APPROVED: 28 November 2023

Annex G

Public consultation on the draft scientific opinion on update of the risk assessment of inorganic arsenic in food

European Food Safety Authority (EFSA)

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1 Introduction

1.1 Rationale for the public consultation and summary of its outcome

In line with EFSA's policy on openness and transparency, and for EFSA to receive comments on its work from the scientific community and stakeholders, EFSA engages in public consultations on key topics. Accordingly, the draft Opinion on the update of the risk assessment of inorganic arsenic in food together with its Annexes was released electronically for public consultation from 24 July 2023 until 10 September 2023 by means of an e-submission tool. The comments were made publicly available immediately after the closure of the public consultation in Open EFSA.

Comments were received in the electronical tool from nine interested parties from seven countries. **Table 1** provides an overview on the interested parties that have submitted comments through the electronic submission.

Table 1: Overview on stakeholder comments

Stakeholder	Category[1]	Country
Raquel Soler-Blasco	Personal capacity	Spain
Norwegian Scientific Committee for Food and Environment, Panel on Contaminants	Other	Norway
Committee on the Toxicity of Chemicals in Food, Consumer Products and the Environment	Public Authority Outside The EU	UK (excluding Northern Ireland)
German Federal Institute for Risk Assessment	Public Authority in EU Member State	Germany
Istituto Zooprofilattico Sperimentale della Puglia e della Basilicata	Public Authority in EU Member State	Italy
Office for Risk Assessment & Research (BuRO), Netherlands Food and Consumer Product Safety Authority	Public Authority in EU Member State	Netherlands
Servicio Nacional de Pesca y Acuicultura	Public Authority Outside The EU	Chile
National institute for public health and the environment (RIVM)	Academia/Research Institute	Netherlands
Asociación Gremial de Mitilicultores de Chile	Industry - Small Or Medium-Sized Enterprise (SME)	Chile

1) As indicated by the stakeholder

1.2 Assessment of comments and use for finalisation of the Opinion

The comments received were duly evaluated by the EFSA WG on inorganic arsenic in food and the CONTAM Panel and wherever appropriate taken into account for the finalisation of the draft Opinion. **Table 2** provides a detailed list with all comments received from interested parties together with EFSA responses and explanations how the comments were considered in the final Opinion. Some comments, especially those suggesting editorial changes, have been directly addressed in the text of the Opinion, if they were considered appropriate.

EFSA wishes to thank all stakeholders providing comments during the public consultation of this draft update of the risk assessment of inorganic arsenic in food.

2 Abbreviations

ADME	Absorption, Distribution, Metabolism, and Excretion
As	Arsenic
BfR	Bundesinstitut für Risikobewertung (German Federal Institute for Risk Assessment)
BMDL	Benchmark Dose Lower Confidence Limit
BMDU	Benchmark Dose Upper Confidence Limit
BMR	Benchmark Response
BuRO	Bureau Risicobeoordeling & onderzoek (Office for Risk Assessment and Research)
BW	Body Weight
CAA	Carotid Artery Atherosclerosis
CES	Critical Effect Size
CI	Confidence Interval
CKD	Chronic Kidney Disease
CoC	Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment
CONTAM Panel	Panel on Contaminants in the Food Chain
DNA	Deoxyribonucleic Acid
DR	Dose-response
EC	European Commission
etc.	Et cetera (and so on)
EU	European Union
GA	Gestational Age
GW	Gestational Week
HC	Head Circumference
ID	Identification
Inf	Infinite
i.e.	Id est (that is)
iAs	Inorganic arsenic
LB	Lower Bound
LOG	Logarithm
L	Liter
MoA	Mode of Action
MOE	Margin of Exposure
ML	Maximum Limit
OHAT	Oral Health Assessment Tool
OR	Odds Ratio
p	Probability
POD	Point of Departure
RA	Risk Assessment
RIVM	Rijksinstituut voor Volksgezondheid en Milieu (National Institute for Public Health and the Environment)
ROB	Risk of Bias
RP	Reference Point
SCC	Squamous Cell Carcinoma
SC	Scientific Committee

SME	Small and Medium-sized Enterprise
TDS	Total Diet Study
TK	Toxicokinetics
UB	Upper Bound
UiAs	Inorganic Arsenic in urine
UK	United Kingdom
US	United States
UV	Ultraviolet
WG	Working Group
WHO	World Health Organization
w-As	Arsenic in water

3 Comments received

Table 2: Stakeholder comments and EFSA responses

Comment number	Stakeholder	Section	Comment	CONTAM Panel response
1	Norwegian Scientific Committee for Food and Environment, Panel on Contaminants	Abstract	Lines 5-11, p. 2 Author Tanja Schwerdtle is mentioned twice.	Corrected.
2	Norwegian Scientific Committee for Food and Environment, Panel on Contaminants	Abstract	In general: First we want to congratulate the Panel with a thorough review of new findings on health effects from iAs exposure. However, several places we find it hard to follow the thinking and we hope our comments can help to improve the opinion. In particular, we think the transformation of all exposure measures prior to modelling into dietary intakes and adding a regional basal dietary exposure is disconnecting the BMD modelling from the findings in the respective publications.	The observed incidences relate to the total exposure. Therefore, if instead using the water iAs concentrations as a basis for modelling this will provide a dose-response shape that differs (to some degree) due to differences in relative dose spacing between the two approaches (see Appendix of Annex E5). Consequently, this may affect both the point estimate of the BMD and its uncertainty. Based on analyses of a sub-set of data for modelled outcomes, the point estimate of the BMD was generally not very different between the two approaches. However, the BMD uncertainty (BMDU to BMDL ratio) became higher (up to a factor 6) under the approach taken (total exposure) compared to first modelling the As concentrations and then adding exposure from food. The BMDLs were then also lower for the approach taken. The CONTAM Panel considers that it is most appropriate to model the (total) dose-response relationship. A subsection

				(3.7.2.3) on this has been added to the uncertainty analysis.
			Line 23: The sentence "In absence of EFSA guidance an MOE of low concern could not be derived" should be deleted. You conclude that the low MOEs indicate a concern and that is sufficient.	Line 23: Sentence was deleted.
			Line 26: "which is supported by the uncertainty analysis" should be deleted. A conclusion takes uncertainties into consideration (based on an uncertainty analysis).	Line 26: Statement has been changed to "… despite the uncertainties…". The EFSA (2018) guidance on uncertainty analysis states that the impact of uncertainties on the assessment conclusions should be characterized.
3	Committee on the Toxicity of Chemicals in Food, Consumer Products and the Environment	Summary	Overall, thorough and clearly laid out draft opinion.	Thank you.
4	German Federal Institute for Risk Assessment	Summary	Lines 73-75, p. 4 The sentence seems contradictory, since clastogens are also mutagens. Suggested rephrasing: "Arsenic is itself a weak inducer of point mutations, but effectively induces chromosomal aberrations…" (compare also line 1410 p. 75)	Lines 73-75: Thank you for your suggestion. The sentence has been rephrased: "Inorganic arsenic is itself a weak inducer of gene mutations, but efficiently induces chromosomal aberrations, micronuclei and aneuploidy *in vitro* and *in vivo*".
			Lines 101-102, p. 5 Contains an incomplete sentence that may be deleted.	Lines 101-102: Corrected.
			Line 108, p. 5 The word "first" in the sentence suggests a further	Line 108: Agree. Deleted.

			transformation step. Suggestion: Either delete or add information on a further step	
			Lines 123-124, p. 6 Check if "skin lesions" should be added to the list "were calculated for skin cancer, lung cancer, bladder cancer, respiratory disease, chronic kidney disease, and ischemic heart disease."	Lines 123-124: Added.
			Lines 132-134, p. 6 What about the other associations judged as causal in lines 87-89 (congenital heart disease, ischemic heart disease, carotid artherosklerosis)?	Lines 132-134: Ischemic heart disease has been added to the list. However, the studies related to congenital heart disease did not meet the EFSA 2022 BMD guidance criteria. Additionally, no studies were modelled for carotid artery atherosclerosis. As a result, the assessment of RP coverage for these health outcomes is not possible.
			Line 133, p. 6 The term "applicable" should be changed to "protective".	Line 133: The sentence has been modified. The term "applicable" has been changed to "cover".
			Lines 143 and 144, p. 6 In EFSA 2021, the terms "95th percentile dietary exposure " and "mean exposure" are used, which seem more appropriate (instead of the terms used here: "high consumption" and "average consumption"; or "high level consumers" and "average consumers" in lines 4170 to 4173 (see also table 34)	Lines 143 and 144: Wording adapted to the one used in the 2021 EFSA scientific report on dietary exposure to inorganic arsenic.
			Line 161, p. 7 The word "is" should be deleted, resulting in the following phrase: "Therefore, dietary exposure to arsenic may be of greater concern for such individuals than for the general population."	Line 161: Deleted.
5	Norwegian Scientific	Summary	Line 32-37: It should be explained that the Commission has asked for an	Lines 32-37: A sentence has been added.

	Committee for Food and Environment, Panel on Contaminants	update of IAs and risk assessments of organic As and that this is the first of four RAs.	
		Line 57-59: Methylate arsenicals in urine are both metabolites from iAs, but may also be consumed as methylated As, e.g Dimethyl As in rice.	Lines 57-59: Indeed, they can additionally originate from complex organic arsenic species including arsenosugars and arsenolipids. Occurrence, exposure, hazard assessment / characterisation will be dealt with in the risk assessment on small organoarsenic species which is currently an ongoing work in progress. Information about the mandate can be found in the background information (1.1.1, lines 312-329)
		Line 82-83: It is not clear if dietary intake is included or not when it refers to water concentration.	Lines 82-83: The definition is based on the drinking water As concentrations reported in the relevant publications. It is not possible to know how much w-As contributed to exposure as drinking water versus use of the water for cooking.
		Line 89: Skin lesions other than cancer?	Line 89: "Other than cancer" has been added when referring to skin lesions.
		Lines 92-93: It is hard to understand why studies and outcomes are considered to be used in hazard characterization at all if they cannot be translated to Europe	Lines 92-93: The CONTAM Panel evaluated all health outcomes associated with arsenic in the literature and found that some outcomes, like arsenic-related skin lesions, seem to be strongly influenced by poor nutrition and poor health. Other outcomes did not show this influence and should be more relevant to European populations.
		Line 101-102 seems redundant (Editorial comment).	Lines 101-102: Corrected.
		Lines 103-106: The meaning of lines is unclear, it should better separate between risk of bias, and between continuous data and results in quantiles. Did you require at least	Lines 103- 106: Text amended for better clarity.

three exposure categories in addition to background or in total?	
Lines 121-124: Nothing is said about follow-up period of the epi studies, please add information.	Lines 121-124: These lines summarise many epi studies. The majority are case-control studies for which the length of the recruitment period is not very relevant. For the six cohort studies the follow-up time varied between 3 and 12 years. Therefore, the following sentence has been added in the Opinion. "For the six cohort studies the follow-up time varied between 3 and 12 years."
Line 129: Was the second skin cancer study on cell carcinoma also a case control study. Please clarify.	Line 129: "Case-control" has been added to this sentence.
Line 132: In this case also the BMD and BMDU should be given, as the background exposure is in the region of the BMDL/BMD.	Line 132: The CONTAM Panel does not think this is needed as BMDL/BMD/BMDU of this study are extensively described in the main body of the text (e.g. 3.2.4.2. Current dose-response analyses and 3.7.2. Assessment of BMD uncertainties.
Line 133: What is meant by applicable? We believe you may mean that these cancers are less sensitive for iAs exposure, so that the reference point also covers for these endpoints? Please rephrase	Line 133: The sentence has been modified. The term "applicable" has changed to "cover".
Line 136: individual – please rephrase to different.	Line 136: Rephrased.
Lines 139-141: We acknowledge that there is no guidance from the Scientific Committee. However, if there is no indication of increased risk at an exposure of 0.06 µg iAs per kg bw, why is it not possible to suggest an uncertainty factor and by that indicate what would be considered as a sufficiently large margin of exposure?	Lines 139-141: The CONTAM Panel notes that an EFSA guidance on the use of human data for risk assessments is needed, in particular on BMD modelling of epidemiological data and for a quantitative risk assessment for genotoxic carcinogens based on epidemiological data.

