COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Statement on potential risks from arsenic in the diet of infants aged 0 to 12 months and children aged 1 to 5 years

Introduction

1. The Scientific Advisory Committee on Nutrition (SACN) is undertaking a review of scientific evidence that will inform the Government's dietary recommendations for infants and young children. The SACN is examining the nutritional basis of the advice. The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) was asked to review the risks of toxicity from chemicals in the diet of infants, most of which has been completed, and young children. The reviews will identify new evidence that has emerged since the Government's recommendations were formulated, and will appraise that evidence to determine whether the advice should be revised. The recommendations cover diet from birth to age five years.

2. This statement addresses the risks from arsenic in the diet of infants and young children. There is one Government dietary recommendation for these age groups relating to arsenic, specifying that toddlers and young children (aged 1 to 4.5 years) should not be given rice drinks as a *substitute* for breast milk, infant formula or cows' milk. This is due to the potential for rice drinks to contain high levels of arsenic, and because of this age group's proportionally higher milk consumption and lower bodyweights compared to other consumers (DH, 2009; FSA, 2009a). In addition, the Department of Health (DH) advises that cows' milk or alternatives are not suitable as drinks for infants under 12 months old. Rice drinks are not suitable alternatives for breast milk or formula at any stage of infancy or early childhood as they are considered to be nutritionally inadequate (FSA, 2009b). The advice regarding rice drink consumption provided on NHS Choices is more precautionary and states that "*children under five shouldn't have rice drinks as they may contain unsafe levels of arsenic*" (NHS Choices, 2015).

3. The European Commission (EC) has set maximum levels (MLs) for inorganic arsenic in rice and rice-based products. The EC noted that rice is an important ingredient in a broad variety of foods intended for infants and young children, and established a separate ML for this commodity when used as an ingredient for the production of such foods. The MLs, which are described in Table 1 and are set out in Commission Regulation 2015/1006, applied from the 1st January 2016.

Table 1. Maximum levels of inorganic arsenic (as the sum of As (III) and As (V)) permitted in rice and rice-based products (Commission Regulation (EU) 2015/1006)

Food Group	Maximum Level (µg/kg)
Non-parboiled milled rice (polished or white rice)	200
Parboiled rice and husked rice	250
Rice waffles, rice wafers, rice crackers and rice cakes	300
Rice destined for the production of foods for infants and young children[a]	100

[a] Foodstuffs listed in this category as defined in Regulation (EU) No 609/2013 on food intended for infants and young children

4. This statement gives an overview of the potential risks from inorganic arsenic in the diets of infants and young children in the UK aged 0 to 12 months and 1 to 5 years, respectively. In this statement, the term 'inorganic arsenic' generally refers to the sum of the species arsenite (As(III)) and arsenate (As(V)), and the monomethylated arsenic forms (MMA as methylarsonous acid (MMA^{III}) and methylarsonic acid (MMA^{V})).

Background

5. Arsenic is a metalloid that occurs in the environment in a variety of forms as the result of both natural and anthropogenic activity. It is generally accepted that inorganic arsenic compounds are more toxic than the organic arsenic compounds that are commonly found in fish, seafood and other marine organisms (arsenobetaine, arsenosugars, and arsenolipids) (EFSA, 2009). Inorganic arsenic in the environment comprises mainly of species in the trivalent or pentavalent oxidative states, present primarily as the oxoanions arsenite (As(III)) and arsenate (As(V)), but also present as thio complexes. In food samples, inorganic arsenic is often reported as arsenite and arsenate, or as the sum of these, even though it is likely bound to thio groups in peptides or proteins in the food itself (EFSA, 2009).

6. Together with food, drinking water is considered to be one of the most significant sources of oral exposure to arsenic. A provisional guideline value of 10 µg of arsenic per litre of drinking water was established by the World Health Organization (WHO) in 1993. This is a pragmatic value that was established in view of the practical difficulties in removing arsenic from drinking water, particularly from small supplies, the practical quantification limit for arsenic, and the fact that in many countries even the provisional guideline value would not be attainable. The WHO stated that every effort should be made to keep concentrations as low as reasonably possible (WHO, 2008).

7. Absorption of arsenic varies depending on the chemical species, the solubility of the chemical form, and the matrix in which it is present; soluble arsenicals in water are highly bioavailable. In humans, inorganic arsenic is rapidly cleared from the blood (FAO/WHO, 2011), and is widely distributed to almost all organs (EFSA, 2009). Inorganic arsenic is metabolised primarily by stepwise reduction of arsenate to arsenite, followed by oxidative addition of methyl groups, although alternative pathways have also been proposed, which include formation of methylated arsenical glutathione metabolites. Ingested inorganic arsenic is excreted via the kidney as arsenate and arsenite, and as the pentavalent metabolites MMA^{V} and dimethylarsinic acid (DMA^{V}), with lesser amounts of the trivalent metabolites MMA^{III} and dimethylarsinous acid (DMA^{III}), and thioarsenical metabolites. Previously it had been assumed that methylation of inorganic arsenic was a detoxification route. It is no longer clear whether or not this is correct as, based on limited data, the simple organic arsenic species MMA^{III} and DMA^{III} appear to be more toxic than inorganic arsenic (arsenite and arsenate), and have high affinity for thiols and cellular proteins, indicative of their chemical reactivity (FAO/WHO, 2011). MMA^{III} is not usually detected in foods (MMA^{V} is a trace species found in some seafood and terrestrial foods), while DMA^{III} is a very unstable reactive species that is difficult to measure and is not detected in foods (DMA^{V} is a minor species in seafood and some terrestrial foods) (EFSA, 2009).

8. The main adverse effects associated with long-term ingestion of inorganic arsenic in humans are skin lesions, cancer, developmental toxicity, neurotoxicity[1], cardiovascular diseases[2], abnormal glucose metabolism, and diabetes[2] (EFSA, 2009). The International Agency for Research on Cancer (IARC) has reviewed arsenic on a number of occasions, concluding that it is a group 1 carcinogen with "*sufficient evidence* in humans for the carcinogenicity of mixed exposure to inorganic arsenic compounds, including arsenic trioxide, arsenite, and arsenate. Inorganic arsenic compounds, including arsenic trioxide, arsenite, and arsenate, cause cancer of the lung, urinary bladder, and skin." (IARC, 2012). There are a number of proposed mechanisms of carcinogenicity of inorganic arsenic, including oxidative damage, epigenetic effects and interference with DNA damage repair, but not direct reaction with DNA (EFSA, 2009; FAO/WHO, 2011; IARC, 2012); inorganic arsenic could therefore be considered an indirectly-acting genotoxic carcinogen.

9. There is some evidence for neurobehavioural effects of inorganic arsenic exposure during childhood, at exposure levels occurring in areas with elevated concentrations in drinking water. Most of the available studies have been performed on relatively small numbers of children, and often lack information on early life exposures to arsenic. Furthermore, neurobehavioural outcomes can be influenced by multiple other factors including age at time of examination, nutrition, and mental stimulation. There is a need for more

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[1] Mainly associated with acute exposure from deliberate poisoning/suicide, or drinking water with high concentrations (EFSA, 2009).
[2] Evidence in areas with relatively low levels of inorganic arsenic exposure is inconclusive for these adverse effects (EFSA, 2009).

longitudinal studies on neurobehavioural outcomes to evaluate the type of effects, the critical windows of exposure, and the dose-response relationship (EFSA, 2009; FAO/WHO, 2011).

10. Although few data are available regarding the toxicity of organic arsenic compounds such as arsenobetaine and the arsenosugars and arsenolipids in humans, exposure to such compounds is not generally considered to be of toxicological concern (EFSA, 2009).

11. The COT has commented on arsenic in food a number of times in the past. In general, the conclusions have been that dietary exposure to organic arsenic was unlikely to constitute a risk to health, but that dietary exposure to inorganic arsenic should be as low as reasonably practicable (ALARP), because it is genotoxic and a known human carcinogen (COT, 2008). In the context of the current statement, the COT noted that additional information on the toxicity of arsenic had emerged since their last evaluation, and that this is reflected in the fact the conclusions of the current assessment differ somewhat from those previously.

Toxicological reference point

12. Risk assessments on exposure to arsenic in food have been published by the European Food Safety Authority (EFSA) Panel on Contaminants in the Food Chain (CONTAM) (EFSA, 2009), and the Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives (JECFA) (FAO/WHO, 2011).

13. The majority of the epidemiological studies have focused on exposures to inorganic arsenic via drinking water, and have not measured or reported total dietary exposure to inorganic arsenic. The EFSA modelled the available dose-response data from key epidemiological studies on cancer and, selecting a benchmark response of 1% extra risk, calculated a range of values for the 95% lower confidence limit of the benchmark dose ($BMDL_{01}$) of 0.3 to 8.0 µg/kg bw/day. This range of $BMDL_{01}$ values was identified for cancers of the lung, skin and urinary bladder, as well as skin lesions, taking into account the possible exposures from water and food in the regions studied (EFSA, 2009). The lowest of these $BMDL_{01}$ values was from a case-control study of 151 lung cancer cases and 419 matched controls, identified from a single hospital in Chile (Ferreccio *et al*., 2000). The COT noted that there were issues with control recruitment and the authors commented this gave expected direction of bias such that there would be under-estimation of risks for highest exposures at >300 µg/L, under-estimation at 100-300 µg/L and over-estimation at 50-99 µg/L. Case-control studies are generally at greater risk of bias than a prospective cohort design, which may affect observed odds ratios.

