LB – UB).

Exposure from Drinking Water

59.   Data for tAs (measurement of the sum of inorganic As species and non-specified organic species) in drinking water was obtained from the Drinking Water

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Inspectorate (DWI) for England and Wales and the Drinking Water Quality Regulator (DWQR) for Scotland and Northern Ireland Water.

60.   The FSA Exposure Assessment Team provided values for water consumption for women of childbearing age, as provided in Table 1. The 97.5th percentile exposure ranged between 0.15 and 0.93 ng/kg bw/day.

Table 1: Mean and 97.5th percentile water consumption for women of childbearing age.

Level of Consumption	Water Consumption (mL)
Median	8
97.5th Percentile	32

Table 2: Mean and standard deviation (SD) concentrations of tAs (assumed all iAs) in tap water sampled in nations of the UK from 2018 to date and median and 97.5th percentile exposure values for women of childbearing age to tAs (assumed all iAs) from drinking water, using the mean upper bound occurrence concentration values from nations of the UK.

Region	N	LB Mean As Concentration (LB SD) (µg/L)	UB Mean As Concentration (UB SD) (µg/L)	Median As Exposure** (µg/kg bw/day)	97.5th Percentile As Exposure** (µg/kg bw/day)
England and Wales*	49638	1.96 (2.04)	2.04 (1.97)	0.00023	0.00093
Scotland	1398	0.06 (0.18)	0.35 (0.14)	0.000040	0.00016
Northern Ireland	1568	0.10 (0.18)	0.32 (0.06)	0.000040	0.00015

LB = Lower Bound: values below the limit of detection assumed to be zero.

UB = Upper Bound: values below the limit of detection assumed to be the same as the limit of detection.

*Occurrence values from 99th percentile concentrations.

**Average body weight of 70.3 kg for women of childbearing age used for exposure calculation. Value provided by the FSA EAT Team from years 1-11 of the rolling NDNS.

Exposure from Air

61.   The Department for Environment, Food and Rural Affairs (Defra) provide data on air pollution throughout the United Kingdom (UK) by using an interactive map. The data showed that across the UK, the majority of areas had an average air concentration of 0.6 ng As/m^3 or below. However, smaller pockets at higher concentrations were seen in the North of England and showed average concentrations between 1.3 and 2.4 ng As/m^3 (Department for Environment Food Rural Affairs, 2020).

62.   The WHO estimates that the average inhalation rate for a 70 kg adult is 20 m^3/day (WHO, 2000). As a worst-case scenario, if an adult female were to be continuously exposed to 2.4 ng As/m^3, this would result in a daily exposure of 48 ng As from the air. For women with an average body weight of 70.3 kg (average body weight for women of childbearing age) (value provided by the FSA Exposure Assessment Team from years 1-11 of the rolling National Diet and Nutrition Survey (NDNS)(Bates et al., 2014, 2016, 2020; Roberts et al., 2018) this gives an exposure of 0.68 ng/kg bw (0.00068 µg/kg bw/day).

63.   This exposure scenario assumed that all As in the particles inhaled was fully absorbed. However, absorption is dependent on particle size and on the number of particles that become trapped in the nasopharynx which then become unavailable resulting in overall lower absorption. Given the assumptions made, the inhalation values calculated here were conservative, hence the actual inhalation would be lower and may only contribute a small proportion of overall As exposure.

Exposure from Soil and Dust

64.   Ingestion of contaminated soil is often a result of "hand-to-mouth" activity and is a more important route of exposure for toddlers and children. However, this can still present a potential source of intake in adults, for example, through the surface of unwashed vegetables.

65.   Table 3 displays the tAs concentrations and exposures from soil for women of childbearing age. Mean and 75th percentile As concentrations from the soil in regions of England are defined as principal, ironstone, and mineralised and in Wales as principal, urban, and mineralised to assess potential exposures of adults through soil ingestion. Across the two regions, exposure (75th percentile) ranged between 0.014 and 0.075 µg/kg bw/day (Ander, Johnson and Palumbo-Roe, 2011; Ander, MR Cave and Johnson, 2013).