			A lack of guidance should not totally prevent EFSA from concluding. As an alternative, we suggest that lines 139-141 are deleted from the Opinion.	This will be addressed in an update of respective guidance by the EFSA Scientific Committee, planned for the near future.
			Lines 142-146: It seems that the background exposure is already incorporated in the reference point. So this margin of exposure is very hard to interpret. What is the uncertainty in that regional background that is added? We cannot see this is explained anywhere, is it supported by biomonitoring data of IAs in urine or nails? Furthermore, the data on cancer risk overlaps with the current exposure, so the risk can be described directly by the data. We think it would be helpful to describe how the exposure distribution overlaps with the BMDL and BMD.	Lines 142-146: The dose metric is the arsenic urinary concentration, which already represents total daily oral intake (drinking water concentrations, regional diet exposure). From this urinary concentration, the CONTAM Panel back calculated the total daily oral intake (taking into account background exposure). The uncertainty analysis describes the probability of the exposure to exceed the BMD. This describes how exposure distribution overlaps. See also response to comment 2.
			Lines 143-144: We suggest that "two fold below" is rephrased into "half of".	Lines 143-144: Corrected.
			Lines 159-162: Are there any specific genetic conditions known? In that case we think it should be mentioned in the summary.	Lines 159 – 162: Metabolism, detoxification, and DNA repair mechanisms play pivotal roles in determining the toxic effects of genotoxic carcinogens including inorganic arsenic. Variations in these processes may account for the inter-individual variability observed in arsenic exposure studies. The implications of alteration in the DNA damage response are extensively addressed in the genotoxicity mode of action section and taken into account in the uncertainty analysis. The issue of the susceptible individuals is already noted in the summary in the paragraph you refer to.

6	German Federal Institute for Risk Assessment	Section 1.1.1 Background	Line 292, p. 13 Missing Unit: 0.3 and 8 µg/kg b. w. and day	Line 292: Inserted.
7	German Federal Institute for Risk Assessment	Section: 1.2.1 Chemistry of inorganic arsenic relevant to its presence in food	Line 377 ff., p. 16 Chemical name, abbreviation and chemical structure not consistent (acid vs. salt). For instance, the abbreviation of methylarsonate should be MA(V) and that of the acid MMA(V); the corresponding chemical structures should be CH3AsO(O-)2 (for methylarsonate) and $CH_3AsO_3H_2$ (for the acid). This should also be considered for the other salts/acid pairs. Having salt and acid in different columns would be a possible approach.	Thanks for this important note. To avoid misunderstandings, the structures have been changed to the fully protonated forms and this has been explained in the footnotes.
8	Istituto Zooprofilattico Sperimentale della Puglia e della Basilicata	Section: 1.2.2 Analytical methods	This section could be updated adding some new references of validated approaches, please see for example: - D'Amore et al (2023) Characterization and Quantification of Arsenic Species in Foodstuffs of Plant Origin by HPLC/ICP-MS. Life (Basel), 13(2), 511. doi: 10.3390/life13020511. - Clemente et al (2021) Arsenic speciation in cooked food and its bioaccessible fraction using X-ray absorption spectroscopy. Food Chemistry, 336, 127587. doi: 10.1016/j.foodchem.2020.127587.	The CONTAM Panel acknowledges this information. This will be taken into account in the ongoing RAs on small and complex organoarsenic species, where an extensive analytical method chapter is planned to be presented.
9	Norwegian Scientific Committee for	Section: 1.2.3	Lines 430-435: The study by Chen et al 2010a had a follow up period of	The CONTAM Panel considers that the follow-up period does not add extra to the

	Food and Environment, Panel on Contaminants	Previous assessments	about 12 years. Follow up time should be added in the tables.	risk assessment performed, and therefore the information was not added.
10	German Federal Institute for Risk Assessment	Section: 1.2.4 Legislation	Lines 511-522, p. 22 Check if 3), 4) and 9) should be a footnote	Lines 511-522: The CONTAM Panel prefers to keep these as legends to the table as any table in an EFSA opinion has to be a standalone table containing all footnotes.
11	Office for Risk Assessment & Research (BuRO), Netherlands Food and Consumer Product Safety Authority	Section: 2.1.2 Evaluation of data	In lines 625-627 the following is stated: "In the updated search on key topics covering the period 2009 to 2010, 81 studies were considered possibly relevant in the pre-evaluation. In the updated search on key topics covering the period 14th of April 2021 to 18th of July 2022, 81 studies were considered relevant after the pre-evaluation." What happened with the period between 2010 and 2021?	This period has been covered by the very first literature search as described in this section.
			In addition, is it correct (and coincidental) that the number of possibly relevant and relevant studies is identical (both 81)?	No. In the additional search covering the period from 1st January to 31st December 2009 indeed 81 potentially relevant publications have been identified. However, in the additional search covering the period from 14th July 2021 – 18 July 2022, 160 potentially relevant publications have been identified. This error has been corrected.
12	Norwegian Scientific Committee for Food and Environment, Panel on Contaminants	Section: 2.1.2 Evaluation of data	Lines 625-627: Is it correct that 81 studies were identified from both of the searches?	Lines 625-627: See response to comment 11 above.
			Lines 630-631: It is not clear how many of the papers that were assessed further.	Lines 630-631: This is not described in the methodology section. The publications actually assessed and considered for the opinion are described in the respective subsections of Section 3.2.2. Chronic effects.

13	German Federal Institute for Risk Assessment	Section: 2.1.3 Transformation of data from epidemiological studies and derivation of benchmark dose calculations	Lines 632-633, p. 27 Check if the word "derivation" should be deleted, resulting in the phrase: "Transformation of data from epidemiological studies and benchmark dose calculations"	Agree. Deleted.
14	Norwegian Scientific Committee for Food and Environment, Panel on Contaminants	Section: 2.1.4 Overview of methodology applied	Line 643: Please describe which tool that was used for risk of bias assessment.	Line 643: The risk of bias assessment used elements included in the OHAT Risk of Bias assessment tool and is in agreement with the draft SC guidance on appraisal of epidemiological studies (EFSA, 2020). This information has now been added in Section 3.2.4.2 under the subheading "Risk of bias analysis". A detailed description of the results from the risk of bias analysis can be found in Annex C.
			Line 645: Why do you indicate that a reference point was established by application of expect knowledge when you apply benchmark dose modelling and excluded studies that could not be modelled? It is not clear what you mean by already existing exposure levels. Do you mean exposure levels in Europe?	Line 645: Indeed, the sentence was incomplete and has been amended.

			Figure 1: It is not clear how you define key studies. The addition of background exposure is not described in the figure. The fact that the study cannot be modelled is not a reason to disregard it. How does this affect the outcome of the risk assessment? This should be discussed.	Figure 1: "Key study" is defined now in a footnote to Figure 1. For completeness, the following sentence has been added to the flowchart "Use of the estimated incidence in the reference category as an informative prior for the background parameter." Studies that could not be modelled were not discarded but taken into account regarding the evidence for the respective health outcome.
			Table 10, with the inclusion exclusion for criteria, would fit better in data and methodologies.	Table 10: Yes. Table 10 could have been placed under "Data and methodologies", but the CONTAM Panel prefers the table in close proximity to the Section 3.2.2.1 "Selection of studies".
15	Servicio Nacional de Pesca y Acuicultura	Section: 3 Assessment	4100.- We would like to consult if the results of the exposure assessment presented were based on total diet studies, through surveys, in this scenario we consult if it will indeed be possible to establish a single limit for the European population.	Line 4100: Occurrence data derived from Total Diet Studies (TDS) were not used for the dietary exposure estimations (see EFSA, 2021). A total of 44 individual dietary surveys from 23 European countries were used to estimate exposure, providing individual exposure estimates by dietary survey and age class. Therefore, the consumption of the different commodities that might contribute to the dietary exposure to iAs in the European population is considered adequately represented.
			4101.- Likewise, the determination of exposure to Inorganic Arsenic was based on a focused group of foods, not on the total diet of an individual, so we asked if in your opinion this method could produce a possible overestimation of exposure. to this compound	Line 4101: The dietary exposure considered the whole diet for each individual participating in the dietary surveys and not only a particular group of foods. To complement the general dietary exposure scenario, different additional exposure scenarios (e.g. in breastfeeding infants, for infants consuming rice-based formulae, etc.) were conducted.
16	German Federal	Section: 3.1 Hazard	Line 652, p. 29, line 676, p. 29, line 1514, p. 79 Headlines and structure:	There are many different types of EFSA Opinions and thus there are no strict rules

	Institute for Risk Assessment	identification and characterization	Used headlines are not in line with other EFSA Opinions and partly suggesting that not all data are addressed, e. g.: i) Toxicokinetics followed just by the subheading "metabolism" raises the question regarding absorption, distribution and excretion, which is considered under "toxicokinetics". However, metabolism is also part of the term "toxicokinetics", therefore we propose either just to use the heading "toxicokinetics" incl. metabolism or to have all ADME subheadings included. ii) Toxicity: The headlines suggest that only genotoxicity, carcinogenicity and observations in humans are addressed and not all toxicity. Maybe toxicity should be added as a header? Furthermore, according to the postulated table of content, 3.2 "Observation in humans" is not part of the "Hazard identification and characterization" (chapter 3.1), but of course it should be. Human observations: the structure of 3.2.2 chronic effects is not intuitive. Maybe the purpose for selection of studies should be added in the headline "Selection of studies considered for hazard characterization".	to be followed with respect to headlines and structure. In the TK section it is clearly stated that the aim is to give a short summary of the crucial steps of TK. In the TK subchapters only the most important new findings that impact on the RA are addressed. Likewise in the sections on Toxicity and Human Observations, only the endpoints and effects which are relevant for this risk assessment are addressed.
17	Istituto Zooprofilattico Sperimentale	Section: 3.1.1.1 Metabolism	The following paper could be interesting for discussion in this part of the opinion. Cao et al (2023)	Thanks for informing us about this paper. As described in Section "Data and Methodology" in Subsection 2.1.1

	della Puglia e della Basilicata		Transformation of arsenic species from seafood consumption during in vitro digestion. Frontiers in Nutrititon, in press (paper ID 1207732).	"Collection of Data" no ADME references have been taken into account after 2021.
18	Office for Risk Assessment & Research (BuRO), Netherlands Food and Consumer Product Safety Authority	Section: 3.1.2.1 Biomarkers of exposure	In this section there is no mention of the use of arsenic concentrations in water as marker. Is there a correlation between water As and urinary As concentrations, especially at low As concentration? Also we miss information on the use of spot urine or do we need 24-h urine samples for accurate arsenic exposure assessment? Note: same comment applies to section 4.3 Biomarkers	The Panel modified the first sentence of the section to clarify this matter. "In its previous Opinion (EFSA CONTAM Panel, 2009) the CONTAM Panel noted that total arsenic in urine is a common biomarker of arsenic exposure as most arsenic compounds originating from oral arsenic intake of food and water are excreted via urine within a few days." The Panel added the following sentences: "Urine collected over 24h is preferred for biomonitoring of arsenic. However, because of difficulties in obtaining 24-h urine samples, first-morning or spot urine samples are usually collected for biomonitoring of arsenic." The Biomarker section is much condensed and is not intended to be used as a textbook. In the interest of brevity and readability of the Opinion the Panel has omitted details such as the one related to sampling regimes for urinary arsenic.
19	Norwegian Scientific Committee for Food and Environment, Panel on Contaminants	Section: 3.1.2.1 Biomarkers of exposure	Line 764: DMA may even come from rice, please add.	Line 764: Thanks for this important note. This information was added.
			Line 766 -770: normalised – use: adjusted.	Lines 766-770: "Normalised" replaced with "adjusted".
20	Norwegian Scientific Committee for Food and Environment,	Section: 3.1.2.3 Markers of	Line 1003: What is meant by differences? Reduction in GA and HC?	Line 1003: The text has been amended making clear that the association is with reduction in gestational age (GA) and head circumference (HC).
			Line 3613-3614: Where is the description of this first risk of bias	Lines 3613-3614: During this initial stage and due to time constraints, the risk of bias

	Panel on Contaminants	epigenetic changes and Section 3.2.4.2. Current dose response analysis	analysis? Was not what is described in line 3614-3615 not already part of the original risk of risk of bias analysis? This is very hard to follow or understand.	assessment considering all the studies (more than 600) did not include a RoB tool and the evaluation was included when reviewing the studies in Section 3.2.2. This was described in Section 3.2.2.1, lines 1556-1557 by the experts. For the studies that have been used for dose-response analysis, the risk of bias assessment used elements of the OHAT risk of bias tool and was performed independently by two experts. Text has been added to clarify this further.
			Line 3625-3626: Mean concentration over time is relatively stable, is that what is meant?	Lines 3625-3626: Yes, now revised for better clarity.
			Line 3631: a comma should be after iAs (editorial).	Line 3631: Corrected.
			Line 3635: Consumption of local food would probably lead to higher exposure than the background which has been used as basis in these calculations, and this will lead to overestimation of the risk (the real exposure is higher than estimated). This should also be considered in this context.	Line 3634 – 3636 states that "the iAs exposure based on As in water plus assumed intake from other food will be subject to misclassification. It is important to note that such misclassification will almost always be nondifferential (not associated with the outcome)." The CONTAM Panel agrees that variation of iAs in local food contributes to the variation in the sum of iAs intake from water and food other than water. It is still likely to be non-differential (not associated with the outcome). Moreover, if As in water is high the additional contribution from other food is likely to be small, and variability in water concentrations and water intake will be a more important source of misclassification.
21	Norwegian Scientific Committee for	Section: 3.1.3 Genotoxicity	Line 1429: The term conclusion should not be used here – rather summary and evaluation.	Line 1429: Agree. Changed to "summary on genotoxicity".