14. The JECFA used a different approach to modelling the dose-response data, including studies in their modelling that had been published after the 2009 EFSA opinion. A BMDL of 3.0 µg/kg bw/day was reported for a 0.5%

increased incidence of lung cancer above background in the study of Chen *et al*. (2010), noting that due to the uncertainty in the exposure estimates this $BMDL_{0.5}$ could be in the range of 2.0 to 7.0 µg/kg bw/day (FAO/WHO, 2011). The COT noted that Chen *et al*. (2010) was a well-conducted prospective cohort study of farmers in north-east Taiwan, with good case ascertainment, published after the EFSA assessment. There were 6888 participants followed for 11 years, with 178 lung cancer cases, most of whom were drinking water from shallow wells with arsenic contamination of the water. The study was able to look at each of well water concentration, number of years duration of drinking well water, and cumulative exposure. There were relatively few cases at lower levels of exposure (arsenic <100 µg/L water) and, while there was a dose response relationship, risk estimates were more precise (statistically significant) at arsenic concentrations >300 µg/L water. Exclusion of those with pesticide exposure (potentially arsenic containing) did not change the findings.

15. The COT noted that lung cancer provided the lowest BMDL values in both assessments and concluded that the JECFA $BMDL_{0.5}$ of 3.0 µg/kg bw/day should be used in the characterisation of the potential risks from exposure to inorganic arsenic. This is because the JECFA value was based on the more robust evidence provided by the Chen study. Also, the JECFA opinion was more recent and supported by more extensive documentation, including more up to date epidemiological literature, and provided full details of the BMDL modelling.

16. The focus of the risk characterisation is on inorganic arsenic since this is the form that is carcinogenic.

Arsenic exposures in infants aged 0 to 12 months and young children aged 1 to 5 years

Sources of arsenic exposure

Human breast milk

17. There are limited data available on the concentration of arsenic in breast milk. Those data that are available often relate to women with high exposures to arsenic (e.g. due to the region they live in, or reliance on highly contaminated water) (EFSA, 2014), and rarely determine the species of arsenic present in samples.

18. A literature search did not identify any appropriate data for arsenic concentrations in breast milk in the UK. Therefore, a value of 0.33 µg/L, derived from a study by Björklund *et al*. (2012), has been used to estimate exposures to arsenic via breast milk in infants aged 0 to 18 months. This value was the median total arsenic concentration of 60 samples of breast milk collected in 2002-2009 from Swedish first-time mothers at 2-3 weeks postpartum. The limit of detection (LOD) was 0.007 µg/L, and the minimum

and maximum reported concentrations were 0.041 and 4.6 µg/L respectively (Björklund *et al*., 2012).

19. Of the studies where arsenic speciation in breast milk has been determined, there is disparity between the proportion of arsenic reported to be present in the inorganic form, with some studies reporting that no inorganic arsenic was detected (Björklund *et al*., 2012), and others reporting that almost all of the arsenic detected was inorganic (Fängström *et al*., 2008). Due to the inconsistent data on the proportion of inorganic arsenic likely to be present in breast milk, the exposure assessments have been performed on the conservative assumption that 100% of the arsenic is inorganic.

Infant formulae and food

20. Concentrations of inorganic arsenic (defined as the sum of As(III) and As(V), and also MMA if present) have recently been measured in an FSA survey of metals and other elements in infant formulae and foods (e.g. commercial infant foods) (referred to as the Infant Metals Survey (FSA, 2016a), and in the composite food samples of the 2014 Total Diet Study (TDS) (FSA, 2016b). With the introduction of MLs for inorganic arsenic in rice and rice-based products, it is possible that some of the exposures from these food products will decrease in time.

21. The mean and 97.5th percentile concentrations of inorganic arsenic (defined as the above) in 60 samples of rice drinks tested by the FSA were 12 and 20 µg/kg, respectively (FSA, 2009c). This testing was performed as part of an FSA survey of total and inorganic arsenic in rice drinks, and the results were used in the exposure assessments upon which the previous recommendations regarding consumption of rice drinks were based. As no new UK data are available, these concentrations have been used in the current exposure assessments for rice drinks.

22. With the introduction of different MLs for inorganic arsenic in rice intended for the production of infant foods, and for inorganic arsenic in rice cakes (i.e. not those intended for infants or young children), questions have been raised about the exposure to arsenic from consumption of rice cakes not specifically marketed for infants (referred to herein as ‘adult’ rice cakes) by those aged 0 to 5 years. Separate exposure assessments have therefore been performed to estimate the level of exposure to inorganic arsenic in infants and young children from the consumption of infant and ‘adult’ rice cakes.

23. Concentrations of inorganic arsenic in infant rice cakes have been measured in the Infant Metals Survey. The mean concentration for composite samples of 6 types of infant rice cakes[3] was 150 µg/kg (n = 6 analytical

[3] The results apply to 6 flavours of infant rice cakes from 2 different brands (4 flavours from brand A and 2 flavours from brand B). Multiple rice cakes of the same flavour were homogenised to create an overall sample size of 700g; one analytical result was provided for each of the 6 flavours.

determinations, median = 147 µg/kg, range = 74 to 256 µg/kg). It is not possible to determine a concentration for 'adult' rice cakes from the TDS as the samples that may have contained rice cakes would have been pooled with other foods for analysis (i.e. there is no 'rice cakes' sub-group).

24. A recent study by Signes-Pastor *et al*. (2016) measured the concentration of inorganic arsenic (as As(III) and As(V)) in several rice-based products commonly consumed by infants including baby rice, rice cereals and rice crackers (i.e. rice cakes (confirmed by personal communication with Dr A. Signes-Pastor, January 2016)). The researchers tested 36 samples of infant rice cakes and 61 samples of 'adult' rice cakes that were purchased from 36 food shops (15 local shops and 21 large supermarkets) in the UK in 2014. The mean and 97.5th percentile concentrations for the infant rice cakes were 127 and 187 µg/kg, respectively (median = 127 µg/kg). For the 'adult' rice cakes, the mean and 97.5th percentile concentrations were 96 and 197 µg/kg, respectively (median = 98 µg/kg) (personal communication with Dr A. Signes-Pastor, January 2016). It is noted that these data do not support the concern that exposure to arsenic from consumption of 'adult' rice cakes would be higher than from consumption of infant rice cakes.

25. The mean inorganic arsenic concentration reported in the Infant Metals Survey has been used in the exposure assessment for infant rice cakes (150 µg/kg). This concentration was used as it was consistent with that reported by Signes-Pastor *et al.* (18% higher). For the assessment of exposures from 'adult' rice cakes, the mean concentration reported by Signes-Pastor *et al*. has been used (96 µg/kg) as it was not possible to derive a value from the 2014 TDS.

Drinking water

26. In water, arsenic is most likely to be present as arsenate (As(V)) if the water is oxygenated, and arsenite (As(III)) under reducing conditions (WHO, 2011). Drinking water can therefore be a major contributor to inorganic arsenic exposure, especially in areas with high natural levels, and when factoring in its use in the preparation of other beverages and food (EFSA, 2009; WHO, 2011)).

27. EU legislation sets a maximum limit of 10 µg/L for arsenic in drinking water (Directive 98/83/EC).

28. Levels of arsenic in drinking water in 2014 from England and Wales, Northern Ireland, and Scotland were provided by the Drinking Water Inspectorate (DWI), Northern Ireland Water, and the Drinking Water Quality Regulator for Scotland, respectively. Median and 97.5th percentile values calculated from these data are shown in Table 2. These values represent the concentration of arsenic in public water supplies, and have been used to calculate exposures to arsenic from drinking water in combination with exposures from food.

Table 2. Median and 97.5th percentile concentrations (μg/L) of inorganic arsenic in water across the UK for 2014. All arsenic in water is assumed to be inorganic.

Country	Number of samples	Median concentration (μg/L)	97.5th Percentile concentration (μg/L)
England and Wales	12479	0.22	2.10
Northern Ireland	392	0.40	0.70
Scotland	1500	0.20	0.90

29. In 2014, Local Authorities held records for approximately 38,700 private water supplies in England, ~14,400 in Wales, ~20,200 in Scotland and ~1,300 in Northern Ireland. Of the private supplies in England and Wales, 67% and 85% served single dwellings respectively. The DWI estimated that in England approximately 570,000 people lived or worked on premises that relied on a private water supply, this figure was ~80,000 for Wales (DWI, 2015a,b).

30. Representative data on the concentration of arsenic in private water supplies in the UK were not available. Private water supplies are not required to be tested in the same manner as public supplies, with supplies that serve single dwellings exempt from monitoring unless requested by the owner. Where sampling of private supplies, especially those serving single dwellings, has been conducted, it is usually to enable a risk assessment because the supply has been identified as potentially high risk and therefore the results are highly likely to be skewed (personal communication from DWI, February 2016). Reports published by the DWI in 2014 indicated that for the period 2011 – 2014, of the 249 samples taken from private water supplies that served single dwellings in England, 5.6% exceeded the maximum limit for arsenic of 10 μg/L. In Wales, for the same period, 8.6% of the 35 samples tested from supplies serving single dwellings exceeded the maximum limit (DWI, 2015a, b).