66.   While there is no recent data for the levels of As measured in household dust in the UK, dust ingestion was considered by the USEPA (United States, Agency for Toxic Substances and Disease Registry (ATSDR). (Syracuse Research Corporation, 2007). An ingestion rate of 50 mg soil/day was assumed based on the Contaminated Land Exposure Assessment (CLEA) model by the Environment Agency (EA) (Jeffries and Martin, 2009), which applied a consensus value from studies by the USEPA and Otte et al., (2001). It is a combined value for soil and dust as most of the evidence used to determine the ingestion rate did not differentiate between soil and household dust. Furthermore, the evidence base for selecting a representative soil ingestion rate for adults was much smaller than that for children, and as such the USEPA cautioned that the value was highly uncertain and based on a low level of confidence.

Table 3: 75th percentile exposure values for women of childbearing age to tAs from soil. Soil tAs concentrations taken from the Defra-commissioned contaminants in the soils of England report (Ander, Johnson and Palumbo-Roe, 2011; Ander, MR Cave and Johnson, 2013) and ingestion of 50 mg soil/day provided by the Environment Agency (2009).

Region	Area Name	Mean Soil Concentration (mg/kg)	Mean percentile Arsenic exposure (µg/kg bw/day) *	75th Percentile Soil Concentration (mg/kg)	75th percentile Arsenic exposure (µg/kg bw/day) *
England	Principal	16	0.011	19	0.014
England	Ironstone	73	0.052	83	0.059
England	Mineralised	181**	0.130	106	0.075
Wales	Principal	24	0.017	24	0.017
Wales	Urban	83	0.059	93	0.066
Wales	Mineralised	33	0.023	33	0.023

Urban: The three South Wales Valleys.

Principal: All samples not assigned to another domain.

Ironstone: Areas where underlying ironstones supply high levels of As. Must have >15% iron oxides.

*Calculated (to 2 significant figures) using mean and 75th percentile data and 50 mg soil/day ingestion. Average body weight for women of childbearing age used for ingestion rate is 70.3 kg. This value is provided by the FSA Exposure Assessment Team from years 1-22 of the rolling National Diet and Nutrition Survey (NDNS) ((Bates et al., 2014, 2016, 2020; Roberts et al., 2018).

**NOTE: Although mean concentration value is higher than 75th percentile, this is correct against the Ander report.

67.   Additional exposure in adults, especially pregnant women can result from Pica behaviour. Pica behaviour is described as the intentional ingestion of substances that are not described as food. Globally, it is thought that pica affects up to 28% of pregnant women, although with a high degree of geographical variability (Fawcett, Fawcett and Mazmanian, 2016). While pica presents a potential route of exposure to As in the maternal diet, it has not been considered further as part of this assessment due to the lack of data on the consumption of soil as part of pica behaviour.

Aggregate Exposure

68.　　Aggregate exposure was derived by combining mean and 97.5th percentile iAs only exposure and tAs exposure from the diet with mean exposure from all other sources (drinking water, air, and soil); dust was not considered as there were insufficient data. Aggregate exposure to As from the diet, drinking water, air, and soil for women of childbearing age are presented in Tables 2 and 3.

Table 4. Aggregate exposure (µg/kg bw/day) to As of childbearing age based on data from the total diet (97.5th percentile), drinking water, air, and soil.

Species of As	Total Diet (LB to UB) [a]	Drinking water [b]	Air	Soil [c]	Total (LB to UB)
iAs only	0.098 – 0.51	0.00023	0.00068	0.017	**0.12 – 0.53**
tAs	3.6 – 3.8	0.00023	0.00068	0.017	**3.6 – 3.8**

Values have been rounded to two significant figures.

[a] The values are from the TDS (FERA, 2015), which also included a negligible contribution from tap water.

[b] Exposure value was based on the highest average for drinking water (from England and Wales data).

[c] Exposure value is based on the highest mean for a principal location.

Table 5. Aggregate exposure (µg/kg bw/day) to As for women of childbearing age based on data from the total diet (mean), drinking water, air, and soil.