	Food and Environment, Panel on Contaminants		Line 1438: Please clarify if the "very low" concentrations are in vitro.	Line 1438: Very low concentrations refer to both *in vitro* and human studies. The experiments on inhibition of specific repair activities have been carried out *in vitro* (see for example inhibition of PARP1 activity) but there is a huge amount of data showing accumulation of DNA breaks and oxidative damage to DNA in humans at low exposure levels (10-40 ug/L) indicating alteration of DNA repair. This sentence has been clarified.
22	German Federal Institute for Risk Assessment	Section: 3.1.3.3 Mode of action for genotoxicity	Line 1409, p. 75 The headline should be rephrased, e.g. "Induction of point mutations"	Line 1409: Because this section covers more than just point mutations, the heading has revised to read "Induction of gene mutations".
23	Office for Risk Assessment & Research (BuRO), Netherlands Food and Consumer Product Safety Authority	Section: 3.2.2.1 Selection of studies	Table 10 and line 1560: Studies without information on data on sun exposure or skin sensitivity to UV light for skin cancer are not included. For skin cancer, another confounder is most likely use/time spent on a tanning bed/solarium. Also the presence of other contaminants as potential confounder, especially in drinking water is not discussed. Can this information be added to the main text of the opinion?	Agree. A sentence was added in the main text stating that data on time spent on a tanning bed/solarium was not available.
24	German Federal Institute for Risk Assessment	Section: 3.2.2.1 Selection of studies	Line 1541, p. 79 It is not clear for what purpose the selection of study is meant (e. g. "Selection of studies considered for hazard characterization").	Line 1541: The heading "Selection of studies" refers to Selection of studies which were considered for risk assessment.
			In addition, the order of the (sub)headings is not clear with 3.2.2 being "Chronic effects" and 3.2.2.1 "Selection of studies", since "Selection of study" is not a chronic effect. Suggestion: Move "Selection of	The order of the (sub)headings in Section 3.2.2: Heading is retained. Disagree that it implies that "selection of studies" is a chronic effect.

			studies" under 3.2.2 as a subheading without number (black, bold).	
			Line 1576, p. 81 Publications in languages of the member states of the European Union such as Spanish, French and German have not been considered from the beginning. BfR suggests to also consider articles in languages other than English.	Line 1576: Indeed, in the initial search only publications in English language were considered. However, during the long period of drafting the opinion, the process of snowballing was carried out which revealed a series of additional studies, all of them in English language. However, your suggestions will be considered for future scientific outputs.
25	Norwegian Scientific Committee for Food and Environment, Panel on Contaminants	Section: 3.2.2.1 Selection of studies	Line 1547: Low to moderate should be defined here. We find other places "defined as arsenic water concentrations of less than approximately 150 µg/L, or biomarker concentrations estimated to result from equivalent doses.	Line 1547: Definition was inserted.
			Please indicate what drinking water concentration of less than 150 µg/L corresponds to in urine and nails.	Assuming, as in the draft Opinion (Section 3.2.4.2) for Europe 1.5 L of drinking water/d and that 90% is excreted in urine, the excretion will be about 200 µg/24h or 100 µg/L, assuming 2 L of urine (Section 3.2.4.2). These are average estimates for a population but will vary between individuals. For some populations (e.g. Bangladesh) with higher intake (e.g. 4 L), the estimates will be 2-3 times higher. All studies included had u-tiAs below the above-mentioned levels. Some studies were excluded due to "too high" As levels in drinking water, but no studies due to "too high" u-tiAs or nail-As."
			Line 1556-1557: Where is risk of bias analysis documented? Please cross refer. Table 10: Were the later updating searches previously	Lines 1556-1557: For all studies some basic information that could be associated with risk of bias is given in Tables 11 to 32, such as design, population size and confounder

			described following the same criteria? If so, it could be included under time period in table 10. Why are cross-sectional studies included?	adjustment. Special concerns were noted in the column "Additional information/confounders". For the studies that could be DR modelled a more detailed RoB analysis was performed independently by two epi experts as detailed in Section 3.2.4.2 under the subheading "Risk of bias analysis". Some notes on the Risk of bias analysis can be found in Annex C. See also response to comment 20. Table 10: Since the updated literature search was following the inclusion criteria in Table 10, the dates in the table have been extended to include studies up to July 18, 2022. Regarding the consideration of cross-sectional studies, studies were not excluded solely based on their study design. The totality of the evidence was considered and then the evaluation followed a tiered approach based on the risk of bias assessment.
26	Committee on the Toxicity of Chemicals in Food, Consumer Products and the Environment	Section: 3.2.2.2 Cancers (Skin cancer)	The relationship between arsenic and skin lesions is well established but noted that the Diamond- Gilbert paper refers to an association between arsenic and invasive SCC only	Our assessment that there is sufficient evidence for an association between low to moderate exposure to inorganic arsenic and skin cancer is based on studies on basal cell carcinoma and squamous cell carcinomas of the skin.
27	Committee on the Toxicity of Chemicals in Food, Consumer	Section: 3.2.2.2 Cancers (Bladder cancer)	Lines 1640-1699; Bladder Cancer - The importance of controlling for the effects of cigarette smoking is addressed in this section, but the possibility of confounding due to	Lines 1640 – 1699: The following sentence on line 1674 has now been inserted: "It should be noted that occupational exposure to bladder carcinogens may be a

	Products and the Environment		occupational exposure to bladder carcinogens is not mentioned. Several of the studies cited were undertaken in Taiwanese populations. Occupational exposure to bladder carcinogens in the Taiwanese (and Chinese) dye and rubber industries is less tightly controlled than in the West, and this is reflected in the different outcomes of recent studies of genetic susceptibility to occupational bladder cancer in these countries compared with those in the US and Europe. This issue is unlikely to have had a marked effect on the results of population-based studies of arsenic exposure; nevertheless, it might have been worth noting it as a possible confounding factor.	confounding factor and it was taken into account in most studies."
28	National institute for public health and the environment (RIVM)	Section: 3.2.2.2 Cancers (Bladder cancer)	Line 1700, Table 12: For most epi studies in Table 12 the number of cases and controls are given per exposure group and in total. However, for the study of Mostafa and Cherry (2015) only the total number was given, and for the study of Baris et al. (2016) only the numbers per exposure group. Could EFSA harmonise the approach across studies in this table, and if not possible, indicate why?	For Baris et al. (2016) the total number was provided, but it has now been modified for clarity. For Mostafa and Cherry (2015) the cases and controls have been added for exposure groups as well.
29	Norwegian Scientific Committee for Food and Environment, Panel on Contaminants	Section: 3.2.2.2 Cancers (Lung cancer)	Line 1734: unit missing before 100 (editorial)	Line 1734: Corrected by inserting " ≥ " before the value 100.
			Table 13, Chen et al 2010a: Do you mean median urinary iAS or water concentration in the fourth column?	Table 13, Chen et al. (2010a): Clarification that the concentrations in the fourth column correspond to arsenic concentrations in water has been provided.

30	National institute for public health and the environment (RIVM)	Section: 3.2.2.2 Cancers (Lung cancer)	Line 1750, Table 13: For most epi studies in Table 13 the number of cases and controls were given per exposure group and in total. As in Table 12, for some studies (including Ferreccio et al. (2000), Smith et al. (2009), Chen et al. (2010), Garcia-Esquinas et al. (2013) and Steinmaus et al. (2014a)) only the total number was given, and for Heck et al. (2009) only the numbers per exposure group in the part of small cell squamous cell carcinomas. Could EFSA harmonise the approach across all studies in this table, and if not possible, indicate why?	This has been harmonised now across all studies in this table.
31	Committee on the Toxicity of Chemicals in Food, Consumer Products and the Environment (UK, excluding Northern Ireland)	Section 3.2.2.4 Developmental toxicity (Birth weight)	Lines 1999-2007, 2016-2022, 2146-2153 and 4562-4567; Locally high exposures to iAS via drinking water - The points made in lines 1999-2007 and 2016-2022 regarding locally high exposures due to the use of private wells are very pertinent. In this context it might also have been worth mentioning that locally high exposures also occur in Bangladesh due to the use of water drawn from artesian wells which reach down to aquifers containing arsenic-contaminated ground water. This was highlighted as a cause for concern by Smith et al in 2000 (Smith AH, Lingas EO, Rahman M. Contamination of drinking-water by arsenic in Bangladesh: a public health emergency. Bull World Health Organ. 2000:1093-103; Ref 1 in the Pierce et al, 2011 paper cited in the opinion).	Yes, as pointed out in the comment, the background of high As levels in drinking water in many areas in Bangladesh is well-known (and unfortunately it was not known or taken into account in several large scale well drilling campaigns aimed at providing drinking water uncontaminated with infectious agents). The CONTAM Panel agrees that misclassification of exposure also must be present in the Bangladesh studies and have now added this in the section "Overall summary on As and Birth weight", hoping that it need not to be repeated everywhere.
			It may be that the relatively small effects on parameters such as birth	Agree. Sentence has been amended to reflect this.

			weight and stillbirth seen at "low to moderate" exposures in Bangladesh under-represent more marked effects in subpopulations exposed to high levels of iAs as a result of using contaminated well water which may have been missed in the strategy of testing of testing only a few wells in each area. This applies to all the data in the opinion that is derived from Bangladesh; the large number of such studies reflects concern about this phenomenon during the last couple of decades. It is not a key issue for the opinion, but it might have been worth mentioning it somewhere and providing a citation.	
32	Norwegian Scientific Committee for Food and Environment, Panel on Contaminants	Section: 3.2.2.4 Developmental toxicity (Birth weight)	Line 2028-2043: there is no discussion or explanation why the associations with birth weight are considered causal. It rather points to conditions that indicate that there are other reasons. And if it cannot be concluded associations are causal or relevant to Europe, why is birth weight considered as critical end point?	For all outcomes under Section 3.2.2, it is concluded if the evidence from epidemiological studies is sufficient or insufficient. The issue on causality is not covered until Section 3.2.3. For birth weight, this is covered in Section 3.2.3.3.
33	German Federal Institute for Risk Assessment	Section: 3.2.2.4 Developmental toxicity	Line 2323, p. 133 Missing cross-reference	Corrected.
34	National institute for public health and the environment (RIVM)	Section: 3.2.2.4 Developmental toxicity (Growth after birth)	Lines 2348 -2351: In the first sentence it is stated that Gardner et al. (2023) found an association between concentration of iAs in urine and children's weight at five years of age. However, in the following sentence it was stated that the same study did not	Corrected.

			find such an association at five years of age. Could EFSA please clarify?	
35	Raquel Soler-Blasco	Section 3.2.2.4 Develop-mental toxicity (Prenatal arsenic exposure and cognition)	Page 141, lines 2418-2424: The authors of the article cited in this paragraph (Soler-Blasco et al. (2022)), want to provide the authors/experts of this Scientific Opinion with complete data on the associations between prenatal exposure and neurodevelopment assessed in childhood (including total arsenic and its metabolites). We believe that this information can help the authors of this document to complete the information in the section, as well as incorporate these data into Table 20 of the same. We would like to thank the authors and editors for considering the study we conducted in this report (see Appendix A for the attachment).	In the draft Opinion sent to the Public Consultation, the CONTAM Panel reported the following on the study of Soler-Blasco et al. (2022): *Soler-Blasco et al. (2022) evaluated maternal urinary arsenic (geometric mean 7.78, 95% CI 7.41, 8.17 µg/g creatinine), in the first trimester and neurodevelopment (McCarthy Scales of Children's Abilities) in Spanish 4–5 years-old children. They found inverse associations between MMA concentrations and the scores for the general, verbal, quantitative, memory, and working memory scales. However, no associations were found between total iAs and developmental scales in multivariate models (no figures for the associations for total iAs are reported in the article, and the study is thus not in table).* The reason the study wasn't included in Table 20, summarizing important epidemiological studies on arsenic exposure and neurodevelopment, was that it didn't provide specific confidence intervals for developmental scales in multivariate models. Moreover, it didn't present the exposure data in categories (see Soler-Blasco et al., 2022: Table 2). However, based on the new information on confidence intervals, the CONTAM Panel was able to conclude that no associations were found between total iAs and developmental scales in multivariate

				models. This information has been included in the Opinion and the study has also been included to Table 20.
36	German Federal Institute for Risk Assessment	Section: 3.2.2.7 Effects on the cardiovascular system	Line 2731, p. 181 Missing cross-reference Line 2927, p. 200 Missing cross-reference Line 2963, p. 201 Missing cross-reference Lines 585-586, p. 25 Missing cross-reference	Corrected.
			Line 569, p. 24 Redundant bracket	Line 569: Corrected.
37	National institute for public health and the environment (RIVM)	Section: 3.2.2.7 Effects on the cardiovascular system (Stroke)	Lines 2672-2685: Eight studies were summarized in Table 25, but one study, (Chen et al., 2013a), is not mentioned in the text. Could EFSA clarify why this study was not mentioned?	The reason is that the study by Wu et al. (2015) is based on the same study base but with more cases. This explanation can be found in the rightmost column of Table 25.
38	National institute for public health and the environment (RIVM)	Section: 3.2.2.7 Effects on the cardiovascular system (Ischemic heart disease (IHD))	Lines 2634-2964: Could EFSA please check this whole section (3.2.2.7 Effects on the cardiovascular system). Certain paragraphs are repeated and some tables are separated from the corresponding text:	Corrected.
39	National institute for public health and the environment (RIVM)	Section: 3.2.3 Critical effects	Lines 3321- 3461: For some endpoints (chronic kidney disease, lung function etc.) the first sentence refers to the section describing the endpoint, whereas this was not done for other endpoints (ischemic heart disease,	Yes, it is a little bit inconsistent, but with no specific intention. The initial "As described in Section 3.2.2 ..." for CAA, lung function and CKD has now been removed.