31. A study by Ander *et al* (2016) reported concentrations of arsenic in samples taken from private water supplies serving single domestic dwellings in Cornwall. A total of 497 samples were tested, having been collected from different properties across Cornwall during spring 2011 and spring 2013. This was a targeted survey that focussed on Cornwall as it is an area known to have high concentrations of arsenic and other elements in the surface environment, and also has a large number of private water supplies (approximately 3,800 in 2014) (Ander *et al*, 2016).

32. Ander *et al* reported a median arsenic concentration of 0.38 μg/L and a 95th percentile concentration of 11.0 μg/L; the LOD was 0.02 μg/L and the minimum and maximum concentrations were <0.02 and 435 μg/L respectively. The authors also reported that 5% of the samples (n = 27) exceeded the maximum limit of 10 μg/L for arsenic in water, 4 samples had concentrations above 100 μg/L (Ander *et al*, 2016).

33. Although the data from Ander *et al* (2016) provide useful insight into the potential concentrations of arsenic in private water supplies serving single domestic dwellings in the UK, they are not considered to be representative of such supplies as the survey was performed in an area known to have high concentrations of arsenic due to the underlying geology and historical anthropogenic activities such as smelting and mining. Hence, it was not possible to perform a meaningful exposure assessment for private water supplies in the UK. Local authorities have procedures in place to identify high risk supplies and to take appropriate action, accordingly.

Environmental

Dust and soil

34. Arsenic can be present in soil both naturally (depending on the type of bedrock, etc.), and as the result of anthropogenic activity (e.g. mining or the use of phosphate fertilisers) (Rawlins *et* al., 2012; EFSA, 2009). The concentration of arsenic in soil therefore varies due to local geology and industrial history. Although concentrations vary, arsenic is ubiquitous in bedrock; this accounts for its presence in water and hence drinking water.

35. In typical surface soils, the most significant inorganic forms of arsenic are arsenite and arsenate, with the latter dominating under aerobic/oxidising conditions (EA, 2009). As organic arsenicals are not expected to be present in soil at high concentrations, for the purposes of the current assessment, it has been assumed that all of the arsenic present in soil is inorganic.

36. The median and 95th percentile "normal background concentrations" of total arsenic reported for the "principal domain"[4] of England were 14 mg/kg and 32 mg/kg, respectively (Department for Environment, Food and Rural Affairs (Defra), 2012 and Ander *et al*., 2011). The corresponding concentrations reported for Wales were 18 mg/kg and 36 mg/kg, respectively (Defra, 2013 and Ander *et al*., 2013). The higher of the medians and 95th percentiles have been used to estimate the exposures to arsenic from soil. No relevant data were available for arsenic concentrations in dust.

37. As the bioavailability of arsenic in soil varies with soil composition, a conservative approach has been taken for the current exposure assessments, in that it has been assumed that the bioavailability is 100%.

Air

38. Both natural (e.g. volcanic eruptions or microbial reduction) and anthropogenic (e.g. coal-fired power generation and smelting) activities

[4] This domain represents the areas which do not contain significantly elevated levels of arsenic due to specific sources of contamination. The area of land covered by the "principal domain" is ~97% of England and ~ 89% of Wales.

release arsenic into the atmosphere, mainly as arsenic trioxide (As_2O_3) particles or bound to particulate matter (EFSA, 2009).

39. EU legislation sets a target value of 6 ng/m^3 for arsenic in air (Directive 2004/107/EC); the Defra Expert Panel on Air Quality Standards recommends an annual mean air quality standard of 3 ng/m^3 total inorganic arsenic in particulate matter less than 10 µm (PM_{10}) (Defra, 2008).

40. Arsenic in atmospheric PM_{10} was measured at 23 sites and as metal deposition was measured at 4 sites across the UK in 2014. Median values from these sites ranged from 0.12 to 1.09 ng/m^3 and 99th percentile values ranged from 0.12 to 4.92 ng/m^3 (Defra, 2015). In the absence of specific information, it is assumed that all of the arsenic present in air is inorganic.

Exposure assessment

41. Consumption data (on an individual bodyweight basis) from the Diet and Nutrition Survey of Infants and Young Children (DNSIYC) (DH, 2013), and from years 1-4 of the National Diet and Nutrition Survey Rolling Programme (NDNS) (Bates *et al.*, 2014) have been used for the estimation of dietary exposures for age groups from 4 to 18 months, and 18 to 60 months, respectively. Bodyweight data used in the estimation of dietary exposure to arsenic in infants 0 to <4 months old and for non-dietary routes of exposure are shown in Table 3 below.

42. Comprehensive exposure assessments have been performed for the dietary sources of exposure to arsenic. The assessments for the non-dietary sources of exposure (i.e. soil and air) have been included to give a more holistic view of exposures, but are not as detailed, as the focus of this statement is the diet of infants and young children.

Table 3. Average bodyweights used in the estimation of arsenic exposures, when individual body weights were not available

Age group (months)	Bodyweight (kg)
0 to <4	5.9[a]
4 to <6	7.8[b]
6 to <9	8.7[b]
9 to <12	9.6[b]
12 to <15	10.6[b]
15 to <18	11.2[b]
18 to <24	12.0[c]
24 to <60	16.1[c]

[a] DH, 1994
[b] DH, 2013
[c] Bates *et al.*, 2014

Infants (0 to 12 months)

Breast milk

43. No consumption data were available for exclusive breastfeeding in infants aged 0 to 6 months. Therefore, the default consumption values used by the COT in other evaluations of the infant diet of 800 and 1200 mL for average and high level consumption (EFSA, 2009) have been used to estimate exposures to inorganic arsenic from breast milk. These estimates were based on a median total arsenic concentration of 0.33 µg/L and the assumption that 100% of this is inorganic arsenic (paragraphs 18 and 19). The ranges of exposure to inorganic arsenic in exclusively breastfed 0 to 6 month olds were 0.034 to 0.045 and 0.051 to 0.067 µg/kg bw/day in average and high level consumers, respectively (Table 4).

Table 4. Estimated inorganic arsenic exposure from exclusive breastfeeding in 0 to 6 month old infants, with breast milk containing total arsenic at 0.33 µg/L.

Arsenic concentration (µg/L)	Exposure (µg/kg bw/day)			
	Average consumer (800 mL/day)		High consumer (1200 mL/day)	
	0 to <4 months	4 to <6 months	0 to <4 months	4 to <6 months
0.33	0.045	0.034	0.067	0.051

Values rounded to 2 significant figures (SF)

44. Data on breast milk consumption for infants aged 4 to 18 months were available from the DNSIYC and the NDNS, and have been used to estimate exposures at these ages (Table 5), based on a median inorganic arsenic concentration of 0.33 µg/L. There were too few records of breast milk consumption for children older than 18 months in the NDNS to allow a reliable exposure assessment, and breast milk is expected to contribute minimally in this age group.

45. Mean exposures to inorganic arsenic for 4 to 18 month olds were 0.0080 to 0.030 µg/kg bw/day, and 97.5th percentile exposures were 0.017 to 0.053 µg/kg bw/day (Table 5).

Table 5. Estimated inorganic arsenic exposure in 4 to 18 month old infants from breast milk, containing total arsenic at 0.33 µg/L.

Exposure (µg/kg bw/day)	Age group (months)				
	4 to <6	6 to <9	9 to <12	12 to <15	15 to <18
Mean	0.030	0.022	0.013	0.010	0.0080
97.5th percentile	0.051	0.053	0.038	0.025	0.017

Values rounded to 2 SF

Infant formulae and complementary foods

46. Arsenic exposure estimates for this category were derived using occurrence data from the Infant Metals Survey (FSA, 2016a), based on both lower bound (LB) and upper bound (UB) concentrations. Exposure estimates for 0 to 4 month olds were calculated for infant formulae using the default consumption values of 800 and 1200 mL (Table 6). Consumption data from the DNSIYC were used to estimate exposures for 4 to 12 month olds (DH, 2013) (Table 7).

47. In 0 to 4 month olds, exposures to inorganic arsenic from ready-to-feed formula were 0 to 0.027 µg/kg bw/day in average consumers, and 0 to 0.041 µg/kg bw/day in high level consumers. Exposures to inorganic arsenic calculated for reconstituted formula incorporating the highest median and 97.5th percentile concentrations for inorganic arsenic in water reported in Table 2 were 0.064 to 0.28 µg/kg bw/day in average consumers, and of 0.091 to 0.42 µg/kg bw/day in high level consumers (Table 6).

Table 6. Estimated average and high level exposures to inorganic arsenic from exclusive feeding on infant formulae for 0 to 4 month olds.