Species of As	Total Diet (LB to UB) [a]	Drinking water *	Air	Soil ^	Total (LB to UB)
iAs	0.043 - 0.26	0.00023	0.00068	0.017	**0.06 - 0.28**

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tAs		0.77 - 0.89	0.00023	0.00068	0.017	**0.79 - 0.91**

Values have been rounded to two significant figures.

[a] The values are from the TDS (FERA, 2015) reported in Appendix 3 in Annex B, Tables 12 and 13, which also includes a negligible contribution from tap water.

*Exposure value is based on the highest average for drinking water (from England and Wales data).

^ Exposure value is based on the highest mean for a principal location.

69. The data showed that relative to the diet, contributions from drinking water, air, and soil are negligible for total exposure.

Risk Characterisation

70. Paragraphs 52 and 53 described the considerations of the COT (COT, 2016) on the value of the MOE. The Committee concluded that in the instance of As an MOE of 10 or above would be unlikely to be of concern.

Food

71. For individual foods with the highest measured levels of iAs only, the resulting mean and 97.5th percentile margin of exposures (MOE) were greater than 10 and are therefore unlikely to be of concern to women of childbearing age. Based on the mean total dietary occurrence of iAs only, the mean and 97.5th percentile exposure resulted in MOEs of 12 and 6 respectively. While mean MOEs were greater than 10 and therefore unlikely to be of concern, 97.5th percentile MOEs were less than 10 and hence could be of potential concern for health.

72. For individual foods with the highest measurements of tAs, the resulting mean and 97.5th percentile MOEs were below 10 and could be a concern for health.

However, this is assuming a worst case scenario where all As in the sample is iAs only.

73.   Although mean and 97.5th percentile MOEs are below 10, these values are a conservative assumption assuming that all As in the sample is iAs only. While the As has been assumed as iAs, the main contribution of As in tAs sample is in the form of AB (organic As), which is also the main form found in crustaceans and bivalve molluscs (Kohlmeyer, Kuballa and Jantzen, 2002). The remaining species are AC (organic As) and a small amount of iAs (usually < 1%). As exposure to As from fish and seafood, is predominantly from organic As, primarily AB, and AB is considered to be of low toxicity, the contribution of As from seafood is unlikely to be of significant risk to human health.

74.   Occurrence data is often reported as tAs without differentiation of organic and inorganic species. Where this has been done, tAs has been considered exclusively as iAs, as a worst-case scenario. However, by doing so the actual exposure to (dietary) iAs may be overestimated and the associated health risks.

Drinking Water

75.   Although it was assumed that As in water is entirely iAs, the MOEs for As in drinking water from the UK were all considerably greater than 10, and therefore, a risk to health from this route of exposure is unlikely.

Air

76.   Assuming all of the reported concentrations in air were iAs as a worst-case scenario, a conservative intake resulted in an MOE of 4,400 and is therefore unlikely to be of concern to human health. In addition, the inhaled exposure levels had a minimal impact on the overall As exposure.

Soil and Dust

77.   As a worst-case scenario it was assumed that As in soil was entirely iAs.

78.   The MOEs calculated for soil ingestion across England and Wales are greater than 10 and therefore, any risks of adverse health effects from exposure to As in soil are likely to be small. The ingestion rate is highly uncertain as it was based upon a small and variable evidence base and the soil ingestion rate is likely to be conservative, particularly in combination with dust. Consequently, the actual soil ingestion rate and As exposure through this route could be much lower.

Aggregate Exposure

79.   A combined exposure assessment, considering exposure to iAs from all sources, resulted in an MOE of 11 based on mean consumption and mean dietary occurrence values of iAs only, and is therefore unlikely to be of concern to human health.

80.   A combined exposure assessment, considering exposure from iAs from all sources, resulted in an MOE of 6 based on 97.5th percentile consumption and mean dietary occurrence values of iAs only. As the MOE is below 10, aggregate exposure is of potential concern to human health.

