Meeting

EFSAs 2023 re-evaluation of the risk to public health from inorganic arsenic in food

This is a paper for discussion.

This does not represent the views of the Committee and should not be cited.

Introduction

1. In July 2023, the EFSA Panel on Contaminants in the Food Chain (CONTAM) published a draft opinion re-evaluating the health risks arising from the presence of inorganic arsenic (iAs) in food. EFSA considered it appropriate to update their assessment as new studies have become available on the toxic effects of iAs, as well as new information on adverse health effects and occurrence data/estimate exposures.

2. EFSA applied a margin of exposure (MOE) approach due to iAs being a genotoxic carcinogen with additional epigenetic effects. While the MOEs raised a health concern for skin cancer, supported by the uncertainty analysis, EFSA was unable to derive a level of low concern due to the use of a human cancer endpoint and the absence of EFSA guidance.

3. Two separate opinions will assess organic As, one the methylated As species and one arsenobetaine, asenolipids and arsenosugars, and potential other organic As species. EFSA is also planning on assessing the combined exposure from inorganic and organic As, once the individual risk assessments have been completed.

4. The deadline for the EFSA public consultation is the **10th September 2023**. Members are asked to send any additional comments to the Secretariat by Wednesday 6th September providing the relevant section or line number where possible.

Background

5. Arsenic (As) occurs in various organic and inorganic forms, both from natural and anthropogenic sources. In water or drinking water As is usually present in inorganic form as the oxo anions arsenite and arsenate, organic As is rare. In food and feed inorganic As (iAs) is predominantly present as thio complexes or as arsenite and arsenate but as iAs bound to thio groups in peptides or proteins is converted to arsenite and arsenate, data on occurrence are predominantly recorded as those two species.

Previous EFSA evaluation of arsenic

6. In 2009, the EFSA Panel on Contaminants in Food (CONTAM) considered skin lesions, cancer, developmental toxicity, neurotoxicity, cardiovascular diseases, abnormal glucose metabolism and diabetes to be the main adverse effects of iAs.

7. As effects had been reported at concentrations lower than the provisional tolerable daily intake (PTDI) established by the FAO/WHO Expert Committee on Food Additives (JECFA) in 1983, EFSA did not considered the PTDI to be appropriate anymore. Modelling dose-response data from epidemiological studies and using a benchmark response of 1% extra risk, EFSA derived benchmark dose (BMDL01) values between 0.3 and 8 µg/kg as reference point, based on the potential of iAs to cause cancer of the skin, urinary bladder and lungs. Based on the estimated exposures at the time, EFSA concluded that there was a possible risk to consumers.

8. For the organic As forms, EFSA concluded that arsenobetaine, the major form of As in fish and seafood, is not of toxicological concern. Due to the lack of data, EFSA was unable to conclude/consider the risk of arsenosugars, arsenolipids, methylarsenate and dimethylarsinate.

9. In 2014, EFSA published a scientific report on the dietary exposure to iAs in the European population. The report identified grain-based products as the main contributor, with rice, milk and dairy products also contributing significantly.

2023 Re-evaluation of arsenic

10. Inorganic As and its metabolites induce DNA based oxidation, DNA single strand breaks and clastogenic and aneugenic events, via oxidative stress,

both *in vitro* and *in vivo* (including in humans). Using adverse outcome pathways (AOPs), oxidative damage has been linked to mutations and chromosomal aberrations, following iAs exposure. While iAs is classified as an indirect genotoxin, as there is no direct interaction with the DNA, iAs is unique due to its ability to inhibit DNA repair at very low concentrations. Hence, EFSA considered that although the interactions with the DNA repair/DDR system may follow a non-linear dose-response relationship, the cell response under chronic iAs exposure would be similar to that of DNA repair/DDR-defective cells that present increased genomic instability and increased risk of disease.

11. As the toxicokinetics of iAs differ considerably between laboratory animals and humans regarding their methylation capacity, toxicity data from animal studies are not suitable for human risk assessment. Hence, EFSA only considered human studies for their 2023 re-evaluation of iAs. Most of the epidemiological studies had not been available for the previous assessment in 2009.

12. Exposures were based on long-term low to moderate levels of iAS, defined as arsenic water concentrations of less than approximately 150 µL, or biomarker concentrations estimated to result from equivalent doses (urine, toenails and hair).

13. EFSA considered there to be sufficient and causal evidence for an association between low to moderate exposures to iAS and cancers of the skin, bladder and lung, spontaneous abortion, stillbirth, infant mortality, congenital heart disease, respiratory disease, chronic kidney disease, neurodevelopmental effects, ischemic heart disease, and carotid artery atherosclerosis from epidemiological studies.