Infant Formula	**Inorganic As Exposure (LB-UB Range) (µg/kg bw/day)**	
	Average consumer (800 mL/day)	**High level consumer (1200 mL/day)**
Ready-to-Feed	0-0.027	0-0.041
Dry Powder [a]	0.014-0.037	0.021-0.055
Dry Powder + median water of 0.4 µg/L [b]	0.064-0.087	0.091-0.13
Dry Powder + 97.5th percentile water of 2.1 µg/L [b]	0.25-0.28	0.38-0.42

Values rounded to 2 SF
[a] Exposure does not include the contribution from water
[b] Calculated assuming reconstituted formula comprises 85% water

48. Total mean exposures (excluding water) to inorganic arsenic from infant formulae, commercial infant foods, and other foods, for 4 to 12 month olds were 0.054 to 0.18 µg/kg bw/day, and 97.5th percentile exposures were 0.23 to 0.45 µg/kg bw/day. Total mean and 97.5th percentile exposures have also been calculated using the highest median and 97.5th percentile concentrations for inorganic arsenic in water reported in Table 2. The resulting total mean exposures were 0.056 to 0.20 µg/kg bw/day, while the 97.5th percentile exposures were 0.23 to 0.54 µg/kg bw/day (Table 7).

Table 7. Estimated exposures to inorganic arsenic from infant formulae, commercial infant foods and other foods for 4 to 12 month olds.

	Inorganic As Exposure (LB-UB Range) (µg/kg bw/d)					
Food	**4 to <6 Months (n=116)**		**6 to <9 Months (n=606)**		**9 to <12 Months (n=686)**	
	Mean	**97.5th**	**Mean**	**97.5th**	**Mean**	**97.5th**
Infant formula	0-0.014	0.0010-0.031	0-0.014	0.0010-0.031	0-0.011	0.0060-0.027
Commercial infant foods	0.044-0.064	0.21-0.26	0.061-0.089	0.20-0.29	0.057-0.082	0.22-0.31
Other foods	0.0090-0.011	0.057-0.063	0.058-0.064	0.28-0.29	0.086-0.096	0.33-0.35
Total (excl. water)	0.054-0.077	0.23-0.28*	0.12-0.16	0.35-0.41*	0.14-0.18	0.40-0.45*
Total (incl. median in water of 0.4 µg/L)	0.056-0.079	0.23-0.29	0.13-0.16	0.37-0.42	0.15-0.18	0.41-0.47
Total (incl. 97.5th percentile in water of 2.1 µg/L)	0.064-0.087	0.26-0.31	0.14-0.18	0.42-0.48	0.17-0.20	0.48-0.54

Values rounded to 2 SF
* Determined from a distribution of consumption of any combination of categories rather than by summation of the respective individual 97.5th percentile consumption value for each of the three food categories

Children aged 12 to 18 months

49. Estimated exposures to inorganic arsenic from food for children aged 12 to 18 months were calculated using occurrence data from both the Infant Metals Survey (FSA, 2016a), and the 2014 TDS (FSA, 2016b). The exposure data derived from the Infant Metals Survey allow estimation of inorganic arsenic exposure in infant formula, commercial infant foods and the most commonly consumed adult foods (‘other foods’) as sold, whereas the results from the TDS are based on analysis of food that is prepared as for consumption. In addition, the Infant Metals Survey included analysis of infant formulae and commercial infant foods which are not included in the TDS. Exposure estimates based on both LB and UB concentrations are provided.

50. The consumption data from the DNSIYC were used for the estimation of exposure for children aged 12 to 18 months (DH, 2013).

Exposure estimates based on the Infant Metals Survey

51. The ranges of total mean and 97.5th percentile exposures (excluding water) to inorganic arsenic from infant formula, commercial infant foods and

other foods were 0.14 to 0.17 and 0.42 to 0.47 µg/kg bw/day, respectively. The total mean exposures including water (calculated using the highest median and 97.5th percentile values in Table 2) were 0.14 to 0.20 µg/kg bw/day, while the 97.5th percentile exposures including water were 0.44 to 0.56 µg/kg bw/day (Table 8).

Table 8. Estimated exposures to inorganic arsenic from infant formulae, commercial infant foods and other foods in children aged 12 to 18 months.

Food	**Inorganic As Exposure (LB-UB Range) (µg/kg bw/d)**			
	12 to <15 Months (n=670)		**15 to <18 Months (n=605)**	
	Mean	**97.5th**	**Mean**	**97.5th**
Infant formula	0.0010-0.0060	0.011-0.028	0.0010-0.0030	0.0090-0.022
Commercial infant foods	0.033-0.047	0.16-0.22	0.019-0.026	0.089-0.13
Other Foods	0.11-0.12	0.37-0.39	0.13-0.14	0.39-0.41
Total (excl. water)	0.14-0.17	0.43-0.47*	0.15-0.17	0.42-0.43*
Total (incl. median in water of 0.4 µg/L)	0.14-0.17	0.45-0.48	0.15-0.17	0.44-0.45
Total (incl. 97.5th percentile in water of 2.1 µg/L)	0.17-0.19	0.52-0.56	0.18-0.20	0.51-0.55

Values rounded to 2 SF
* Determined from a distribution of consumption of any combination of categories rather than by summation of the respective individual 97.5th percentile consumption value for each of the three food categories

Exposure estimates based on the TDS

52. Table 9 shows the estimated inorganic arsenic exposures calculated using the TDS data for children aged 12 to 18 months. The inorganic arsenic concentration for tap water in the TDS was reported as <1 µg/L, which is similar to, but less precise than, the data reported for water across the UK in Table 2. The calculation was therefore performed using the highest median (0.4 µg/L) and 97.5th percentile (2.1 µg/L) inorganic arsenic concentrations in water reported in Table 2.

53. This results in total mean and 97.5th percentile exposures to inorganic arsenic from a combination of all food groups of 0.13 to 0.69 and 0.32 to 1.2 µg/kg bw/day, respectively (Table 9). These are higher than those estimated from the Infant Metals Survey due to the inclusion of a greater number of

foods in the exposure estimate for the TDS. Overall the figures in Table 9 demonstrate that the arsenic content of water has a negligible impact on total dietary exposure to inorganic arsenic of young children in the UK.

Table 9. Estimated dietary exposure to inorganic arsenic based on the TDS data in children aged 12 to 18 months.

Arsenic concentration in the water	Inorganic As Exposure (LB-UB Range) (µg/kg bw/day)			
	12 to <15 Months (n=670)		15 to <18 Months (n=605)	
	Mean	97.5th	Mean	97.5th
0.4 µg/L	0.13-0.63	0.32-1.2	0.14-0.67	0.33-1.1
2.1 µg/L	0.15-0.65	0.35-1.2	0.16-0.69	0.35-1.1

Values rounded to 2 SF

54. In general, the food groups making the highest contribution to inorganic arsenic exposure were miscellaneous cereals (including rice and some rice products) and potatoes.

Children aged 18 months to 5 years

55. Exposure estimates for these age groups were derived using occurrence data from the 2014 TDS, and consumption data from the NDNS (Bates *et al*., 2014).

56. Table 10 shows the inorganic arsenic exposures that were calculated using the TDS data for children aged 18 months to 5 years. As described in paragraph 52, the exposures have been estimated using the highest median (0.4 µg/L) and 97.5th percentile (2.1 µg/L) inorganic arsenic concentrations in water reported in Table 2. This results in total mean and 97.5th percentile exposures to inorganic arsenic from a combination of all food groups of 0.13 to 0.78 and 0.26 to 1.2 µg/kg bw/day, respectively (Table 10). Overall the figures in Table 10 demonstrate that the arsenic content of water has a negligible impact on total dietary exposure to inorganic arsenic of young children in the UK.

Table 10. Estimated dietary exposure to inorganic arsenic in children aged 18 months to 5 years.

Arsenic concentration in water	Inorganic As Exposure (LB-UB Range) (µg/kg bw/day)			
	18 to <24 Months (n=70)		24 to <60 Months (n=429)	
	Mean	97.5th	Mean	97.5th
0.4 µg/L	0.15-0.76	0.29-1.2	0.13-0.62	0.26-0.99

2.1 µg/L	0.17-0.78	0.32-1.2	0.14-0.64	0.28-1.0

Values rounded to 2 SF

57. As with the younger children, the food groups making the highest contribution to inorganic arsenic exposure in the TDS were miscellaneous cereals (including rice and some rice products) and potatoes (FSA, 2016b).

Exposures from the consumption of rice drinks

58. This assessment has considered exposures in young children aged 1 to 5 years only as the DH advise that cows' milk and alternatives (i.e. rice drinks) are not suitable for infants under 12 months old (paragraph 2). There are very few consumers of rice drinks recorded in the DNSIYC and the NDNS (5 in total for 1 to 5 year olds). Therefore, the exposure estimates have been based on the consumption values for cows' milk, assuming that there is complete replacement of cows' milk with rice drinks. Mean and 97.5th percentile inorganic arsenic concentrations of 12 and 20 µg/kg in rice drinks (FSA, 2009b), have also been used (paragraph 21).

59. For young children aged 1 to 5 years, average and high level exposures range from 0.22 to 0.60 and 0.60 to 1.5 µg/kg bw/day, respectively (Table 11). The highest value for the range of high level exposures from rice drinks (for 12 to <15 month olds, 1.5 µg/kg bw/day) is more than double the upper bound mean exposure values estimated from the TDS data for this age range (Table 9). The highest values for the range of high level exposures for the remaining age groups (15 to 60 month olds) were between 1.5 and 2 times higher than the upper bound mean exposure values estimated from the TDS data for the same age groups (Tables 9 and 10).