81.   A combined exposure assessment, considering exposure to tAs from all sources, assuming that all As in the sample was iAs only, resulted in an MOE of 3 based on mean consumption and mean dietary occurrence values. As the resulting MOE is below 10, there is likely to be concern to human health. However, given the assumption that all As in the sample is iAs, this is likely to be an overestimation of risk from exposure.

82.   A combined exposure assessment, considering exposure to tAs from all sources, assuming that all As in the sample was iAs only, resulted in an MOE of 1 based on 97.5th percentile consumption and mean dietary occurrence values. As the MOE is below 10, aggregate exposure is of potential concern to human health. As the resulting MOE is below 10, there is likely to be concern to human health. However, given the assumption that all As in the sample is iAs, this is likely to be an overestimation of risk from exposure.

83.   Aggregate exposure was likely driven by iAs exposure from the diet, with potential concerns for adverse health effects resulting from the entire diet for high consumers (97.5th percentile). Contributions from drinking water, air and soil (including dust) were small and unlikely to be of concern (MOEs > 10).

Conclusions

84.   Arsenic is a heavy metal pollutant that is abundant in the environment and is present in the general diet of the population, including women of childbearing age through ingestion of foods such as fish, seafood, and rice. Arsenic is proven to exist in different forms and many species have been identified.

85.   JECFA (FAO/WHO, 2011) derived a BMDL$_{0.5}$ of 3.0 µg/kg bw/day for a 0.5% increase in the incidence of lung cancer which has been used in the present assessment to conclude on the potential risks of iAs from the maternal diet. Based on the evaluation by JECFA and guidance from the COC, the COT had previously determined that MOEs of 10 or above would be considered unlikely to be of concern to human health (COT, 2016).

86.   The MOEs calculated for iAs exposure (from the foods with the highest measured concentrations of iAs) from the diet were greater than 10 for mean and 97.5th percentile exposure and therefore unlikely to be of concern to women of childbearing age.

87.   The MOEs calculated for iAs exposure only (from mean dietary exposure) from the diet, the mean and 97.5th percentile exposure resulted in MOEs of 12 and 6 respectively. While mean MOEs were greater than 10 and therefore unlikely to be of concern, 97.5th percentile MOEs were less than 10 and hence of potential concern for health.

88.   The MOEs calculated for As exposure (assumed to be iAs) from drinking water, air and soil for the UK are all greater than 10 and therefore unlikely to be of concern to human health.

89.   As there are different sources of iAs exposure, it was important to also consider the overall risk. The aggregate exposure for iAs only from all sources for average consumers resulted in an MOE of 11, while the MOE for high consumers was 6. A risk to the health of women of childbearing age, specifically for high consumers, cannot be excluded.

90.   The main contribution to As exposure came from dietary sources; non-dietary sources such as water, air, soil, and dust contributed negligible quantities.

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Abbreviations

Table 6: List of abbreviations and their full meanings.

Abbreviation	Meaning
ADME	Absorption, Distribution, Metabolism and Elimination
ALARP	As Low as Reasonably Practicable
AB	Arsenobetaine
AC	Arsenocholine
ADME	Absorption, Distribution, Metabolism, Excretion
As	Arsenic
As(III)	Arsenite
As(V)	Arsenate
ATP	Adenosine triphosphate
BMDL	Benchmark dose level
CHD	Congenital heart disease
CLEA	Environment Agency in their Contaminated Land Exposure Assessment
COC	Committee on Carcinogenicity
COT	Committee on Toxicity
CONTAM	The Panel on Contaminants in the Food Chain
Defra	Department for Environment, Food and Rural Affairs
DMA	Dimethylmonoarsenate
DMA(III)	Dimethylarsinite
DMA(V)	Dimethylarsinic acid
DMAA(III)	Dimethylarsinous acid
DMAA(V)	Dimethylarsinic acid
DNA	Deoxyribonucleic acid
DWI	Drinking water inspectorate
DWQR	Drinking Water Quality Regulator
EA	Environment Agency
EC	European Commission
EFSA	The European Food Safety Authority