14. While epidemiological studies from Bangladesh and China reported skin lesions, EFSA considered it difficult to extrapolate those findings to populations with more adequate nutrition, such as Europe. The same considerations were applied to epidemiological studies from Bangladesh on the causal effect of iAs exposure and decreased birthweight. The average birthweight in Europe is higher and malnutrition less common. In addition, results from other countries, i.e. Chile, Taiwan, Mongolia, Mexico, US, are inconsistent.

15. EFSA considered there to be insufficient evidence for an association between low to moderate iAs exposure and cancer of the breast, prostate, liver, kidney, pancreas and gallbladder, male fertility, neurotoxicity, stroke and hypertension, glucose metabolism, diabetes and metabolic syndrome.

BMD modelling and derivation of a reference point

16. Studies were considered for dose-response modelling if a) the overall risk of bias in the data was low, b) the data showed a significant association with iAs (as a continuous variable) and/or a statistically significant trend test and/or increase of risk in the upper exposure category and c) results for at least three exposure categories were reported.

17. iAs concentrations in drinking water (measured as total As) were first transformed into dietary exposures by applying default or reported water intakes and adding region specific estimates to account for the contribution from food. Total urinary iAs concentrations were transformed into dietary exposures by applying default factors for urine volume and creatinine excretion. For further details, please see Annex D of the draft opinion.

18. The data used for dose-response analysis were adjusted incidences and resulting number of cases based on adjusted risk ratios reported in the studies and the provided or estimated population size from cohort and case-control studies, respectively.

19. The risk of bias had already been considered as part of the inclusion/exclusion criteria for the selection of studies, however an additional comparative risk-of-bias-assessment was conducted for the selected studies. EFSA considered this level of scrutiny necessary as a comparative assessment of the evidence providing the modelling inputs across different endpoints and health outcomes would enhance the informed deliberations related to the derivation of the reference point.

20. In total, 20 epidemiological studies were considered adequate by EFSA to use for benchmark dose response (BMD) modelling and the results from the BMD calculations were considered further for derivation of an appropriate reference point (RP). The BMD analysis was performed using the EFSA “Bayesian BMD” webtool and the EFSA guidance on BMD modelling (EFSA, 2022). However, EFSA acknowledged that the guidance does not specifically address modelling of human data.

21. Results of the epidemiological studies were reported as crude and adjusted risk estimates in the form of incident rates (IR), incident rate ratio (IRR), hazard ratio (HR), odds ratio (OR) and prevalence ratios (PRs). Since the current

BMD approach does not model relative risk estimates, the relative estimates had to be transformed to natural numbers/integers. EFSA applied the approach by JECFA to do so (FAO/WHO, 2011). Details can be found on lines 3750-3799 and Annex D of the draft opinion.

22. The EFSA guidance does not provide formal guidance on the selection of the appropriate benchmark response (BMR) for human data. Previous assessments have considered appropriate BMRs on a case-by-case basis and applied lower values than the default BMR for quantal experimental animal data of 10%. In this instance, EFSA decided to apply a relative increase of 5% of the background incidences, estimated from the lowest exposure category, after adjustment for cofounders. For the considered endpoints a BMR of 1-5% was regarded as relevant to public health.

23. The lowest BMDLs (≤ 0.15 µg iAs/kg bw per day) were calculated for cancers of the skin, lung and bladder, respiratory disease, chronic kidney disease and ischemic heart disease. As a RP EFSA derived a BMDL05 of 0.06 µg iAs/kg bw per day from a case-control study on squamous cell carcinoma (skin cancer). The study (Gilbert-Diamond et al., 2013) was carried out in the US and considered to be of good quality and low risk of bias. The choice of RP was supported by a second study (Leonardi et al., 2012), looking at basal cell carcinoma (skin cancer) incidences in a population from Hungary, Romania and Slovakia. While the BMDL05 in the latter study was much lower (0.01 µg/kg bw per day) and had five doses compared to the three doses in the US study, EFSA considered the study by Leonardi et al. (2012) to have a slightly higher risk of bias due to using hospital controls, and not population controls as the Gilbert-Diamond et al. (2013) study. The results when modelling the Gilbert-Diamond study using a BMR of 1% or 10% showed lower and higher BMDs and BMDLs, respectively, but differences were, however, not very large, which EFSA considered to further strengthen the validity of the RP. The BMDL05 when modelling the study by Leonardi et al. (2012) was about 10 times lower than the median dose in the lowest dose category, and the BMD was below the dose in the reference category, which EFSA considered to make the estimate uncertain. In addition to the above uncertainties in the modelling, squamous cell carcinoma is a more serious type of skin cancer than basal cell carcinoma.