Table 11. Estimated inorganic arsenic exposures from rice drinks for young children aged 1 to 5 years, using consumption data for cows' milk as a proxy.

Inorganic arsenic concentration	**Consumption level**	**Exposure (µg/kg bw/day)**			
		Age group (months)			
		12 to <15	**15 to <18**	**18 to <24**	**24 to <60**
Mean (12 µg/L)	Average[a]	0.36	0.34	0.32	0.22
	High[b]	0.91	0.78	0.86	0.60
97.5th percentile (20 µg/L)	Average[a]	0.60	0.57	0.53	0.36
	High[b]	1.5	1.3	1.4	1.0

Values rounded to 2 SF

[a] Based on mean consumption from the DNSIYC and the NDNS

[b] Based on 97.5th percentile consumption from the DNSIYC and the NDNS

60. Based on upper bound mean exposures for the total diet (calculated with the highest median water concentration), and on the mean concentration for inorganic arsenic in rice drinks (12 µg/L), consumption of up to about 50 mL of rice drink per day would result in less than a 10% increase in background exposure to arsenic from the total diet for this age group.

Exposures from the consumption of rice cakes

61. Exposures have been estimated using consumption data from the DNSIYC (DH, 2013) and the NDNS (Bates *et al*., 2014); separate consumption data were available for infant and ‘adult’ rice cakes. Rice cakes marketed for infants have an approximate weight of 2 g per cake while the weight of one ‘adult’ rice cake is ~10 g. A mean inorganic arsenic concentration of 150 µg/kg has been used in the assessment of infant rice cake consumption (Table 12), while a mean concentration of 96 µg/kg has been used for the assessment of ‘adult’ rice cakes (Table 13) (paragraph 25).

62. For infants aged <6 months, mean and 97.5th percentile exposures to inorganic arsenic from the consumption of infant rice cakes are 0.0060 and 0.011 µg/kg bw/day, respectively, although these values are based on a very limited number of consumers. For infants aged 6 to 12 months mean and 97.5th percentile exposures to inorganic arsenic from the consumption of infant rice cakes range from 0.023 to 0.031 and 0.068 to 0.11 µg/kg bw/day, while those from the consumption of ‘adult’ rice cakes range from 0.018 to 0.025 and from 0.035 to 0.057 µg/kg bw/day, respectively. There were no consumers of ‘adult’ rice cakes aged < 6 months.

63. For young children aged 1 to 5 years, mean and 97.5th percentile exposures from the consumption of infant rice cakes range from 0.026 to 0.035 and 0.070 to 0.12 µg/kg bw/day, while those from the consumption of ‘adult’ rice cakes range from 0.025 to 0.066 and from 0.058 to 0.11 µg/kg bw/day, respectively. The highest value of the range of 97.5th percentile exposures from infant rice cakes (for 12 to <15 month olds, 0.12 µg/kg bw/day) is ~20% of the upper bound mean exposure estimated from the TDS data for this age group (Table 9).

Table 12. Estimated inorganic arsenic exposures from infant rice cakes for infants and young children aged 4 months to 5 years.

Consumption and Exposure	**Age group (months)**						
	4 to <6	**6 to <9**	**9 to <12**	**12 to <15**	**15 to <18**	**18 to <24**	**24 to <60**
Mean consumption (g/day)	0.30	1.4	2.0	2.5	2.6	2.1	3.2
97.5th percentile consumption (g/day)	0.47	4.0	6.6	8.0	6.0	5.5	6.4

Mean consumption (g/kg bw/day)	0.040	0.16	0.21	0.23	0.23	0.18	0.20
97.5th percentile consumption (g/kg bw/day)	0.070	0.45	0.73	0.81	0.52	0.47	0.47
Mean exposure (µg/kg bw/day)	0.0060	0.023	0.031	0.035	0.035	0.026	0.029
97.5th percentile exposure (µg/kg bw/day)	0.011	0.068	0.11	0.12	0.078	0.070	0.071

Values rounded to 2 SF

Table 13. Estimated inorganic arsenic exposures from 'adult' rice cakes for infants and young children aged 4 months to 5 years.

Consumption and Exposure	**Age group (months)**						
	4 to <6	**6 to <9**	**9 to <12**	**12 to <15**	**15 to <18**	**18 to <24**	**24 to <60**
Mean consumption (g/day)	n/a	1.8	2.4	2.7	2.8	7.2	4.6
97.5th percentile consumption (g/day)	n/a	3.3	5.3	8.8	7.8	12.	7.5
Mean consumption (g/kg bw/day)	n/a	0.19	0.26	0.26	0.26	0.69	0.31
97.5th percentile consumption (g/kg bw/day)	n/a	0.36	0.59	0.80	0.73	1.2	0.61
Mean exposure (µg/kg bw/day)	n/a	0.018	0.025	0.025	0.025	0.066	0.030
97.5th percentile exposure (µg/kg bw/day)	n/a	0.035	0.057	0.077	0.070	0.11	0.058

Values rounded to 2 SF

Soil/dust

64. Potential exposures of UK infants aged 6 to 12 months and young children aged 1 to 5 years to arsenic in soil and dust were calculated assuming ingestion of 60 or 100 mg/day, respectively (US EPA, 2011a). Younger infants, who are less able to move around and come into contact with soil and dust, are likely to consume less soil and dust than children of these age groups. Median and 95th percentile soil arsenic concentrations of 18 and 36 mg/kg respectively were used in these exposure estimations (paragraph 36), and it has been assumed that all of the arsenic present in soil is inorganic (paragraph 35) (Table 14).

65. Data specific to dust were not available therefore for the purposes of this evaluation, it is assumed that concentrations in dust were the same as in soil, resulting in a relatively conservative exposure estimate.

Table 14. Possible inorganic arsenic exposures from soil and dust in infants and young children aged 6 months to 5 years.

Arsenic concentration (mg/kg)	Exposure (µg/kg bw/day)					
	Age (months)					
	6 to <9	9 to <12	12 to <15	15 to <18	18 to <24	24 to <60
18 (Median)	0.12	0.11	0.17	0.16	0.15	0.11
36 (95th percentile)	0.25	0.23	0.34	0.32	0.30	0.22

Values rounded to 2 SF

Air

66. Potential exposures of UK infants aged 0 to 12 months and young children aged 1 to 5 years to arsenic in air were estimated using the body weights shown in Table 3, and by assuming the mean ventilation rates presented in Table 15; these rates have been derived from the US EPA exposure factors handbook (US EPA, 2011b). The resulting exposures are presented in Table 16.

Table 15. Mean ventilation rates used in the estimation of arsenic exposures from air (derived from US EPA, 2011b)

Age group (months)	Ventilation rate (m^3/day)
0 to <4	3.5
4 to <6	4.1
6 to <9	5.4
9 to <12	5.4
12 to <15	8.0
15 to <18	8.0
18 to <24	8.0
24 to <60	10.1

67. The arsenic concentrations used in the exposure calculations were the lowest and highest median values and lowest and highest 99th percentile values of 0.12, 1.09, 0.12 and 4.92 ng/m^3, respectively, from monitoring sites in the UK (paragraph 40). It has been assumed that all of the arsenic present in air is inorganic (paragraph 40). These exposures are approximately 2 to 3 orders of magnitude lower than those estimated from other sources.

Table 16. Possible exposures to inorganic arsenic in infants and young children from the air

Arsenic concentration (ng/m^3)	**Exposure (µg/kg bw/day)**							
	Ages (months)							
	0 to <4	**4 to <6**	**6 to <9**	**9 to <12**	**12 to <15**	**15 to <18**	**18 to <24**	**24 to <60**
0.12 (lowest median value)	0.000070	0.000060	0.000070	0.000070	0.000090	0.000090	0.000080	0.000080
1.09 (highest median value)	0.00065	0.00057	0.00068	0.00061	0.00082	0.00078	0.00073	0.00068
0.12 (lowest 99th percentile value)	0.000070	0.000060	0.000070	0.000070	0.000090	0.000090	0.000080	0.000080
4.92 (highest 99th percentile value)	0.0029	0.0026	0.0031	0.0028	0.0037	0.0035	0.0033	0.0031

Values rounded to 2 SF

Risk Characterisation

68. 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.

69. 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 benchmark response. 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).

70. 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.

71. Table 17 summarises the estimated exposures to inorganic arsenic from the diet of infants and young children aged 0 to 5 years. Based on dietary exposures alone, the MOEs for 0 to 4 month olds that are either exclusively breastfed or exclusively fed ready-to-feed infant formula range from 40 to 100 at average and high level exposure. The MOEs for 0 to 4 month olds that are exclusively fed with reconstituted dry infant formula are between 20 and 50 when reconstituted with water with the median concentration of arsenic, but are equal to or less than 10 when reconstituted using water with the 97.5th percentile arsenic concentration.

72. Dietary exposures estimated using the Infant Metals Survey generate MOEs from 20 to 50 for average consumers aged 4 to 18 months when water is taken into account at both the median and 97.5th percentile arsenic concentrations. Based on the Infant Metals Survey, the MOEs are equal to or less than 10 for high level consumers in the same age group.

73. Using the TDS to estimate dietary exposures for infants aged 12 to 18 months, and young children aged 18 months to 5 years, generates MOEs when including water at the median and 97.5th percentile arsenic concentrations that are between 4 and 20 for average consumers, and between 3 and 10 for high level consumers.