FAO	Food and Agriculture Organisation
FSA	Food Standards Agency
GI	Gastrointestinal
IgG	Total immunoglobin
IARC	International Agency for Research
iAs	Inorganic Arsenic
JECFA	The Joint FAO/WHO Expert Committee on Food Additives
LB	Lower bound
METTL3	Methyltransferase-like-3
ML	Maximum Levels
MA(V)	Methylarsonate
MMA(III)	Methylarsonous acid
MMA(V)	Methylarsonic acid
MoA	Mechanism of Action
MOE	Margin of Exposure
NDNS	National Diet and Nutrition Survey
P_{app}	Permeability coefficient value
RNA	Ribonucleic acid
ROS	Reactive oxygen species
SACN	The Scientific Advisory Committee on Nutrition
tAs	Total Arsenic
TDS	Total diet study
TTP	Time to pregnancy
UB	Upper bound
UK	United Kingdom
USEPA	United States Environmental Protection Agency
WHO	World Health Organisation

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Appendix 1: Names and Abbreviations for Arsenic Species (EFSA CONTAM, 2009)

Table 1: List of names, abbreviations, and comments for different As species.

Name	Abbreviation	Comment
Inorganic arsenic	iAs	The total sum of As(III) and As(V).
Arsenite	As(III)	Highly toxic compound found at low levels in most foods.
Arsenate	As(V)	Highly toxic compound that is found at trace to low levels in foods.
Arsenobetaine	AB	Non-toxic arsenic species abundant in most seafoods.
Arsenocholine	AC	Found in seafood at trace levels. This species of As is readily oxidised to AB in biological systems.
Arsenosugars	N/A	Abundant arsenic species found in seafoods.
Arsenolipids	N/A	Arsenic species found in fatty fish and fish oils.
Arsenic containing fatty acids	AsFA	Group of fat soluble arsenic species present in fish and seafood.
Arsenic containing hydrocarbons	AsHC	One of the groups of arsenolipids.
Methylarsonate	MA(V)	A metabolite of As found in human urine. Found in trace levels in seafood and terrestrial foods.
Methylarsonite	MA(III)	A toxic metabolite of iAs found in human urine. Species not normally detected in foods.
Methylarsenate	MA	N/A
Dimethylarsinate	DMA(V)	Minor arsenic species in seafoods and some terrestrial foods; the major human urine metabolite of iAs, arsenosugars and arsenolipids.
Dimethylarsinite	DMA(III)	An unstable, reactive metabolite of iAs found in human urine. Species not normally detected in foods as difficult to measure due to its instability. Species is highly toxic.
Dimethylmonoarsenate	DMA	N/A
Methylarsonous acid	MMA(III)	N/A
Methylarsonic acid	MAA(V)	N/A

Dimethylarsinous acid	DMAA(III)	N/A
Dimethylarsinic acid	DMAA(V)	N/A
Dimethylarsonic acid	DMMAA(III)	N/A
Trimethylarsine oxide	TMAO	Arsenic species found in seafood.
Tetramethylarsonium ion	TETRA	Arsenic species found in seafood.
Trimethylarsonio propionate	TMAP	Arsenic species present in seafoods.
Thio-dimethylarsinate	Thio-DMA	A metabolite of iAs and arsenosugars found in human urine.

Appendix 2: Dietary Exposure from iAs and tAs using the TDS

The UK TDS is performed routinely to calculate trends in exposure and calculate background exposure of varying commodities in the diet. 'The key principle of a TDS is that it is representative of the whole diet. It is different from many surveys in that foods are prepared as if for consumption (rather than being analysed as sold), before being pooled into groups prior to analysis. This TDS involved the purchase of 24 retail samples (one from each of the identified local authorities) for each of the 138 categories of foods established by the FSA (3312 individual samples in total)' (FERA, 2015).

Table 2: Estimated iAs population-based exposure from food consumed by women of childbearing age using data obtained from the TDS.