			infant mortality and skin lesions, etc.). As a result, it seems like there is a distinction between two 'kinds' of endpoints. Is this EFSA's intention?	
40	Norwegian Scientific Committee for Food and Environment, Panel on Contaminants	Section 3.2.3.1 Skin, bladder and lung cancer and Section: 3.2.3.2 Skin lesions	Lines 3357-58: sentence is hard to understand. Is it this meant: ....specific genetic and epigenetic changes in tumors seen after iAs exposure when compared with….	Lines 3357 -58: Yes. Corrected.
			Line 3361: Can causation be explained better? E.g is there a clear dose-response? Bladder is just briefly mentioned above for MN.	See also response to comment 47. To clarify that this section provides additional information about biological plausibility and does not repeat dose-response findings from the epidemiological studies, the last sentence has been rephrased, first paragraph, line 3330 to: Additional information about biologically plausible mechanisms per endpoint is provided in the text below.
41	National institute for public health and the environment (RIVM)	Section: 3.2.3.3 Decreased birth weight	Lines 3374-3382: It is stated several times that the data from Bangladesh are considered to contain possible confounders which might make it less applicable to Europe. However, if these are truly confounders would that not mean that a causal relationship between exposure to arsenic and body weight is more tentative, even in Bangladesh? I.e., can we consider that the effect of arsenic on birthweight is moderated by nutrition (as in the study by Lin et al, 2019)?	It is true that there are several potential confounders that will affect associations between iAs exposure and birth weight (BW) in the Bangladesh (and other) studies. These are, however taken into account in the analyses in the studies by Kile et al. (2016) and Rahman et al. (2017). Much of the association seemed to be mediated by gestational age (GA). And yes, both BW and GA are affected by nutrition and the data from these Bangladeshi studies suggest that children with poor nutrition and short GA are more affected by iAs exposure. Therefore, the results may be less relevant for European populations.
42	Norwegian Scientific Committee for Food and	Section: 3.2.3.3 Decreased birth weight	Lines 3374-3380: If the evidence for association is insufficient for other countries than Bangladesh and the results for Bangladesh cannot be	Lines 3374 – 3380: Please see response to comment 41.

	Environment, Panel on Contaminants		generalized to Europe, why is causal relationship concluded? Some mechanisms are suggested, but there are no other arguments why this association in Bangladesh is causal. So why was causality concluded, and why was it considered among critical effects?	
			Lines 3381-3382: A decrease in birth weight is relevant for Europe, is it the remaining effect size that is not meaningful? If so, why is the endpoint considered critical?	Lines 3381 – 3382: Yes, the phrasing was not logical, and the last sentence has been revised therefore. Even if it is uncertain if the association occurs also in Europe, it is listed among the potential critical effects.
43	Norwegian Scientific Committee for Food and Environment, Panel on Contaminants	Section: 3.2.3.4 Spontaneous abortion and stillbirth	Lines 3384-3395: Is the evidence from observational studies sufficient to conclude on causality? We understand there is animal evidence at high doses, but the proposed mechanisms are only suggestive. Spontaneous abortion is common in Europe, so it is a relevant outcome, but not if the associations in Bangladesh can be explained by other factors than iAs exposure.	Lines 3384 – 3395 The reasoning is the same as for comment 41. The association in Bangladesh is considered causal, but it may be less relevant for the European population.
44	Norwegian Scientific Committee for Food and Environment, Panel on Contaminants	Section: 3.2.3.5 Infant mortality	Causality needs better explanation – is it linked to congenital heart disease? If not clearly causal, it should not be among the critical effects.	No, it is not linked to congenital heart disease. But decreased birth weight, preterm birth, and effects on lung function and respiratory disease are likely to contribute to infant mortality, and causality of these outcomes has been discussed. This is now clarified by a minor change of last sentence.
45	National institute for public health and the environment (RIVM)	Section: 3.2.3.7 Neurodevelopmental effects	Lines 3421-3423: 'As described above….' Could EFSA add a reference to the section in which this was mentioned?	The section on critical effects has been harmonised by removing the initial "As described in Section 3.2.3 ..." for CAA, lung function and CKD.

46	Norwegian Scientific Committee for Food and Environment, Panel on Contaminants	Section: 3.2.3.7 Neurodevelopmental effects	Lines 3421-29: Is causality for impaired cognition based on the possible mechanisms? What about dose-response?	Yes, as it is written in the Opinion: "Several biologically plausible mechanisms for impaired neurodevelopment, including cognition, have been described…" Regarding dose-response see comment 47.
			Line 3429: Please add impaired before cognition.	Line 3429: Added.
47	Norwegian Scientific Committee for Food and Environment, Panel on Contaminants	Section: 3.2.3.8 Ischemic heart disease	3431-3437: Reasons for causality is not well explained, association and some possible MoA is all that is described, and dose-response, consistency, effect size, independent cohorts is not described, and it is not so clear why the outcome is among critical effects. Same comment applies to the rest of the endpoints in section 3.2.3.	The independent cohorts (from several countries), dose-response, consistency and effect size are described in Section 3.2.2 and were not repeated here. What is added here is that several plausible mechanisms have been described.
48	National institute for public health and the environment (RIVM)	Section: 3.2.4 Dose-response analyses	Lines 3514 - 3931: The general approach is novel and has merit, however the software and the data are not really designed to perform the analysis. The following two issues hamper the correct derivation of a (reference) BMDL here: (1) Applying this approach assumes that the incidence in the lowest exposure group is a good approximation of the background incidence at the hypothetical zero arsenic exposure level. However, the exposure in the lowest group is, in reality, infinitely higher than zero (dose/zero=inf). A better estimate of the background could be made by fitting a DR model to the individual data (preferred) or categorizing the data into more exposure groups. Such	Ad (1) The CONTAM Panel agrees that it would be ideal to perform a dose response (DR) analysis having knowledge of the response at zero exposure. This is, however, not possible since for all studies considered the population under scrutiny was exposed (from drinking water or other dietary sources). The CONTAM Panel also acknowledges that if individual data had been available, the response (incidence) at a very low dose (below the median of the lowest exposure category reported in the publication) could have been estimated and other models could have been used in order as well to better account for confounding effects. Splitting the data into more exposure categories would have been useful. However, it would have required access to individual data, not only on exposure and response, but also on all potential confounders and other covariates

			data may allow a more precise estimation of the lower end of the dose-response curve including an estimate of background. (2) This approach (or rather the software) neglects to take into account the uncertainty in the incidence of the lowest exposure group, which will influence the value of the BMR (or "value for CES"). Hence the width of the BMD CI could/would be underestimated and the BMDL overestimated.	considered in the study. Such individual data were not available, therefore, the best approach considered by the epidemiology experts was to use the response in the lowest exposure category as a proxy for the "background" response. The epidemiology experts consulted considered that it is likely that the response in this group is representative also for individuals with even lower exposure than the median in this category. The experts considered that the knowledge to include in the modelling process is related to the expected shape of the dose-response curve below the lowest exposure group. They would like to restrict the shape to be flat. In order to ensure this, an informative prior for the background centred at the reported incidence for the lowest exposure group would need to be included. Of course, the values themselves are study dependent, but the knowledge that is included is independent of the study and it is in relation to have a flat line below the lowest reported exposure. To ensure that incidence remains flat under the lowest exposure, the prior distribution for the background incidence was assumed to be centred around the reported incidence for the lowest exposure group with a small variance. Ad (2) The CONTAM Panel agrees that some uncertainty might be expected in the response in the background group, but the variation around the background incidence was considered to be small. Setting the prior for the background response as it was mentioned before was based on expert

knowledge as also recommended in the EFSA 2022 guidance on BMD modelling. The experts expressed consensus that the dose-response curve should be flat from the lowest reported exposure downwards. The reason for this was that this exposure category was generally representative for the whole study population in terms of other (than iAs exposure) known predictors for the disease/outcome in the study and should be the best estimate of the true response. Moreover, *the software* does not neglect the uncertainty in the incidence of the lowest exposure group. If other assumptions were to be considered, the tool allows to include different priors for the hypothetical background incidence. Nevertheless, the CONTAM Panel acknowledges that there might be uncertainty around the reported response. The uncertainty can be expected to be highest for studies with a relatively small number of cases per exposure category, namely the study by Chen et al. (2010b) on bladder cancer, the studies by Milton et al. (2005) on stillbirth and spontaneous abortion, and the study by Hsueh et al. (2009) on chronic kidney disease. But for example, the studies on skin cancer and ischemic heart disease had >50 cases in the lowest exposure category (and very large numbers in the source populations) Moreover, also the data for the other categories carry some information on the likely response in background category. For most DR modelling the variability considered around the most likely value used was 1% relative change. Additionally, as a sensitivity analysis for specific studies,

				models were also fitted assuming weakly informative (equivalent to non-informative priors in the context of non-linear models) prior for the background response. Similar results were obtained, indicating again the robustness of the results despite the prior used for the background response.
49	Norwegian Scientific Committee for Food and Environment, Panel on Contaminants	Section: 3.2.4.1 Previous dose response analyses	Line 3483: It is hard to understand the meaning. Is it meant that 50-200 ug iAs/day comes from food in addition to iAs from 3-5 L water per day? What was the concentration in the water? This is a high volume to drink, is it perhaps partly the water used for cooking? Is that not considered in the exposure calculation from food?	It is correct that the CONTAM Panel had considered for Asian population a range of 50-200 µg iAs/day from diet and a water consumption of 3-5 L water per day. It was mentioned in the text that this volume included both drinking water and water used for cooking. In the current opinion, this volume was not considered in the exposure calculation from food and used the following: - For Chen et al. (2010) (Taiwanese population) the arsenic concentration ranged from <10 to >300 (µg/L). The Panel used a value of 36 µg iAs/day from diet, a water consumption of 3 L per day, and a default body weight of 55 kg. -For Bangladesh population, the total daily exposures (µg/kg bw per day) were calculated using a default water consumption of 4 L per day, a default exposure via food of 60 µg iAs/day and a default body weight of 55 kg.
50	Office for Risk Assessment & Research (BuRO), Netherlands	Section: 3.2.4.2 Current dose-	Lines 3517-3523: "Studies that were considered for dose-response modelling had to meet three criteria: i) the overall risk of bias was considered low, ii) the statistical analysis on the	Lines 3517-3523: Regarding the Gilbert-Diamond study: It meets the three criteria: i) Overall low risk of bias (see Table 33)

	Food and Consumer Product Safety Authority	response analyses	association between iAs exposure and the risk of the outcome reported by the authors had to show a statistically significant association with iAs as a continuous variable, a statistically significant trend test and/or a statistically significant increase of risk in the upper exposure category/ies, iii) results for at least three exposure categories (including the reference category) had to be reported." The study that was selected to derive a RP was the study by Gilbert-Diamond et al., 2013. Can you explain how these requirements match for this key study? Note: same comment applies to section 4.9 Dose response analysis approach.	ii) The risk of the outcome showed a statistically significant association between iAs (in urine) as a continuous variable as reported by the authors (page 1157 left column; The OR was 1.37 (95% CI: 1.04, 1.80) for each unit increase of ln-transformed u-tiAs. iii) Results for three exposure categories were reported.
			For lung cancer, the following is stated (lines 3542-3547): "The studies from Ferreccio et al. (2000), Smith et al. (2009), Chen et al. (2010a), and Steinmaus et al. (2013, 2014a) meet the above-mentioned criteria for dose-response modelling. However, since the Chilean case-control studies by Steinmaus et al. (2013, 2014a) are larger and have better methodological quality than the studies based on the previously used case-control study by Ferreccio et al. (2000) and reanalyzed by Smith et al. (2009) are from the same Chilean region, these results were not modelled." Please rephrase the sentence, especially the part from "and reanalyzed" as it contains two verbs and is not self-evident ("are larger […] are from the same […]"). Was the reason not to use results from	Lines 3542-3547: Lung cancer: Yes, sentences have now been revised. However, the Chilean case-control studies by Steinmaus et al. (2013, 2014a) from the same region are larger and have better methodological quality than the studies based on the previously used case-control study by Ferreccio et al. (2000) and reanalyzed by Smith et al. (2009), and therefore the latter results were not modelled. The Chen et al. (2010a) was modelled, see Table 33.