74. Overall, the ranges of MOEs obtained based on the median and 97.5th percentile concentrations of arsenic in water are generally the same, for each age group; this demonstrates that the arsenic content of water has a negligible impact on total dietary exposure to inorganic arsenic of UK infants and young children.

75. Table 18 summarises the estimated exposures to inorganic arsenic for infants and young children aged 6 months to 5 years from soil and dust. The MOEs based on exposure to soil and dust with a median concentration of arsenic ranged from 20 to 30, while those based on exposure to a high level of arsenic in soil and dust were 9 or 10. The MOEs based on exposure to arsenic in air have not been presented in a table but ranged from approximately 800 to 48,000.

Table 17. Summary of estimated dietary exposures to inorganic arsenic, and corresponding MOEs compared to the $BMDL_{0.5}$ of 3.0 µg/kg bw/day

		Exclusive breast milk	Exclusive infant formula			Total diet including water with median arsenic level (0.4 µg/L)					Total diet including water with 97.5^{th} percentile arsenic level (2.1 µg/L)				
			Ready to feed	Dry powder reconstituted[c] with water with arsenic at											
				Median (0.4 µg/L)	97.5^{th} percentile (2.1 µg/L)										
Survey/Consumption data		N/A	Infant Metals Survey	Infant Metals Survey	Infant Metals Survey	Infant Metals Survey/ DNSIYC	Infant Metals Survey/ DNSIYC	TDS/ DNSIYC	TDS/ NDNS	TDS/ NDNS	Infant Metals Survey/ DNSIYC	Infant Metals Survey/ DNSIYC	TDS/ DNSIYC	TDS/ NDNS	TDS/ NDNS
Age (months)		**0 to <4**	**0 to <4**	**0 to <4**	**0 to <4**	**4 to <12**	**12 to <18**	**12 to <18**	**18 to <24**	**24 to <60**	**4 to <12**	**12 to <18**	**12 to <18**	**18 to <24**	**24 to <60**
Estimated dietary exposures (µg/kg bw/day)[a]	Average consumer	0.045	0-0.027	0.064-0.087	0.25-0.28	0.056-0.18	0.14-0.17	0.13-0.67	0.15-0.76	0.13-0.62	0.064-0.20	0.17-0.20	0.15-0.69	0.17-0.78	0.14-0.64
	High level consumer	0.067	0-0.041	0.091-0.13	0.38-0.42	0.23-0.47	0.44-0.48	0.32-1.2	0.29-1.2	0.26-0.99	0.26-0.54	0.51-0.56	0.35-1.2	0.32-1.2	0.28-1.0
MOE[b]	Average consumer	70	100	30-50	10	20-50	20	4-20	4-20	5-20	20-50	20	4-20	4-20	5-20
	High level consumer	40	70	20-30	7-8	6-10	6-7	3-9	3-10	3-10	6-10	5-6	3-9	3-9	3-10

[a] Values are rounded to 2SF; a range represents the lowest lower bound to highest upper bound estimates for the age range
[b] The MOE is calculated by dividing the $BMDL_{0.5}$ of 3.0 µg/kg bw/day by the respective dietary exposure and rounding to 1 SF. The range relates to the upper bound to lower bound estimates of exposure, only one MOE is shown when the estimated dietary exposures generated the same value.
[c] Based on the assumption that reconstituted infant formula comprises 85% water

Table 18. Possible inorganic arsenic exposures (µg/kg bw/day) from soil and dust in infants and young children aged 6 months to 5 years, and corresponding MOEs compared to the $BMDL_{0.5}$ of 3.0 µg/kg bw/day

		Age (months)					
		6 to 9	**9 to 12**	**12 to 15**	**15 to 18**	**18 to 24**	**24 to 60**
Estimated exposures (µg/kg bw/day)[a]	Average	0.12	0.11	0.17	0.16	0.15	0.11
	High level	0.25	0.23	0.34	0.32	0.30	0.22
MOE[b]	Average	20	30	20	20	20	30
	High level	10	10	9	9	10	10

[a] Values are rounded to 2SF
[b] The MOE is calculated by dividing the $BMDL_{0.5}$ of 3.0 µg/kg bw/day by the respective dietary exposure and rounding to 1 SF

76. As toxicity will depend on total exposure to inorganic arsenic from all sources, it is important to consider combined exposures from food, water, and non-dietary sources. Tables 19 to 21 summarise the aggregate exposures and corresponding MOEs for each age group for inorganic arsenic based on exposures from breast milk, the total diet including water, and soil and dust, where these exposures are available. Exposures from water have been taken into account by using the estimates generated for the total diet including water, based on both the highest median and 97.5th percentile water concentrations. Exposures from air have not been incorporated as they are too low to have an impact on the MOEs.

77. The aggregate exposures have been estimated by adding the mean/average exposure estimates from all but one source to the 97.5th percentile/high level exposure estimate for the remaining source. Where a range of dietary exposures from lower bound to upper bound were available, both estimates have been used.

78. Aggregate exposures have not been calculated for 0 to 4 month olds as this age group were considered to be exclusively breast- or formula-fed, with no exposure to other foods or to soil and dust. These exposures have been presented in table 17 and discussed in paragraph 71.

79. Table 19 shows the aggregate exposure estimates and MOEs for infants aged 4 to 6 months. The aggregate exposures for this age group are based on the exposure estimates for breast milk and the total diet including water. Estimates from exposures via soil were not included as infants <6 months are less able to move around and come into contact with soil and dust. For 4 to 6 month olds, most of the aggregate exposures result in MOEs that are above 20. For a combination of mean breast milk exposures plus 97.5th percentile total diet exposure with the median or 97.5th percentile concentration of inorganic arsenic in the water, the MOEs are equal to or marginally below 10.

Table 19. Exposures to inorganic arsenic for infants aged 4 to 6 months aggregated from breast milk and the total diet including water, and the corresponding MOEs when compared to the $BMDL_{0.5}$ of 3.0 µg/kg bw/day

Exposure combination[a]			Exposure (µg/kg bw/day)	MOE[b]
Mean breast milk	Mean total diet incl. As in water at	Median conc. (0.4 µg/L)	0.090-0.11	30-40
		97.5th percentile conc. (2.1 µg/L)	0.10-0.12	30
97.5th percentile breast milk	Mean total diet incl. As in water at	Median conc. (0.4 µg/L)	0.11-0.13	20-30
		97.5th percentile conc. (2.1 µg/L)	0.12-0.14	20-30
Mean breast milk	**97.5th percentile total diet** incl. As in water at	Median conc. (0.4 µg/L)	0.27-0.32	9-10
		97.5th percentile conc. (2.1 µg/L)	0.29-0.34	9-10

Exposures have been rounded to 2 SF
[a] Breast milk from Table 4, and total diet including water from Table 7
[b] The MOE is calculated by dividing the $BMDL_{0.5}$ of 3.0 µg/kg bw/day by the respective exposure combination, rounded to 1 SF. The range relates to the upper bound to lower bound estimates of exposure, only one MOE is shown when the estimated aggregate exposures generated the same value

80. Table 20 shows the aggregate exposure estimates and MOEs for infants aged 6 to 9, 9 to 12, 12 to 15, and 15 to 18 months. The aggregate exposures for these age groups are based on the exposure estimates for breast milk, the total diet including water, and soil and dust. For 6 to 18 month olds, all of the aggregate exposures result in MOEs that are equal to or less than 10.

Table 20. Aggregate exposures to inorganic arsenic for infants aged 6 to 18 months based on exposures from breast milk, the total diet including water, and soil/dust, and the corresponding MOEs when compared to the $BMDL_{0.5}$ of 3.0 µg/kg bw/day

Exposure combination[a]			**Age (months)**							
			6 to 9		**9 to 12**		**12 to 15**		**15 to 18**	
			Exposure (µg/kg bw/day)	**MOE**[b]	**Exposure (µg/kg bw/day)**	**MOE**[b]	**Exposure (µg/kg bw/day)**	**MOE**[b]	**Exposure (µg/kg bw/day)**	**MOE**[b]
Mean breast milk plus median soil[c]	Mean total diet incl. As in water at	Median conc. (0.4 µg/L)	0.27-0.31[e]	10	0.28-0.31[e]	10	0.31-0.81[f]	4-10	0.31-0.84[f]	4-10
		97.5th percentile conc. (2.1 µg/L)	0.29-0.32[e]	9-10	0.30-0.33[e]	9-10	0.33-0.83[f]	4-9	0.33-0.86[f]	4-9
97.5th percentile breast milk plus median soil[c]	Mean total diet incl. As in water at	Median conc. (0.4 µg/L)	0.30-0.34[e]	9-10	0.30-0.33[e]	9-10	0.32-0.83[f]	4-9	0.32-0.85[f]	4-9
		97.5th percentile conc. (2.1 µg/L)	0.32-0.35[e]	9	0.32-0.35[e]	9	0.34-0.85[f]	4-9	0. 34-0.87[f]	3-9
Mean breast milk plus median soil[c]	**97.5th percentile total diet** incl. As in water at	Median conc. (0.4 µg/L)	0.51-0.57[e]	5-6	0.54-0.59[e]	5-6	0.50-1.3[f]	2-6	0.50-1.3[f]	2-6
		97.5th percentile conc. (2.1 µg/L)	0.57-0.63[e]	5	0.61-0.66[e]	5	0.53-1.4[f]	2-6	0.52-1.3[f]	2-6
Mean breast milk plus **95th percentile soil**[d]	Mean total diet incl. As in water at	Median conc. (0.4 µg/L)	0.40-0.43[e]	7-8	0.39-0.42[e]	7-8	0.48-0.98[f]	3-6	0.47-1.0[f]	3-6
		97.5th percentile conc. (2.1 µg/L)	0.41-0.45[e]	7	0.41-0.44[e]	7	0.50-1.0[f]	3-6	0.49-1.0[f]	3-6