24. EFSA concluded that the RP of 0.06 µg iAs/kg bw per day was also applicable for cancers of the lung and bladder, skin lesions, chronic kidney disease, respiratory disease, spontaneous abortion, stillbirth, infant mortality and neurodevelopmental effects.

25. As iAs, and its trivalent and pentavalent methylated metabolites, are genotoxic carcinogens, and both threshold and non-threshold mechanisms could apply, EFSA concluded that it would not be appropriate to set a health-based guidance value (HBGV) but to apply a margin of exposure (MOE) approach instead. However, EFSA was unable to derive a level of low concern, as there is no precedents and hence no guidance in EFSA for identifying a level of low concern, when using a BMDL derived from human cancer data.

Uncertainties and uncertainty analysis

26. EFSA did not identify any major uncertainties with respect to chemical characterisation and analytical methods, but identified several uncertainties related to the hazard and risk characterisation.

27. For the margin of exposure (risk characterisation metric), the impact of uncertainties related to epigenetics, genotoxicity, administration, distribution, metabolism and excretion (ADME) and biomarkers of exposure. EFSA considered these uncertainties to be of low impact. Given the assessment on the risk of bias undertaken low impact was also given to uncertainties related to the validity of the epidemiological studies used for dose-response modelling.

28. However, other uncertainties related to the epidemiological studies, dose response analysis of critical endpoints and selection of an RP were given medium priority. This included uncertainties in the intake of As contaminated water (default values) and the assumed dietary intake of iAs (rarely quantified in studies, estimated from the literature). For the dose-response analysis the small sample size of some of the individual studies were given medium priority, and despite significant dose-response associations, the odd ratios in separate exposure categories were not always statistically significant. Residual confounding is always a possibility with epidemiological studies, with some studies over-adjusting for covariates in the causal chain.

29. EFSA noted that the uncertainties described above may not be covered by the estimated BMD credible interval. In addition, the relative low BMR selected may have an impact on the uncertainty in the RP. Therefore, EFSA performed a more detailed quantitative analysis of the BMD uncertainty. To further address identified uncertainties related to the epidemiological studies, the quantification of uncertainty included sensitivity analysis. Sensitivity analysis was performed on selected exposure categories, the midpoints in the exposure categories and the estimated sizes of the source populations for case-control studies.

30. Uncertainties in the exposure assessment were discussed in the EFSA opinion/report on exposure in 2021, and concerned the occurrence and consumption data, the linkage of the data and use of a factor for preparation of food consumed. Uncertainties in exposure were considered to both over- or underestimate, but they were not prioritized.

31. EFSA noted that using the target BMR relevant for public health, i.e., a BMR of 5% relative increase of the background incidence after adjustment for cofounders, results in an approach that does not create undue uncertainty around the BMD.

32. Monte Carlo simulations were applied to support the quantification of the overall uncertainty and the probability of an MOE 1 for each critical effect and exposure scenario was estimated. Based on the critical skin cancer study selected, mean exposures are unlikely ($p = 0.17$) to exceed the estimated BMD, while exposures at the 95^{th} percentile are likely ($p = 0.7$) to exceed the estimated BMD. Considering the BMD from the second skin cancer study, it is likely/very likely that both exposure scenarios exceed the estimated BMD. However, it is unlikely ($p \leq 0.16$) that any of the BMDs from studies on bladder and lung cancer are exceeded. For lung cancer this also applies when the BMD was associated with a BMR of 1% instead of 5%.

33. Results for the sensitivity analysis showed that all metrics analysed for the different exposure matrices were similar. For the midpoints used for dose-response modelling, results showed that doubling of Y has an effect on the BMDL, BMD and BMDU estimates. However, EFSA concluded that for the data considered, this had no practical impact on the probability of exceeding the BMD for mean exposures. For the 95th percentile exposure the probability changed from very unlikely to unlikely in two out of three cases. EFSA also concluded that based on their sensitivity analysis the assessed increase or decrease in population size by 10 or 20% had a negligible effect on BMD estimates and the probability of exceeding the BMDs.

34. Accounting for the sensitivity analysis and qualitive considerations of the impact of the remaining uncertainties, EFSA considered that the conclusions reached based on the approximate probability scale are relevant to the general population.

35. For the full uncertainty analysis see Section 3.7 and the respective Annexes of the draft opinion.

Exposure assessment

36. Commission Recommendation (EU) 2015/1381 recommended that Member States monitor the presence of As (inorganic and total As, and other relevant species) in a variety of food during 2016, 2017 and 2018.

37. The newly available occurrence data were assessed in 2021 in an updated consumer exposure assessment and the results from this assessment have been used in the 2023 EFSA draft opinion.

38. Using the RP of 0.06 µg iAs/kg bw per day, the MOEs for average and high adult consumers ranged from 2-0.4 and 0.86-0.18, respectively.