			Ferreccio et al. (2000) and Smith et al. (2009) that they were from the same region, that the studies by Steinmaus et al (2013, 2014a) were larger (include a larger number of people?), or both? What about the study by Chen et al. (2010a)? Were there other reasons not to include these studies?	
			For infant mortality (lines 3569-3571), the text end is not conclusive: "The studies by Milton et al. (2005), Rahman et al. (2007), and Rahman et al. (2010) meet the above-mentioned criteria for dose-response modelling. These studies are from Bangladesh, but associations have also been shown in Mongolia and Chile." Please add a remark on what was done with these data.	Lines 3569-3571: The studies from Mongolia and Chile support the association but did not meet the criteria for modelling (Mongolia: only two exposure categories; Chile: exposure only as a continuous variable). The studies by Milton et al. (2005) and Rahman et al. (2010) were modelled, but the modelling results did not meet the 2022 EFSA BMD guidance criteria. This is mentioned in lines 3879 – 3880.
51	German Federal Institute for Risk Assessment	Section: 3.2.4.2 Current dose-response analyses	Line 3519, p. 256 (also section 4.9, line 4574, p. 300) The criteria for only including statistically significant studies is overly restrictive and leads to selective reporting. It results in loss of valuable information, especially when data/studies are scarce. As long as the studies have low risk of systematic error (bias), each result should be included since small studies (although they may have statistically non-significant results) may also be of good quality and reveal relevant effect estimates when combined with other studies (e.g. in a meta-analysis).	Line 3519, p. 256: In the assessment of the evidence of an association the CONTAM Panel also included studies showing statistically non-significant results. Regarding the BMD analysis, and given the differences expected between the study population, the selection for the informative distribution to be used for the background incidence (considering that unexposed groups were not available for any of the studies) would introduce extra uncertainties in the assessment.
			Lines 3529-3530, p. 256 This decision makes sense, as it aims at using a small BMR while staying in the range	Lines 3529 -3530: Noted.

			of stable estimates. BfR considers this decision pragmatic.	
			Lines 3635-3637, p. 259 The exposure misclassification resulting from exposure measurement in drinking water plus a fixed estimate of intake from other food sources is claimed to be non-differential (independent from the outcome) and as a result attenuates the association. As described by Yland et. al. (https://pubmed.ncbi.nlm.nih.gov/35231925/), misclassification can bias away from the null in the categorized and continuous exposures. As a result, a quantitative bias analysis for misclassification of exposure is recommended. In addition, BfR recommends the following reformulation: In general, non-differential misclassification leads to a bias towards the null, so a reported increased risk can be assumed to be underestimated.	Lines 3635-3637: Yes, it is correct that nondifferential misclassification does not always attenuate a true association, especially in small data sets. This is nicely demonstrated in the paper referred to by BfR. The sentences were revised as proposed by BfR.
			Lines 3743-3747, p. 263 Each of the benchmark dose (BMD) analyses was performed using only one study at a time. BfR suggests using the data from multiple studies to estimate dose-response curves and BMD.	Lines 3743-3747: The CONTAM Panel recognizes that advancement of the analysis by combining data from multiple studies could increase efficiency. However, the combination of data (meta-analysis) poses challenges due to differences in study characteristics and study quality. Also, the original data would be needed for all studies which was not available. In addition, considering other developments in the opinion (BMR definition, approach to uncertainty analysis), the Panel considered it balanced not to extend the analysis on too many fronts simultaneously. The combination of data was not regarded as

			crucial (even though it may add to the efficiency) for the assessment, and identification of the most relevant study was instead preferred to preserve.
		Line 3748, p. 263 & line 3869, p. 267 Suggestion: Replace "human data" by "epidemiological data". Justification: The BMD guidance is applicable to any species. The problem with epidemiological data is that no control group exists.	Line 3748, p. 263 & line 3869, p. 267: Replaced.
		Lines 3841-3844, p. 266 BfR does not agree that in a generic epidemiological study the background should be centered around the effect observed at the lowest exposure group. While it is evident that this assumption together with the possibility to specify a prior for the background addresses technical problems, there are at least three reasons against such procedure. (1) In fact this assumption is equivalent to the assumption that the lowest exposure group experiences no harm from the exposure, which may or may not be true depending on other factors. (2) The chosen procedure gives the low-dose points excessive weight. (3) Some model fits as presented in annexes E1 to E4 seem to be impaired by this assumption. This is addressed in two examples below: Example 1 (Annex E1, Ahsan et al. (2006) skin lesions, pp. 4-9) Please consider removing or modifying the background prior. Justification: In the figure on page 8, it seems that the blue points all lie on a line. Therefore, a fit without the assumed background prior is	See response to comment 48.

			expected to have a much lower BMD. On the other hand, the background prior as specified on page 4 seems to be quite narrow. Example 2 (Annex E1, Chen et al. (2010b) bladder cancer, pp. 10-15) Please consider removing or modifying the background prior. Justification: In the figure on page 14, it seems that all models except QuadExp are compelled to hit the low dose point while not decreasing further. Therefore, a fit without the assumed background prior is expected to show a lower background.	
			Lines 3853-3854, p. 266 The use of the lowest dose as background prior exerts an overtly large influence on the result. It seems that the background prior forces the curve too strongly. BfR suggests exploring ways to reduce this influence. The assumed prior distributions used in the concrete BMDL calculations (annex E1 to E4) generally seem quite narrow. BfR suggests considering the uncertainty generated by the extrapolation of the lowest dose group to the background; the prior should reflect this uncertainty. A solution could be to use a wider prior	See response to comment 48.
52	National institute for public health and the environment (RIVM)	Section: 3.2.4.2 Current dose-response analyses	Lines 3514 - 3931: The general approach is novel and has merit, however the software and the data are not really designed to perform the analysis. The following two issues hamper the correct derivation of a (reference) BMDL here: (1) Applying this approach assumes that the incidence in the lowest exposure group	Lines 3514-3931: See response to comment 48.

			is a good approximation of the background incidence at the hypothetical zero arsenic exposure level. However, the exposure in the lowest group is, in reality, infinitely higher than zero (dose/zero=inf). A better estimate of the background could be made by fitting a DR model to the individual data (preferred) or categorizing the data into more exposure groups. Such data may allow a more precise estimation of the lower end of the dose-response curve including an estimate of background. (2) This approach (or rather the software) neglects to take into account the uncertainty in the incidence of the lowest exposure group, which will influence the value of the BMR (or "value for CES"). Hence the width of the BMD CI could/would be underestimated and the BMDL overestimated.	
			Lines 3525 – 3529: RIVM considers grouping epidemiology data into exposure categories for the BMD analysis is only a reasonable methodology when a large number of exposure groups are created. Grouping exposure into categories means that the observed individuals with varying exposure are assigned a certain mean exposure value. This introduces error which is not accounted for in the current BMD modelling software, where it is assumed that the variation in the exposure is close to zero or negligible small (compared to the variation in the	Lines 3525 – 3529: For the inorganic arsenic draft Opinion, the CONTAM Panel had access to summarised data only. Consequently, it was not possible to categorize the data into more exposure groups. The CONTAM Panel recognizes that employing individual data and incorporating more exposure groups would have been favourable for benchmark dose modelling. Unfortunately, getting these data was not feasible since it would have not only required obtaining individual data on exposure and response but also

			observed response). RIVM would like to ask EFSA to retrieve the original raw data from the studies (i.e. data of the exposure level and effect of each individual) or request that the data are categorised into more exposure groups. Preferably the raw data are used for the BMD analysis. If this is not feasible, it is advised that the data categorised into more exposure groups are analysed.	additional information regarding potential confounders and other covariates.
			Lines 3529 – 3531: RIVM would like to ask EFSA to explain in more detail the choice of BMRs on the BMD analysis, including some descriptive text stating the intended BMR (see our comment on lines 3817-3851) and particularly the detailed steps of the BMD analysis	Lines 3817-3851: The first of the two paragraphs that are referenced intends to motivate the type of BMR definition used, i.e., relative risk instead of extra risk (used in the past). Then, the second paragraph motivates the selected response value/change (5%) under this BMR definition. The text has been refined to better clarify this. Also, regarding terminology, the terms "BMR", "BMD", "BMDL", "BMDU" are quite generic and can be considered to apply under any response definition or data type. For quantal data, the more specific terms, "extra risk" and "additional risk" are also used, or used in combination with "BMR" for clarification. The Panel defined the BMR applied as "BMR expressed in terms of relative increase of the background incidence after adjustment for confounders".
53	Norwegian Scientific Committee for Food and Environment, Panel on Contaminants	Section: 3.2.4.2 Current dose-response analyses (Overview of	Line 3517: Referring to comments above, it is not so clear why all endpoints were considered as critical effects. The risk of bias analysis took only into account one type of risk of bias, it seems insufficient.	All endpoints were not considered as critical effects. Firstly, only endpoints were selected for which the evidence was assessed as "sufficient" for an association btw iAs exposure and the endpoint. Secondly, the association had to be considered causal (including risk of bias). If

		the approach)		so, BMD modelling was tried (but could not always be kept since criteria were not met). The risk of bias analysis took into account many types of risk of bias, as mentioned in Section 3.2 4.2 under the subheading "Risk of bias analysis" and the corresponding columns in Table 33. The main types were Selection bias (including bias in selection of cases and/or controls), Information bias (including misclassification of exposure and/or bias in the classification of cases and the diagnoses), and Confounding ("positive" or "negative").
			Line 3530: Please move 5% earlier in the sentence. (To use a 5% relative increase of the background incidence after.....).	Done.
54	Norwegian Scientific Committee for Food and Environment, Panel on Contaminants	Section: 3.2.4.2 Current dose-response analyses (Studies selected for dose-response modelling)	Line 3551 Onwards: some endpoints were "parked" in the previous section so why do they return here for dose response assessment?. If it is dismissed e.g. due to being not relevant for the EU population then it should not be mentioned here. It seems repetitive.	Two endpoints (birth weight, and carotid artery atherosclerosis) for which associations with iAs exposure were considered likely to be causal were not modelled. The reasons are given in the respective paragraphs (iAs exposure as a continuous variable).
55	National institute for public health and the environment (RIVM)	Section: 3.2.4.2 Current dose-response analyses (Studies selected for dose-	Lines 3543 – 3547: RIVM believes that the word "and" is missing prior to the phrase "are from the same Chilean region" in this sentence.	Lines 3543–3547: Sentence amended as proposed.
			Lines 3562-3567: It would be helpful for the reader to repeat here that no studies on birthweight were included in the doseresponse modelling, including	Lines 3562-3567: Agree. Such a sentence has also been included in this section.

		response modelling)	a link to the sections where this has been discussed.	
56	National institute for public health and the environment (RIVM)	Section: 3.2.4.2 Current dose-response analyses (Conversion of water and urine iAs concentrations to inorganic arsenic exposures)	Lines 3668-3672: EFSA states here that 'this approach to be the most appropriate method to derive BMDs'. Could EFSA elaborate as to why this method is considered most appropriate?	See response to comment 2.
			Lines 3678-3681: "For European populations, for average iAs exposure via food, a value of 7.7 µg iAs/day was assumed. This value is based on the UB median mean exposure of European adults of 0.11 µg iAs/kg bw per day estimated by EFSA in the recent report on iAs dietary exposure (EFSA, 2021; see also Table 34 of Section 3.5.1.) and a body weight of 70 kg". Use of the UB estimate of exposure is conservative and might lead in an overestimation of iAs exposure via drinking water. Could EFSA elaborate as to why the UB median mean exposure scenario was chosen? When this scenario is used, please consider mentioning that the UB value is conservative.	Lines 3678-3681: 1. BMD modelling: The only study from Europe in Table 33 is the one by Leonardi et al. (2012) on skin cancer. A sensitivity analysis was performed using the LB dietary estimate of 2.8 µg iAs/day. It resulted in a BMD of 0.021 and a BMDL of 0.004, so less than half of the values shown in Table 33. Since the study by Gilbert-Diamond was preferred, changing the assumed intake to the LB would not affect the RP. 2. MOE: Indeed, the UB scenario is most conservative, and often becomes a limiting scenario. However, as part of the uncertainty analysis the whole range between the LB and UB is considered (for both the mean and 95th percentile of exposure). On top of this, BMD uncertainty is also accounted. The likelihood of exceeding the BMD (i.e., an MOE < 1, See Table 37) was then estimated.