Exposures have been rounded to 2 SF, MOEs have been rounded to 1 SF
[a] Breast milk from Table 5, total diet including water from Tables 7 and 9, and soil from Table 14
[b] The MOE is calculated by dividing the $BMDL_{0.5}$ of 3.0 µg/kg bw/day by the respective exposure combination. The range relates to the upper bound to lower bound estimates of exposure, only one MOE is shown when the estimated aggregate exposures generated the same value
[c] Based on ingestion of soil with the median concentration of inorganic arsenic (18 mg/kg)
[d] Based on ingestion of soil with the 95th percentile concentration of inorganic arsenic (36 mg/kg)
[e] Based on the results of the infant metals survey
[f] Based on the results of the TDS

81. Table 21 shows the aggregate exposure estimates and MOEs for young children aged 18 to 60 months. The aggregate exposures for these age groups are based only on the exposure estimates for the total diet including water, and soil and dust, as breast milk is expected to contribute minimally in children older than 18 months. For 18 to 60 month olds, the aggregate exposures generally result in MOEs that are equal to or less than 10.

Table 21. Aggregate exposures to inorganic arsenic for young children aged 18 to 60 months based on exposures from the total diet including water, and soil/dust, and the corresponding MOEs when compared to the $BMDL_{0.5}$ of 3.0 µg/kg bw/day

Exposure combination[a]			**Age (months)**			
			18 to 24		**24 to 60**	
			Exposure (µg/kg bw/day)	**MOE**[b]	**Exposure (µg/kg bw/day)**	**MOE**[b]
Median soil[c]	Mean total diet incl. As in water at	Median conc. (0.4 µg/L)	0.30-0.91	3-10	0.24-0.74	4-10
		97.5th percentile conc. (2.1 µg/L)	0.32-0.93	3-9	0.26-0.75	4-10
Median soil[c]	**97.5th percentile total diet** incl. As in water at	Median conc. (0.4 µg/L)	0.44-1.3	2-7	0.37-1.1	3-8
		97.5th percentile conc. (2.1 µg/L)	0.47-1.3	2-6	0.39-1.1	3-8
95th percentile soil[d]	Mean total diet incl. As in water at	Median conc. (0.4 µg/L)	0.45-1.1	3-7	0.35-0.85	4-9
		97.5th percentile conc. (2.1 µg/L)	0.47-1.1	3-6	0.37-0.87	4-8

Exposures have been rounded to 2 SF, MOEs have been rounded to 1 SF
[a] Total diet including water from Table 10, and soil from Table 14
[b] The MOE is calculated by dividing the $BMDL_{0.5}$ of 3.0 µg/kg bw/day by the respective exposure combination The range relates to the upper bound to lower bound estimates of exposure, only one MOE is shown when the estimated aggregate exposures generated the same value
[c] Based on ingestion of soil with the median concentration of inorganic arsenic (18 mg/kg)
[d] Based on ingestion of soil with the 95th percentile concentration of inorganic arsenic (36 mg/kg)

Risk characterisation for specific food products

Rice drinks

82. Table 22 summarises the MOEs for the estimated exposures for 1 to 5 year olds calculated for rice drinks using the mean concentration of inorganic arsenic (12 µg/L), and assuming complete replacement of cows' milk with rice drinks. The MOEs for average consumers from all age groups are equal to or marginally less than 10, while the MOEs for all high level consumers are equal to or less than 5 from this source alone.

Table 22. Range of possible exposures to inorganic arsenic from rice drinks with a mean concentration of inorganic arsenic of 12 μg/L, and the corresponding MOEs when they are compared to the $BMDL_{0.5}$ of 3.0 μg/kg bw/day

Consumer	**Age group (months)**							
	12 to 15		**15 to 18**		**18 to 24**		**24 to 60**	
	Exposure (μg/kg bw/day)	**MOE[a]**	**Exposure (μg/kg bw/day)**	**MOE[a]**	**Exposure (μg/kg bw/day)**	**MOE[a]**	**Exposure (μg/kg bw/day)**	**MOE[a]**
Average	0.36	8	0.34	9	0.32	10	0.22	10
High	0.91	3	0.77	4	0.86	3	0.60	5

Exposures have been rounded to 2 SF, MOEs have been rounded to 1 SF
[a] The MOE is calculated by dividing the $BMDL_{0.5}$ of 3.0 μg/kg bw/day by the respective exposure

83. It has been estimated that, for those aged 1 to 5 years, consumption of about 50mL of rice drink per day would not cause an appreciable increase in background exposure to inorganic arsenic (paragraph 60).

Rice cakes

84. Tables 23 and 24 summarise the MOEs for the estimated exposures from the consumption of infant and ‘adult’ rice cakes by infants and young children aged 4 months to 5 years. All of the MOEs from rice cake consumption are greater than 20. The MOEs for infants aged 4 to 18 months from infant rice cake consumption are generally lower than those from ‘adult’ rice cake consumption; this is explained by the fact that although the consumption of infant and ‘adult’ rice cakes by this age group was similar, the concentration of inorganic arsenic used to assess exposure from infant rice cakes was approximately 50% greater than that used to assess ‘adult’ rice cakes. For 18 to 24 month olds, the MOEs from ‘adult’ rice cake consumption are lower than those from infant rice cake consumption; this is due to the fact that this age group consumed considerably more ‘adult’ rice cakes than they did infant rice cakes (~2 to 3 times greater). The MOEs from the consumption of infant rice cakes and of ‘adult’ rice cakes for young children aged 24 to 60 months are relatively similar.

85. The exposures from the consumption of rice cakes can be considered in addition to those from the total diet, bearing in mind that this would result in a degree of double-counting due to the inclusion of rice cakes in the total diet exposure assessments. Adding the highest of the 97.5th percentile exposures for infants < 12 month olds (0.11 μg/kg bw/day from consumption of infant rice cakes) to the highest mean exposure from the total diet[5] for the same age group (0.18 μg/kg bw/day) would result in an increase

[5] Total diet including the median water concentration

of approximately 40% above the mean total diet exposure. Adding the highest of the 97.5th percentile exposures for 1 to 5 year olds (0.12 µg/kg bw/day from 12 to 18 month olds consuming infant rice cakes) to the highest mean exposure from the total diet[5] for the same age group (0.67 µg/kg bw/day) would result in an increase of ~15% above the mean total diet exposure.

Table 23. Range of possible exposures to inorganic arsenic from infant rice cakes, and the corresponding MOEs when they are compared to the $BMDL_{0.5}$ of 3.0 µg/kg bw/day

Consumer	Age group (months)							
	4 to 12		12 to 18		18 to 24		24 to 60	
	Exposure (µg/kg bw/day)	MOE[a]	Exposure (µg/kg bw/day)	MOE[a]	Exposure (µg/kg bw/day)	MOE[a]	Exposure (µg/kg bw/day)	MOE[a]
Average	0.031[b]	100	0.035[b]	90	0.026	100	0.029	100
High	0.11[b]	30	0.12[b]	20	0.070	40	0.071	40

Exposures have been rounded to 2 SF, MOEs have been rounded to 1 SF
[a] The MOE is calculated by dividing the $BMDL_{0.5}$ of 3.0 µg/kg bw/day by the respective exposure
[b] Based on highest estimate for this age range

Table 24. Range of possible exposures to inorganic arsenic from 'adult' rice cakes, and the corresponding MOEs when they are compared to the $BMDL_{0.5}$ of 3.0 µg/kg bw/day

Consumer	Age group (months)							
	4 to 12		12 to 18		18 to 24		24 to 60	
	Exposure (µg/kg bw/day)	MOE[a]	Exposure (µg/kg bw/day)	MOE[a]	Exposure (µg/kg bw/day)	MOE[a]	Exposure (µg/kg bw/day)	MOE[a]
Average	0.025[b]	100	0.025[b]	100	0.066	50	0.030	100
High	0.057[b]	50	0.077[b]	40	0.11	30	0.058	50

* Exposures have been rounded to 2 SF, MOEs have been rounded to 1 SF
[a] The MOE is calculated by dividing the $BMDL_{0.5}$ of 3.0 µg/kg bw/day by the respective exposure
[b] Based on highest estimate for this age range

Conclusions

86. Arsenic occurs in the environment in a variety of forms as the result of natural and anthropogenic activity. It is generally accepted that inorganic arsenic compounds are more toxic than the organic arsenic compounds that are commonly found in fish, seafood and other marine organisms (arsenobetaine, arsenosugars, and arsenolipids). Inorganic arsenic in the environment is present primarily as As(III) and As(V).