Conclusions

39. The probability that mean exposures exceed the associated BMDs range from unlikely (~ 0.17) to likely (~0.86), considering the conditional uncertainty analysis and the two skin cancer studies.

40. 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, hence EFSA concluded that the MOEs raise a health concern for skin cancer.

41. While MOEs in children are smaller, due to the higher dietary exposure to iAS, this does not necessarily indicate a higher risk. The effects of iAs are based on long term exposure and as most epidemiological studies were conducted in adults, their dietary exposure during early life would have also been higher. EFSA therefore concluded that children would be covered by the risk characterisation.

42. EFSA however did note, that susceptible individuals of higher genetic risk may not be adequately represented in the epidemiological studies and hence dietary exposure may be of greater concern for such individuals than for the general population.

43. EFSA noted that guidance is needed on the use of human data for risk assessments, especially for BMDL modelling and the subsequent assessment of genotoxic carcinogens based on human data. EFSA also recommended that further evidence on a) the relevance of As induced epigenetic alterations, b) the mode of interaction of As with DNA, c) the mechanism underlying genomic instability caused by As, d) the health effects of pre- and perinatal exposure, e)

impact of As induced alterations during early life on development of certain diseases in adult life and f) the role of inter-individual variation in susceptibility, with a focus on biotransformation and differences in DBA repair. EFSA also noted that several recommendations made regarding the dietary exposure assessment in 2021 were still valid.

Secretariat

July 2023

Abbreviations

ADME	Absorption, distribution, metabolism, excretion
AOP	Adverse outcome pathway
As	Arsenic
iAs	Inorganic arsenic
BMD	Benchmark dose response modelling
BMDL	BMD lower confidence interval
BMR	Benchmark dose response
bw	Body weight
HBGV	Health based guidance value
HR	Hazard ratio
IR	Incidence rate

IRR	Incident rate ratio
MOE	Margin of exposure
PR	Prevalence ratio
PTDI	Provisional tolerable daily intake
RP	Reference point
UF	Uncertainty factor
WoE	Weight of evidence
CONTAM	EFSA Panel on Contaminants in the Food Chain
EU	European Union
EFSA	European Food Safety Authority
FAO	Food and Agriculture Organisation
JEFA	Joint FAO/WHO Expert Committee on Food Additives
WHO	World Health Organisation

Annex 1

EFSAs 2023 re-evaluation of the risk to public health from inorganic arsenic in food

Public Consultation: (europa.eu)

Other references

EFSA Panel on Contaminants in the Food Chain (CONTAM), 2009. Scientific Opinion on Arsenic in Food. EFSA Journal, 7(10):1351.

Scientific Opinion on Arsenic in Food | EFSA (europa.eu)

EFSA (European Food Safety Authority), 2021. Scientific report on the chronic dietary exposure to inorganic arsenic. EFSA Journal, 19(1):6380.

Chronic dietary exposure to inorganic arsenic | EFSA (europa.eu)

FAO/WHO (Food and Agriculture Organization/ World Health Organization), 1983. Evaluation of certain food additives and contaminants. WHO Food Additive Report Series, No. 18. International Programme on Chemical Safety, World Health Organization, Geneva.

Evaluation of certain food additives and contaminants : twenty-seventh report of the Joint FAO/WHO Expert Committee on Food Additives [meeting held in Geneva from 11 to 20 April 1983]

FAO/WHO (Food and Agriculture Organization/ World Health Organization), 2011a. Food Standards Programme Codex Committee on Contaminants in Foods. Fifth session. Working document for information and use in discussions related to contaminants and toxins in the GSCTFF. CF/5 INF/1.

FAO/WHO (Food and Agriculture Organization/World Health Organization), 2011b. Safety evaluation of certain contaminants in food. WHO Food Additives Series, No. 63/FAO JECFA Monographs 8. Geneva, Switzerland: World Health Organization and Rome, Italy: Food and Agriculture Organization of the United Nations.

Gilbert-Diamond D, Li Z, Perry AE, Spencer SK, Gandolfi AJ, Karagas MR (2013). A population-based case–control study of urinary arsenic species and squamous cell carcinoma in New Hampshire, USA. Environmental Health Perspective, 21(10):1154.

https://doi.org/10.1289/ehp.1206178

Leonardi G, Vahter M, Clemens F, Goessler W, Gurzau E, Hemminki K, Hough R, Koppova K, Kumar R, 5819 Rudnai P, Surdu S and Fletcher T (2012). Inorganic arsenic and basal cell carcinoma in areas of Hungary, Romania, and Slovakia: A case-control study. Environmental Health Perspective, 120:721-726.

https://doi.org/10.1289/ehp.1103534