57	Norwegian Scientific Committee for Food and Environment, Panel on Contaminants	Section: 3.2.4.2 Current dose-response analyses (Conversion of water and urine iAs concentrations to inorganic arsenic exposures)	Lines 3668-3669: please explain why CONTAM considers this approach most appropriate. It seems to add a high uncertainty to the data. Has CONTAM considered any sensitivity assessment to see if the assumptions made have a large impact?	Lines 3668 – 3669: See response to comment 56 above. Yes, sensitivity analyses were performed, checking what would be the BMDs/BMDLs if only water-As concentrations were modelled and the assumed exposure from other food was added afterwards. In the cases tested the BMD/BMDL was higher if only water-As was modelled and exposure from other food was added afterwards.
			Lines 3678 – 3681: Exposure from water is included in the previous exposure calculation in EFSA 2021, and water is among the main contributors The contribution from water should therefore be subtracted from the contribution from food in European studies based on water concentration.	Lines 3678 – 3681: "Yes, the CONTAM Panel acknowledges the logic of the comment. As in drinking water accounted for about 25% of the UB estimate (median 2.0 out of 7.7 µg/day). 1. The only European study modelled based on water-As concentrations is the study by Leonardi et al. (2012). In this study the w-As concentrations in the two lowest quintiles were <1 µg/L. 2. Assuming that the contribution from other food than drinking water was 5.7 µg/d instead of 7.7 µg/d would somewhat decrease the BMD/BMDL presented in Table 33. A sensitivity analysis has already been presented for a dietary contribution of 2.8 µg/day (see response to comment 56), and 5.7 µg/d lies between 2.8 and 7.7 µg/d."
			Line 3686-3687: What is the basis for assuming 1 ug/L? Is it from the study? Then please indicate so. Is it confirmed by biomonitoring that the mean background exposure in Colorado is twice that in Europe?	The lowest water As was ≤2 µg/L) in the study so 1 µg/L was the midpoint between 0 and 2.
			Line 3708-3714: Assuming that the well water has high iAs, and that	Line 3708-3714: The CONTAM Panel agrees that it is difficult to distinguish the

			Lindberg included other water sources into the estimate of 45 ug/L from food, it is not easy to see how Vather could distinguish drinking water from food based on this explanation. What is the W in the equation	contribution from drinking water and other dietary sources in the Bangladeshi studies. If W in the equation is set to 1 ug/L the U-As would be 20, and if it is set to 0 ug/L U-As would be 20. If U-iAs is assumed to be 30 µg/L and a urinary volume is assumed to be 2L the excretion would be 60 µg/day (minus 0.5 x 4L of drinking water). These rough calculations also fit reasonably with the ratio of 76 for individuals with low water-As (in the same paper). They are also compatible with the As concentrations in Bangladeshi rice (same paper) of 10 – 50 µg/day. In addition, vegetables contain some As, and cooking of rice and vegetables will add to exposure. The text is also now revised, adding more details and the fact that the estimate is uncertain.
			Line 3722: What was the justification to deviate from the default? Why is the mid-point selected? It seems not to fit well with a urinary volume of 2L.	Line 3722: The value of 1.5 L was already assumed for the opinion in 2009. The default of 2 L is for total liquid intake, not just for drinking water (for which iAs concentrations are reported). The CONTAM Panel thinks that the justification of using 1.5 L is well explained in the respective paragraph.
			Line 3727: The intake from rice belongs to food, so this argument should not apply.	Line 3727: The line refers to the total water consumption in rice consumers as reported by FAO/WHO. Therefore, the CONTAM Panel disagrees that the argument should not apply.
58	National institute for public health and the environment (RIVM)	Section: 3.2.4.2 Current dose-response analyses (Calculation	Lines 3744 – 3747: RIVM would like to ask EFSA to also conduct the BMD analysis according to the 2017 EFSA Guidance on the use of the BMD approach in risk assessment (EFSA Scientific Committee, 2017), instead of the 2022 EFSA Guidance (EFSA	Lines 3744 – 3747: The CONTAM Panel applied the updated EFSA BMD guidance (EFSA Scientific Committee, 2022) in the risk assessment as there was no compelling reason to deviate.

		of benchmark doses)	Scientific Committee, 2022). As EFSA knows, RIVM has a number of reservations about the 2022 EFSA Guidance on the use of the BMD approach in risk assessment. Details of these reservations can be found at https://www.efsa.europa.eu/en/supporting/pub/en-7585.	EFSA is aware of the reservations of RIVM towards the EFSA 2022 BMD guidance, and the replies can be found here: https://www.efsa.europa.eu/en/supporting/pub/en-7585
59	Norwegian Scientific Committee for Food and Environment, Panel on Contaminants	Section: 3.2.4.2 Current dose-response analyses (Transformations of relative risk estimates to quantal data)	Line 3780 "If the outcome was not one with a low incidence (>1%) …" Should it not be <1%?	Line 3780: Corrected.
60	National institute for public health and the environment (RIVM)	Section: 3.2.4.2 Current dose-response analyses (Selection of the benchmark response for critical effects)	Lines 3817-3851: This section is confusing. As, this section is important for understanding the approach and meaning of the BMDL, RIVM would like to ask EFSA to improve the explanation of the approach and to clarify the differences between the current approach and the approach used in the last opinion. Furthermore, RIVM would suggest to use a slightly different terminology for BMR and BMDL, when performing a BMD analysis using relative risk. For example, relative risk benchmark response (i.e. RBMR/ relative risk BMR) and relative risk benchmark dose lower confidence limit (i.e. RBMDL/ relative risk BMDL).	See response to comment 48 (response to lines 3529 – 3531).

			Lines 3853 – 3858: Could EFSA justify this way of applying priors in the BMD analysis? If understood correctly, EFSA estimated the incidence of the reference category from a dataset, and used this estimation as a prior on the background parameter when performing BMD analysis using the same dataset. However, since this estimation is based on the dataset to be analyzed, no additional information was added. Therefore, the estimated incidence of the reference category is not really a prior for analyzing that dataset. A prior (for the BMD analysis) is additional information on the probability distribution of certain model parameters, in this case on the dose-response model parameter. This additional information should be obtained a priori, preferably based on a large number of studies. EFSA BMD guidance (2022) recommends to "justify and document the prior distribution, based on all information that could contribute to the definition of that informative prior, and should not be subjectively selective in this process". In addition, the prior for the background is derived from the lowest exposure group where the (mean) exposure is not zero. Without additional information it is not	Lines 3853 – 3858 onwards: see response to comment 48.

			justified to use the response in lowest (non-zero) exposure group as a proxy (or prior) for the response at dose zero. Note that the exposure in the lowest group in Gilbert-Diamond (2013) is 0.063 ug/kg bw/day, which is a factor infinitely higher than an exposure of zero. Also note that, the (measured) incidence at this exposure (of 0.063 ug/kg bw/day from Gilbert-Diamond 2013) is set as background (informative background parameter) while the resulting BMDL (of 0.062 ug/kg bw/day) of this analysis is set as Reference Point. Could EFSA explain the rationale behind setting the Reference Point to a value that is (in the analysis) considered as a background exposure with a background response? RIVM also noticed that in other BMD analyses (in Annex E1), the derived BMDLs are lower than the exposures in the lowest exposure groups (which relate to incidences designated as informative background priors), for instance Ahsan et al. (2006) skin lesions, relative BMR 5%; Chen et al. (2010b) bladder cancer, relative BMR	Further to that, the model incidence does not necessarily need to correspond to the observed value, the BMDL is based on the estimated background incidence and the increase associated with a relevant effect, using the model results associated to that identified effect, which could correspond to an exposure lower than the midpoint reported for the lowest quantile. Additionally, it is referring to exposures that are centred at the value used in the BMD analysis, but individual exposures in that group are scattered around that value. The Bayesian framework allows for the incorporation of additional information to the modelling process. Specifically, it can include an informative prior on the background incidence which allows estimations below the lowest exposure group.

			5%; Cherry et al. (2008) stillbirth, relative BMR 5%; Gilbert-Diamond et al. (2013) skin cancer, relative BMR 5%; etc. This means that the BMDLs derived by EFSA associate with incidences that are lower than the assumed background incidences. Could EFSA explain the rationale of this?	
61	Committee on the Toxicity of Chemicals in Food, Consumer Products and the Environment.	Section: 3.2.4.2 Current dose-response analyses (Results of dose-response analyses)	The BMD modelling approach taken is Bayesian – so different to that use in previous opinions. The Committee was unable to fully replicate the modelling. The results do not fit with the Scientific Committee recommendations so may not be appropriate- the modelling is extrapolating beyond observable range.	Different version of the Bayesian WEB application might produce slightly different results, a full description of the procedure taken has been inserted to ensure reproducibility. The Bayesian framework allows for the incorporation of additional information to the modelling process. Specifically, it can include an informative prior on the background incidence which allows estimations below the lowest exposure group.
62	Office for Risk Assessment & Research (BuRO), Netherlands Food and Consumer Product Safety Authority	Section: 3.2.5 Identification of a Reference Point for hazard assessment	The study from which the BMDL was derived is a study conducted in the United States. For a number of studies in different regions of the world, it is claimed that effects are not representative for Europe (e.g. birth weight in Bangladesh, section 3.2.4.2). Could you please include a short explanation in the main text why the study on skin cancer from the United States is representative for effects in Europe? Section 3.1.1 (Toxicokinetics) indicates that the level of arsenic methylation is crucial for its toxic effects, and that "there is high inter-species, inter-population and inter-individual variability for arsenic methylation and also other aspects of toxicokinetics". Furthermore, the	For skin lesions and decreased birth weight, nutrition status and socioeconomic factors are important risk factors. For skin cancer, UV exposure and sensitivity for UV radiation are important risk factors. The US and Europe were considered much more similar with respect to these factors than Bangladesh and Europe. And yes, the Panel has now clarified this better in the text. Yes, there are inter-population differences in arsenic methylation, but such differences are not to be expected between the North-East US and overall Europe. Differences in sensitivity occur within Europe and are acknowledged in the Uncertainty section. The dietary exposure in the study by

			dietary exposure in the US was reported to be twice as high as that in Europe. Can anything be said about possible adaptation to higher exposure? Overall, what can be said about the representativeness of the US study for Europe? Possibly, other differences between the populations may also be mentioned here. A study carried out in Europe was considered but not used for risk assessment. Is this due to the fact that concentrations of As were measured only in water, or are there more/other reasons? Line 3939 states: "However, the study by Leonardi et al. (2012) used hospital controls and was therefore considered having a slightly higher risk of bias than the study by Gilbert-Diamond (2013), which used population controls." What is meant, what is "a slightly higher risk of bias"? Was the control group appropriate or not?	Gilbert-Diamond et al. (2013), based on u-tiAs in the lowest exposure category, is not higher than the estimate for Europe. Regarding the control group in the study by Gilbert-Diamond et al. (2013), it is well-known that hospital controls are not as good as population controls. Although the authors of the study by Leonardi et al. (2012) did an appropriate selection of which diagnoses should be used, there is some risk of bias – namely that these patients had a higher or lower risk of skin cancer, or of skin cancer being diagnosed, than the general population from which the cases were selected. So, the control group is OK, but not as good as it would have been if population controls had been selected.
63	National institute for public health and the environment (RIVM)	Section: 3.2.5 Identification of a Reference Point for hazard assessment	Line 3935-3936: Could EFSA improve the readability of the following sentence "The BMDL05 was much lower 0.01 µg/kg bw per day than that of the study by Gilbert-Diamond et al. (2013)." For example, could EFSA add '0.01 µg/kg bw per day' behind BMDL05 in line 3932, instead of stating this figure in line 3935? Furthermore, could EFSA state the BMDL05 of Gilbert-Diamond in line 3935/3936.	Line 3935-3936: Text was revised accordingly to improve readability.

			Line 3960: The text between brackets ('except for cancer') gives the impression that the reference point is not protective for lung cancer. Is this EFSA's intention? If not, EFSA could consider changing the wording to, e.g., 'lung cancer will be discussed below'.	Line 3960: Text has been revised.
			Lines 3969-3973: In this paragraph two studies with a low BMDL were compared to other studies, which were considered more valid by EFSA. The purpose of these comparisons is not clear. Did EFSA compare the studies to argue that the low BMDL from these two studies are not reliable? Could EFSA adjust the text to clarify this?	Lines 3969-3973: The study by Ahsan et al. (2006) and Pierce et al. (2011) are compared. They are based on the same population and the study by Pierce et al. (2011) is considered more reliable. This is already written in the text.
64	German Federal Institute for Risk Assessment	Section: 3.2.5 Identification of a Reference Point for hazard assessment	Line 3955, p. 272 Typo: BMDL05s should be BMDLs05 or just BMDLs	Changed to $BMDL_{05}$ values.
65	Norwegian Scientific Committee for Food and Environment, Panel on Contaminants	Section: 3.2.5 Identification of a Reference Point for hazard assessment	Line 3950: Would this be the case if you did not add the background exposure from food? Would the BMDL be below the lowest water concentration category?	Line 3950: In that case, the point estimate of the BMD would not be below the dose in the reference category and the BMDL would be only slightly below it (1.1 times). See also the response to comment 56 on why modelling based on total exposure was preferred vs. modelling based on water concentrations (and then adding exposure from food as a second step).
			Line 3956-3957: This would mean that the study has a higher ROB under outcome assessment. It is referred to a risk of bias analysis before (which we did not find), was this not captured?	Line 3956-3957: Yes, the ROB was considered as not low (L), but moderate (M), see Table 33. The meaning of the "/" sign in the column on Information bias has now been clarified in the footnote.