87. The general population is exposed to arsenic through food, drinking water, air, soil and dust. Food and water are the most important sources of oral exposure to arsenic. Infants and young children can also be exposed to arsenic via breast milk or infant formula.

88. Absorption of arsenic compounds varies depending on the chemical species, the solubility of its form, and the matrix in which it is present; soluble arsenicals in water are highly bioavailable. In humans, inorganic arsenic is rapidly cleared from the blood and widely distributed to almost all organs. Inorganic arsenic is metabolised by reduction of As(V) to As(III), followed by oxidative addition of methyl groups. Ingested inorganic arsenic is excreted via the kidney as As(V) and As(III), and as the metabolites MMA^{III}, MMA^{V}, DMA^{III}, and DMA^{V}. Previously it had been assumed that methylation of inorganic arsenic was a detoxification route, but it is no longer clear whether or not this is correct as, based on limited data, the simple organic arsenic species MMA^{III} and DMA^{III} appear to be more toxic than inorganic arsenic (As(V) and As(III)).

89. The main adverse effects associated with long-term exposure to inorganic arsenic in humans are skin lesions, cancer, developmental toxicity, neurotoxicity, cardiovascular diseases, abnormal glucose metabolism, and diabetes, although the evidence for some of these effects is stronger than for others. The IARC has reviewed arsenic on a number of occasions, concluding that it is a group 1 carcinogen that causes cancer of the lung, urinary bladder, and skin in humans. It does not appear to be directly genotoxic.

90. Although few data are available regarding the toxicity of organic arsenic compounds such as arsenobetaine and the arsenosugars and arsenolipids in humans, exposure to such compounds is not generally considered to be of toxicological concern.

91. The EFSA and the JECFA have published risk assessments on exposure to arsenic in food. Based on the available epidemiological studies, the EFSA calculated a range of values for the $BMDL_{01}$ of 0.3 to 8.0 µg/kg bw/day, this range was identified for cancers of the lung, skin and urinary bladder, as well as skin lesions. Using a different approach to modelling the dose-response data, and studies that had been published after the EFSA assessment, the JECFA calculated a BMDL of 3.0 µg/kg bw/day for a 0.5% increased incidence of lung cancer.

92. The Committee concluded that the JECFA $BMDL_{0.5}$ of 3.0 µg/kg bw/day identified for lung cancer should be used in the characterisation of the potential risks from exposure to inorganic arsenic. This was because the JECFA risk assessment was based on more robust and recent evidence than that available to the EFSA. The focus of the risk characterisation would be on inorganic arsenic since this is the form that is carcinogenic. An MOE approach would be used to compare the exposure estimates to the BMDL.

93. The Committee notes that as there is no precedent for interpreting MOEs that have been calculated based on a BMDL derived from an

epidemiological study and relating to a low cancer incidence, such interpretation must be done on a case-by-case basis. The JECFA BMDL used in this case was based on human data and a 0.5% increased incidence of lung cancer in a well-conducted prospective cohort study, in which the risk of cancer increased with duration of exposure, over several decades. Taking this into account, together with the fact that inorganic arsenic does not appear to be directly genotoxic, the Committee concludes that in this instance an MOE of 10 or above would be considered of a low concern.

94. Based on dietary exposures alone, the MOEs for 0 to 4 month olds that are either exclusively breastfed or exclusively fed ready-to-feed infant formula range from 40 to 100 at average and high level exposure. The MOEs for 0 to 4 month olds that are exclusively fed reconstituted infant formula are between 20 and 50 for formula reconstituted with water with an average concentration of inorganic arsenic, but are between 7 and 10 for that reconstituted using water with a high inorganic arsenic concentration.

95. The estimated dietary exposures for 4 to 12 month olds generated MOEs from 20 to 50 for average consumers and from 6 to 10 for high level consumers, when water is included at average and high inorganic arsenic concentrations.

96. For infants and young children aged 12 months to 5 years, the estimated dietary exposures generated MOEs of between 4 and 20 for average consumers and between 3 and 10 for high level consumers, when water with both average and high inorganic arsenic concentrations is included.

97. The MOEs generated for those aged 6 months to 5 years based on exposure to soil and dust with an average concentration of arsenic ranged from 20 to 30, while those based on exposure to a high level of arsenic in soil and dust were 9 or 10. The MOEs based on exposure to arsenic in air for 0 to 5 year olds ranged from approximately 800 to 48,000.

98. As toxicity would depend on total exposure to inorganic arsenic from dietary and non-dietary sources, aggregate exposures were estimated and assessed. These aggregate exposures were estimated for those aged from 4 months up to 5 years by adding the average exposure estimates from all but one source to the high level exposure estimate for the remaining source, to avoid compounding conservatism. Exposures from water were taken into account by using estimates generated for the total diet including water, which had been based on both average and high level water arsenic concentrations. Exposures from air were not included as they were considered too low to have an impact on the MOEs.

99. Based on these aggregate exposures, the MOEs for infants aged 4 to 6 months ranged from 9 to 40, while the MOEs for infants aged 6 to 12 months ranged from 5 to 10, and those for young children aged 1 to 5 years ranged from 2 to 10.

100. The FSA currently recommends that toddlers and young children (aged 1 to 4.5 years) should not be given rice drinks as a *substitute* for breast milk, infant formula or cows' milk due to the potential for rice drinks to contain high levels of arsenic, and because of this age group's proportionally higher milk consumption and lower bodyweights compared to other consumers. The Committee concludes that the current estimates of exposure to inorganic arsenic from rice drinks support the FSA's advice not to use rice drinks as a *substitute*, and that this advice should therefore remain in place. However, Members agreed that consumption of up to 50 mL of rice drink per day by those aged 1-5 years would not make an appreciable difference to total dietary exposure to inorganic arsenic, contributing less than 10%.

101. Due to the introduction of different MLs for inorganic arsenic in rice intended for the production of infant foods including infant rice cakes, and for inorganic arsenic in 'adult' rice cakes (i.e. not those intended for infants or young children), exposure assessments were performed to estimate the level of exposure to inorganic arsenic from the consumption of infant and 'adult' rice cakes by those aged 0 to 5 years. The MOEs derived based on these exposure estimates ranged from 20 to 100 and do not indicate an increased risk from consumption of either of these food products.

102. There are uncertainties in the assessment of risks to infants and young children from exposure to inorganic arsenic because, for some sources of exposure (e.g. breast milk and soil), it has been necessary to assume that all of the arsenic present in that source is inorganic. This was the case for sources where inorganic arsenic has not been measured, and consistent information about the proportion of inorganic arsenic likely to be present in that source of exposure has not necessarily been available. Such assumptions could potentially result in over-estimation of the exposures to inorganic arsenic.

103. Overall, the inorganic arsenic exposures for exclusively breastfed or formula-fed UK infants aged 0 to 4 months generated MOEs that were generally greater than 10 and would therefore be considered of low concern. There could be a small risk to high level consumers of infant formula that has been reconstituted with water containing a high level of inorganic arsenic as this scenario generated MOEs that were marginally less than 10. Total exposure to inorganic arsenic, from dietary and non-dietary sources, in infants and young children aged 4 to 12 months and 1 to 5 years generally generated MOEs of less than 10 and could therefore pose a risk to health. When comparing the estimated exposures from different sources, it becomes apparent that in these age groups, dietary sources generally contribute more significantly to exposure than non-dietary sources such as soil and dust. It is therefore reiterated that efforts to reduce the levels of inorganic arsenic in food and water should continue.

COT Statement 2016/06

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Abbreviations

ALARP – As low as reasonably practicable

As – Arsenic

As(III) – Arsenite

As(V) – Arsenate

BMDL – 95% lower confidence limit of the benchmark dose

bw – body weight

COC – Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment

COT – Committee on Toxicity

Defra – Department for Environment, Food and Rural Affairs

DH – Department of Health

DMA^{III} – Dimethylarsinous acid

DMA^{V} – Dimethylarsinic acid

DNSIYC – Diet and Nutrition Survey of Infants and Young Children

DWI – Drinking Water Inspectorate

EA – Environment Agency

EC – European Commission

EFSA – European Food Safety Authority

EU – European Union

FAO – Food and Agriculture Organization

FSA – Food Standards Agency

g - grams

IARC – International Agency for Research on Cancer

IMS – Infant metals survey

incl. - including

JECFA – Joint FAO/WHO Expert Committee on Food Additives

kg - kilogram

LB – Lower bound

LOD – Limit of detection

µg/kg – micrograms/kilogram

µg/L – micrograms/litre

m^3/day – cubic metres/day

mg – milligram

mg/day – milligrams/day

mg/kg – milligrams/kilogram

mL – millilitre

mL/day – millilitres/day

ML – Maximum level

MMA^{III} – Methylarsonous acid

MMA^{V} – Methylarsonic acid

MOE – Margin of Exposure

n – number

NDNS – National Diet and Nutrition Survey

ng/m^3 – nanograms/cubic metre

NHS – National Health Service

SACN – Scientific Advisory Committee on Nutrition

SF – significant figures

TDS – Total Diet Study

UB – Upper bound

UK – United Kingdom

US EPA – United States Environmental Protection Agency

WHO – World Health Organization

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