Food Groups	Mean iAs Exposure – LB to UB (µg/kg/day) * for Females 16-49 years	P97.5 iAs Exposure – LB to UB (µg/kg/day) * for Females 16-49 years
Bread	0-0.012	0-0.031
Misc. Cereals	0.027	0.076
Carcass meat	0-0.0041	0-0.019
Offal	0-0.00015	0-0.0026
Meat products	0-0.0064	0-0.027
Poultry	0-0.0093	0-0.033
Fish and seafood	0-0.0044	0-0.021
Fats and oils	0-0.0021	0-0.0064
Eggs	0-0.0034	0-0.016
Sugars and confectionary	0-0.0040	0-0.016
Green vegetables	0-0.0067	0-0.028
Potatoes	0.016	0.048
Other vegetables	0-0.016	0-0.052
Canned vegetables	0-0.0063	0-0.029

Fresh fruit	0-0.014	0-0.054
Fruit products	0-0.0092	0-0.051
Non-alcoholic beverages	0-0.062	0-0.15
Milk	0-0.0054	0-0.020
Dairy products	0-0.0096	0-0.036
Nuts and seeds	0-0.0010	0-0.0088
Alcoholic beverages	0-0.005	0-0.033
Meat alternatives	0-0.00057	0-0.0071
Snacks	0-0.0013	0-0.006
Desserts	0-0.0024	0-0.015
Condiments	0-0.0060	0-0.023
Tap water only	0-0.021	0-0.092
Bottled water still or carbonated	0-0.0051	0-0.041
Total^	0.043-0.26	0.098-0.51

*Values have been rounded to two significant figures.

LB - Lower bound; UB - Upper bound.

^P97.5th total values were determined from a distribution of consumption of any combination of food / drink categories rather than by summation of the individual 97.5th percentiles values for each category.

Table 3: Estimated population based tAs exposure from food consumed by women of childbearing age using data obtained from the TDS (FERA, 2015).

Food Groups	Mean tAs Exposure – LB to UB (µg/kg bw/day) * for Females 16-49 years	P97.5 tAs Exposure – LB to UB (µg/kg bw/day) * for Females 16-49 years
Bread	0-0.006	0-0.015
Misc. Cereals	0.018	0.053
Carcass meat	0-0.0021	0-0.0094

Offal	0-0.000077	0-0.0013
Meat products	0-0.0016	0-0.0069
Poultry	0.0062	0.022
Fish and seafood	0.74	3.6
Fats and oils	0-0.00052	0-0.0016
Eggs	0-0.00085	0-0.0040
Sugars and confectionary	0-0.001	0-0.004
Green vegetables	0-0.0017	0-0.0069
Potatoes	0-0.0066	0-0.019
Other vegetables	0-0.0081	0-0.026
Canned vegetables	0-0.0016	0-0.0073
Fresh fruit	0-0.0070	0-0.027
Fruit products	0-0.0023	0-0.013
Non-alcoholic beverages	0-0.062	0-0.15
Milk	0-0.0054	0-0.02
Dairy products	0-0.0024	0-0.0090
Nuts and seeds	0.00043	0.0037
Alcoholic beverages	0-0.005	0-0.033
Meat alternatives	0.00019	0.0024
Snacks	0.0012	0.0055
Desserts	0.00059	0.0038
Condiments	0.0055	0.021
Tap water only	0-0.0084	0-0.037
Bottled water still or carbonated	0-0.0020	0-0.017
Total^	0.77-0.89	3.6-3.8

*Values have been rounded to two significant figures.

LB - Lower bound; UB - Upper bound.

^P97.5th total values were determined from a distribution of consumption of any combination of food / drink categories rather than by summation of the individual 97.5th percentiles values for each category.

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Search Terms

The references cited in this discussion paper are of publications found in Ebsco, Pubmed, Scopus and Springer, searched using Lit fetch. The publications retrieved were selected using the following search terms:

Arsenic, Arsenolipids, Arsenosugars, Arsenobetaine, Arsenocholine, Organoarsenic.	**AND**	Pregnancy, Preconception, Lactation, Fertility, Pregnancy Chances, Birth Outcomes Absorption, Distribution, Metabolism.