				Regarding not finding the risk of bias analysis, see response to comment 14.
			Line 3977-3978: We think the use of the word appropriate is misleading here. The RP covers for the other outcomes, but it is not the RP for these other outcomes	Lines 3977-3978: The sentence has been modified as proposed, also elsewhere in the Opinion.
66	Office for Risk Assessment & Research (BuRO), Netherlands Food and Consumer Product Safety Authority	Section: 3.3 Consideration of the approach to risk characterisation	Line 4030-4032. EFSA states "There are no precedents in EFSA for identification of an MOE of low concern, when using a BMDL derived from human cancer data. Therefore, the Panel decided not to determine a value for an MOE of low concern." A harmonized approach to derive an MOE for human data is definitely needed to accurately use a BMDL derived on human data in risk assessment. In the current opinion uncertainties related to intraspecies difference which are normally considered for the MOE are only described qualitatively: e.g. line 159-162 "Although risk characterization is based on the results of relatively large epidemiological studies, susceptible individuals of higher genetic risk may not be adequately represented in these studies. Therefore, dietary exposure to arsenic may be of greater concern for such individuals than for the general population." If this is recognized as a not too conservative approach and representing a true situation, should an MOE of 10 be considered?	As stated in the response to comment number 5, the CONTAM Panel notes that an EFSA guidance on the use of human data for risk assessments is needed, in particular on BMD modelling of epidemiological data and for a quantitative risk assessment for genotoxic carcinogens based on epidemiological data. This will be addressed in an update of respective guidance by the EFSA Scientific Committee, planned for the near future. With respect to genetically susceptible individuals, it is not known whether or not they are represented in the epidemiological studies, and therefore this susceptibility is addressed in the Uncertainty Analysis rather than by application of a factor of 10 in the MOE.
67	German Federal Institute for	Section: 3.3 Consideration of the	Line 3980, p. 272 Sometimes British English and sometimes American	The Opinion will be copy edited before publication, ensuring that exclusively British English is used.

	Risk Assessment	approach to risk characterisation	English is used (e.g. characterisation vs. characterization)	
68	Norwegian Scientific Committee for Food and Environment, Panel on Contaminants	Section: 3.3 Consideration of the approach to risk characterisation	Line 4030-4031: "There are no precedents in EFSA for identification of an MOE of low concern, when using a BMDL derived from human cancer data." This opinion could set precedence by discussing the issue appropriately. We think these lines should be deleted.	Line 4030-4031: See response to comment 5.
			Line 3980: The chapter is unexpected at this location in the opinion. It would fit better just before the risk characterization.	Line 3980: The CONTAM Panel appreciates this suggestion but prefers to keep this section.
69	German Federal Institute for Risk Assessment	Section: 3.4.1 Occurrence data used in the present assessment	Line 4097, p. 276 Missing cross-reference	Corrected.
70	Office for Risk Assessment & Research (BuRO), Netherlands Food and Consumer Product Safety Authority	Section: 3.5 Exposure assessment	The Reference Point (RP) has been derived from a study in which exposure was expressed in u-tiAs. The section about exposure presents values expressed as iAs. The text presented here does not explain how dietary exposure estimates expressed as iAs can be related to u-tiAs for risk assessment. Can this be added or clarified in the text of the main document? Furthermore, please clarify how the reported exposure levels (both calculated by EFSA as reported in epidemiological studies) relate to the different speciation and/or	The conversion of u-tiAs to exposures for the derivation of the BMDLs is explained in Section 3.2.4. Dose-response analyses.

			methylation forms and how this can be justified.	
71	Asociación Gremial de Mitilicultores de Chile	Section: 3.5 Exposure assessment	4100.- Quisiéramos consultar si los resultados de la evaluación de la exposición presentados fueron basados en estudios de dieta total, a través de encuestas , en este escenario consultamos si efectivamente será posible establecer un solo límite para la población europea. EFSA translation: We would like to check whether the exposure results were based on Total Diet Studies data using dietary surveys. In this scenario we would like to consult if just one limit will be established for the European population	Lines 4100: See response to comment 15.
			4101.- Asimismo, la determinación a la exposición a Arsénico Inorgánico estuvo basada en un grupo focalizado de alimentos, no en la dieta total de un individuo, frente a lo que consultamos si a su juicio este método puede producir una posible sobreestimación de la exposición a este compuesto. EFSA translation: In addition, the exposure to iAs was based on a particular group of foods and not in the total diet of a particular individual. Based on this, we would like to know whether this approach might	Lines 4101: See response to comment 15.

			imply an overestimation of the exposure to this compound?	
72	National institute for public health and the environment (RIVM)	Section: 3.5.1 Exposure assessment used for the present Opinion	Lines 4158-4161: 'dietary exposure estimates in the 2021 EFSA scientific report were in good agreement with recently published scientific literature that also made use of measured iAs to estimate dietary exposure to iAs'. No references to these new assessments published in scientific literature were provided. Could EFSA please add references?	References are mentioned already in the 2021 EFSA scientific report which is cited here. It is not seemed necessary to introduce further references.
73	German Federal Institute for Risk Assessment	Section: 3.5.1 Exposure assessment used for the present Opinion	Line 4118, p. 277 Missing cross-reference Line 4139, p. 279 Missing cross-reference	Corrected.
74	National institute for public health and the environment (RIVM)	Section: 3.6 Risk characterization	Lines 4167-4169: RIVM understands that there is no EFSA Guidance for deriving a minimal MoE of low concern for cancer data, above which there is low concern for health effects. However, RIVM would prefer that a minimal MoE be derived for inorganic arsenic as it is important for risk managers to be able to decide whether risk management action are necessary. Furthermore, RIVM would like to request EFSA to draft an EFSA guidance on this topic as soon as possible.	Lines 4167-4169: As stated in the response to comment number 5, the CONTAM Panel notes that an EFSA guidance on the use of human data for risk assessments is needed, in particular on BMD modelling of epidemiological data and for a quantitative risk assessment for genotoxic carcinogens based on epidemiological data. This will be addressed in an update of respective guidance by the EFSA Scientific Committee, planned for the near future. Until such guidance has been agreed, the CONTAM Panel considers that derivation of an MOE of low concern would lack rigor. As noted in the EFSA opinion on risk assessment of substances that are genotoxic and carcinogenic (EFSA Scientific Committee, 2005), judgement on the acceptability of the MOE is for risk managers. The opinion

				explains that an MOE of 1 describes the exposure level that could be associated with a 5% increase relative to the background incidence for skin cancer, based on the available data.
			Lines 4178-4183: RIVM acknowledges that the most critical (lowest) BMDL05 results from increased incidences of skin cancer and is therefore appropriately used as a reference point for risk assessment, and that children are covered by the risk assessment for adults. Despite this, RIVM would like to ask EFSA to consider also conducting a risk assessment in children, as also effect were described where long-term exposure argumentation is less applicable. RIVM would suggest to included (neuro)developmental effects in children. RIVM considers such an assessment as useful and appropriate, because it would allow a more full contextualization of potential risks for different European populations. Could EFSA also keep in mind our preference for deriving a minimal MoE of low concern, when a MoE calculation is performed?	Lines 4178-4183: The CONTAM Panel decided to have only a single RP. Regarding neurodevelopmental effects in children the BMDL for prenatal exposure (maternal in GW 8) was 1.36 µg/BW per day (Table 33), so well above the RP for skin cancer. For children's exposure (10 years of age) was 0.54 µg/BW per day. This is 9 times the RP for skin cancer. The 95th percentile UB exposure for children is 0.54 – 0.84 µg/BW per day in the various age groups. If the MOE for neurodevelopmental effects in children with high level exposure would have been calculated, it would be around 1.
75	German Federal Institute for Risk Assessment	Section: 3.6 Risk characterization	Lines 4176-4177, p. 280 It was stated that the considered reference point (of 0.06 µg iAs/kg bw per day obtained from a study on skin cancer) should also be considered applicable to (protective for may be the better wording) the other endpoints (lung cancer, bladder cancer, skin lesions, chronic kidney disease, respiratory disease, spontaneous abortion, stillbirth, infant mortality and	Lines 4176-4177: The CONTAM Panel agrees that the concern is not specific to skin cancer and it would be helpful to provide more information for risk managers. The following sentences will be added to the Opinion: "The CONTAM Panel noted that the BMDLs for some of the studies on lung cancer, bladder cancer, ischemic heart disease and chronic kidney disease were in the range 0.10–0.15 µg/kg bw per day, which is also within the range

			neurodevelopmental effects). In fact, for some of the other endpoints the respective BMDL05 is in the range of 0.06 µg iAs/kg bw per day (e. g. for lung function, CKD). Therefore, the overall conclusion "[…] MOEs raise a health concern for skin cancer" is not complete. Suggestion: Either just state "MOEs raise a health concern" or check if other endpoints should be mentioned as well, since the calculated MOEs for some of the other endpoints with BMDL05 values in the range of the one from the skin cancer study should also raise a health concern.	of dietary exposure estimates. Therefore, there is a possible concern also for these endpoints."
			Lines 4178-4183 The paragraph states that children are not at greater risk compared to adults, although their dietary exposure is higher. The text indicates this to refer to cancer. This should be spelled out more clearly. Also, it should be briefly explained why the RP for skin cancer is considered sufficiently conservative with regard to systemic exposure. Moreover, please note that in the view of the BfR, there are concerns regarding potential neurodevelopmental effects. For this endpoint any assumption that the higher dietary exposure of children does not result in a greater risk would be questionable. The exposure of children at high exposure levels (95th percentile dietary exposure, UB) exceeds the BMDL5 of 0.54 µg t-iAs/kg bw per day for neurodevelopmental effects and MOEs are below 2 for most children at mean dietary exposure (UB) and high exposure (LB). This	Lines 4178-4183: See response to comment 74.

			should be considered in the risk characterization.	
			Additionally, it should be mentioned that BMDLs for other endpoints are close to the BMDL for skin cancer. This is true for skin lesions, lung function and chronic kidney disease. An explanation should be included whether children are at higher risks for these endpoints due to higher exposure compared to adults	This has been added as described above and the paragraph relating to dietary exposure of younger age groups also covers skin lesions, lung function and chronic kidney disease.
76	Committee on the Toxicity of Chemicals in Food, Consumer Products and the Environment (UK excluding Northern Ireland)	Section 3.7 Uncertainty analysis	Uncertainty analysis – the analysis is difficult to understand and the and the nomenclature used confusing as it reads as though it is statistical p values. It needs to be very clear where expert elicitation has been used.	Clarification of which part of the uncertainty analysis is data-driven, and what is based on qualitative consideration, has been made in the beginning of the uncertainty analysis (Section 3.7, third paragraph). Note that no expert knowledge elicitation (to derive quantitative estimates) has been performed. Also, to be clearer, the term "p" used in this section has been changed to "probability".
77	Norwegian Scientific Committee for Food and Environment, Panel on Contaminants	Section: 3.7 Uncertainty analysis	The uncertainty in the translation of UiAs or water concentration to dietary intake is not addressed.	As noted in the uncertainty analysis (Section 3.7.1) there is uncertainty in the exposure assessment in all studies. The text in the Section 3.7.1, has been slightly revised to clarify that this also includes the transformation from urinary to dietary exposure.
			Line 4229: The exposure via food based on the literature seems to be a major uncertainty. Some more reflection should be added in the uncertainties.	Line 4229: It has also been clarified in Section 3.7.1 how the considered/assumed intake from water and food varies between studies.
			Table 35: Description of uncertainty is too general on epidemiological studies	The uncertainty analysis, and the CONTAM protocol for collections of uncertainties are broader than the critical study. The listings in this Table are therefore more general.

			and could be more specific for the critical endpoint.	However, some updates and additional information have been added in the text discussing Table 35 that also highlights the critical study.
			Line 4289-4290: Something is missing in the sentence.	Line 4289-4290: The sentence has been corrected.
78	National institute for public health and the environment (RIVM)	Section: 3.7.1 Identification and prioritization of uncertainties	Lines 4248-4249: Could EFSA consider including a short summary of the most important uncertainties of the exposure assessment described in EFSA (2021)?	The CONTAM Panel regards it best to keep the general presentation provided of those uncertainties in the end of Section 3.7.1, with reference to the 2021 publication, rather than making any prioritization that would extend beyond that report. These uncertainties are simply considered (qualitatively) as given in the 2021 report.
79	German Federal Institute for Risk Assessment	Section: 3.7.2.1 Comparison of relative BMRs of 1 to 10%	Lines 4267 ff., page 286 BfR is missing an explanation why BMDL05 was used for other outcomes such as lung function or ischemic heart disease. According to this opinion, 1-5 % relative BMR is regarded as relevant for public health and as the 5 % BMR does not create undue uncertainty around the BMD, this response rate was used for all the relevant end points. Comparison of relative BMRs of 1 to 10 % was, however, only done for the cancer endpoints (uncertainty based on BMDL/BMDU ratio and probability of exceeding the BMD, table 36).	The CONTAM Panel decided to only present results for the cancer endpoints in this section. However, results for all critical data sets were derived, and the result discussed in Section 3.7.2.1 provided a similar picture for other outcomes. A couple of sentences on this have been added in the end of Section 3.7.2.1.
80	Committee on the Toxicity of Chemicals in Food, Consumer Products and the Environment.	Section: 3.7.3.2 General results	This is one of the section (line 4362) where it is unclear whether this refers to statistical p values or probability achieved by elicitation.	"p" refers to the probability of exceeding the BMD (MOE < 1). This probability was estimated using the data-driven approach described in the section before this (3.7.3.1). Clarification that the approach is data-driven is e.g., better clarified in the overarching Section 3.7.3, and associated

				subsections. Also, "p" has been changed to "probability".
81	German Federal Institute for Risk Assessment	Section: 3.7.3.3 Sensitivity analysis related to exposure categories and midpoints used for dose-response modelling	Line 4401, p. 292 Check if plural should be used "Analyses".	Corrected to "analyses".
82	German Federal Institute for Risk Assessment	Section: 3.7.3.4 Sensitivity analysis related to estimation of population size	Lines 4446-4447, p. 293 Item 5 claims no sensitivity analysis regarding the case estimates was deemed necessary. However, we recommend a sensitivity analysis especially with regard to the exposure misclassification since qualitative assessment of low risk of bias only reveals information about the existence of bias, and not its effect on the direction, magnitude and uncertainty of the estimate.	The performed sensitivity analyses may be extended in different ways. If the probability of exceeding the BMD (e.g., considering mean exposure) across all studies was low, it might have been more important to confirm or discharge this by more sensitivity analyses, trying to cover more uncertainty. However, considering the uncertainty covered, a concern is also suggested for the mean exposure, if jointly considering both studies on skin cancer. Therefore, the CONTAM Panel regards that the current analysis is adequate enough.
83	Norwegian Scientific Committee for Food and Environment, Panel on Contaminants	Section: 4 Conclusions (Section: 4.9 Dose response analysis approach)	Line 4589: do you mean potential critical studies? Or delete critical, they cannot all be critical	Line 4589 - Has been reworded to "..potentially critical studies..
84	German Federal Institute for	Section: 4 Conclusions (Section: 4.2	Line 4496, p. 296 Please rephrase: "is crucial" and not "being crucial". Otherwise this is not a sentence.	Corrected.

	Risk Assessment	Toxicokinetics)		
85	Office for Risk Assessment & Research (BuRO), Netherlands Food and Consumer Product Safety Authority	Section: 4 Conclusions (Section: 4.3 Biomarkers of exposure)	In this section there is no mention of the use of arsenic concentrations in water as marker. Is there a correlation between water As and urinary As concentrations, especially at low As concentration? Also we miss information on the use of spot urine or do we need 24-h urine samples for accurate arsenic exposure assessment? Note: same comment applies to section 3.1.2.1.	This Opinion concerns arsenic in food, which is why arsenic concentrations in water are not considered as a marker. Yes, there is a correlation between oral arsenic intake and urinary arsenic concentrations. Please see revision of Section 3.1.2.1.
86	Office for Risk Assessment & Research (BuRO), Netherlands Food and Consumer Product Safety Authority	Section: 4 Conclusions (Section: 4.8 Observations in humans and selection of critical studies)	Line 4546. The CONTAM Panel only considered studies including study subjects with exposure to long-term low to moderate levels of arsenic, defined as arsenic water concentrations of less than approximately 150 µg/L, or biomarker concentrations estimated to result from equivalent doses. Can you specify "biomarker concentrations estimated to result from equivalent doses"?	See response to comment 25 above. A definition has been added in the Opinion.
87	Office for Risk Assessment & Research (BuRO), Netherlands Food and Consumer Product Safety Authority	Section: 4 Conclusions (Section: 4.9 Dose response analysis approach)	Line 4573-4579: "Studies that were considered for dose-response modelling had to meet three criteria: i) the overall risk of bias was considered low, ii) the statistical analysis on the association between iAs exposure and the risk of the outcome reported by the authors had to show a statistically significant association with iAs as a continuous variable, a statistically significant trend test and/or a statistically significant increase of risk in the upper exposure category/ies, iii) results for at least three exposure	See response to comment 50 above.

			categories (including the reference category) had to be reported." The study that was selected to derive a RP was the study by Gilbert-Diamond et al., 2013. Can you explain how these requirements match for this key study? Note: same comment applies to section 3.2.4.2 Current dose response	
88	German Federal Institute for Risk Assessment	Section: 4 Conclusions (Section: 4.9 Dose response analysis approach)	Line 4574, p. 300 (also section 3.2.4.2, line 3519, p. 256) The criteria for only including statistically significant studies is overly restrictive and leads to selective reporting. It results in loss of valuable information, especially when data/studies are scarce. As long as the studies have low risk of systematic error (bias), each result should be included since small studies (although they may have statistically non-significant results) may also be of good quality and reveal relevant effect estimates when combined with other studies (e.g. in a meta-analysis).	See response to comment 51 above.
89	German Federal Institute for Risk Assessment	Section: 4 Conclusions (Section: 4.10 Identification of a Reference Point)	Line 4595, p. 300 Check if skin lesion should be added.	Added.
90	Committee on the Toxicity of Chemicals in Food, Consumer Products and	Section: 4 Conclusions (Section: 4.12 Risk characterisation)	No MoE of low concern would be established as there is a lack of precedent (lines 4615-4617 and elsewhere). A lack of precedent for establishing a level of low concern does not stand up to scientific	See response to comment 5 above. In addition, the CONTAM Panel would like to explain again why it decided for the respective approach:

	the Environment (UK excluding Northern Ireland)		reasoning. If no decision is ever made without a precedent . then surely nothing will ever change? Indeed there are many examples of using MOEs to establish minimal risk levels that could be applied here, including the CoC Guidance on cancer risk characterisation methods, which states in paragraph 18: "The derivation of a minimal risk level for a genotoxic and carcinogenic contaminant of impurity involves assessment of all available dose-response data for carcinogenicity to determine an appropriate POD and use of expert judgement to identify a suitable margin between this POD and a level of exposure which would result in a minimal risk. One proposal is that a suitable margin might be 10,000, which parallels the MOE approach, where and MOE of 10,000 is considered to be unlikely to be of concern when based on a BMDL 10 from an animal study." Given the established MOE for arsenic in the EFSA reports were between 2-0.4 (line 4173), establishing a level where the MOE would be >10,000 may be impractical, it would seem nevertheless to be a wiser justification than to dismiss the need with a lack of precedent. Although an animal study would warrant an MoE of 10, 000 it would not be mechanistically appropriate in this instance. Indirect genotoxicity and inhibition of DNA would have thresholds, albeit very low. Arsenic is genotoxic and carcinogenic,	Inorganic As is a genotoxic carcinogen. Both thresholded and non-thresholded mechanisms could apply for the different genotoxic effects of iAs and its trivalent and pentavalent methylated metabolites. Therefore, the CONTAM Panel concluded that it is appropriate to apply a margin of exposure (MOE) approach for risk characterization rather than establishing a health-based guidance value. There are no precedents in EFSA for identification of an MOE of low concern, when using a BMDL derived from human cancer data. Therefore, the Panel decided not to determine a value for an MOE of low concern.

			but not necessarily a genotoxic carcinogen.	
91	National institute for public health and the environment (RIVM)	Section: 4 Conclusions (Section: 4.13 Overall uncertainty in the risk characterisation)	Lines 4637-4640: EFSA estimated the probability that the mean exposure exceeds the BMDs. RIVM would like to ask EFSA to elaborate on how this relates to the probability of a risk for public health.	The CONTAM Panel considers that since the estimated probability ranges from unlikely to likely, if considering both studies on skin cancer, this analysis supports the health concern identified under the regular analysis. So, the uncertainty analysis does not refine results to such a degree that the overall conclusion might change.
92	Servicio Nacional de Pesca y Acuicultura	Section: 5 Recommendations	4641.- The need to carry out more studies in relation to epigenetic alterations and genotoxicity associated with chronic exposure in low and medium doses of the iAs forms is mentioned, in this regard we request clarification: Is there a specific or limited time horizon to carry out or expect possible results from these investigations? Is there a plan or incentive idea to fund research in this regard?	4641: Recommendations in opinions of the CONTAM Panel are general and not directed to certain institutions but should instigate research. EFSA, does not carry out primary research, but has in the past commissioned studies. Currently, there are no plans for EFSA to fund such research.
			Will the results of those investigations necessarily result in a reassessment of the risks assessed in this document?	That is possible. Note that EFSA has no mandate in risk characterisation.
			Do you consider as probable a scenario in which the acceptable limits of iAs in food are substantially modified on a routine basis, understood as routine on an annual or even semi-annual basis?	Note that setting maximum levels for contaminants is not within the remit of EFSA and therefore, the CONTAM Panel cannot provide an answer to this.
			4641 It is suggested to encourage research into mitigation processes to	4641: Noted.

			reduce the content of inorganic arsenic in different foods	
			4641.-It is recommended to continue reviewing studies on topics of great importance such as kinetics of the formation and degradation of inorganic arsenic, proposed mechanisms for its reduction, instrumental methods used for its determination, experimental results generated both in experimental models and in usual processing. of various foods.	4641: Noted.
			4641.- Due to the variability of products that contain arsenic, their method of preparation and consumption habits, the level of exposure to inorganic arsenic, we would like to consult on how we intend to address this situation in the future.	4641: In Europe, risk assessment (EFSA) is separated from risk management. EFSA carried out the dietary exposure assessment to iAs as part of the risk assessment and identified the food commodities with highest iAs concentrations as well as those contributing the most to the iAs dietary exposure. With this information, risk managers (European Commission) put in place different measures aiming to diminish the dietary exposure to iAs and, therefore, the health risks linked to its exposure. As an example, new Maximum Limits (MLs) were established for various food items and existing MLs were reviewed (Commission Regulation (EC) No 2015/1006 and Commission Regulation (EU) 2023/465)
93	National institute for public health and the	Section: Annexes	Annex E1 Gilbert-Diamond et al. (2013) There are six BMD analyses reported in Annex E1, without clear	The details of the input data and parameters used in the BMD analyses are documented clearly under the respective study heading.

	environment (RIVM)		explanation of the difference between them. Could EFSA clarify this? Additional comment BMD analysis Among other issues, RIVM would like to point out two issues related to the BMD analyses in Annex E1. The first issue concerns the distribution of the BMD. In Annex E1, each BMD analysis is reported, including the figure showing the distribution of the BMD based on model averaging (see attachment). In the figure, the BMD distribution is shown by the coloured area, captioned as 'Model Averaged'. Looking at some analyses reported by EFSA, RIVM noticed that the distributions of the BMD in some analyses go even below 0 (and the associated probabilities are quite non-neglectable). This means some of the analyses indicate that there is a reasonable chance that the estimated BMD has a negative value. This is not possible since a BMD is just a dose or an exposure concentration. For this issue, see for example the analyses of: - Ahsan et al. (2006) skin lesions relative BMR 5%; - Chen et al. (2010b) bladder cancer relative BMR 5%; - Chen et al. (2010b) bladder cancer, relative BMR 5% (Sensitivity analysis: The highest exposure point estimate doubled); - Gilbert-Diamond et al. (2013) skin cancer, relative BMR 5% (Without an	In Annex E1, the first BMD report concerning Gilbert-Diamond et al.'s (2013) study presents the study's main modelling results (the preferred estimate for the study). The second report shows the modelling results without using an informative background prior. The subsequent four BMD reports cover the results of sensitivity analyses, where the source population of the study was reduced/increased by 10-20 percent. The other issue observed is due to the transformation is used to represent the dose (LOG 10). On this scale the 0 dose would correspond to -∞, but it has been set to a specific value which is based on the lowest exposure value for the data analysed. When presenting the posterior distribution of the BMD, this is affecting the plot. The issue is acknowledged by the CONTAM Panel, and it only happens if the BMD posterior distribution is located below the lowest dose/exposure group. This graphical presentation issue is being worked on. The CONTAM Panel is certain that the full posterior distribution is ensured to be above zero.

informative background prior (included only in the uncertainty analysis));

The second issue relates to the derivation of the BMD confidence interval. Based on the distribution of the BMD, the 95% one-sided lower bound (i.e. BMDL) and the 95% one-sided upper bound (i.e. BMDU) of the 90% BMD confidence interval are derived. The BMDL and BMDU are marked by the vertical green lines on top of the distribution of the BMD. However, by checking the location of the BMDL in the BMD distribution, it is not clear how the BMDL was determined. It seems to RIVM that, for some analyses, the probability below the BMDL is obviously larger than 5%. For this issue, see for example:
- Ahsan et al. (2006) skin lesions relative BMR 5%;
- Chen et al. (2010b) bladder cancer relative BMR 5%;
- Chen et al. (2010b) bladder cancer, relative BMR 5% (Sensitivity analysis: The highest exposure point estimate doubled);
- Gilbert-Diamond et al. (2013) skin cancer, relative BMR 5% (Without an informative background prior (included only in the uncertainty analysis));
- James et al. (2015) ischemic heart disease, relative BMR 5%;
- Milton et al. (2005) stillbirth, relative BMR 5%

(see Appendix B for the attachment)

Appendix A Attachment to Public Consultation comment number 35

This appendix contains the attachment for Public Consultation comment number 35, submitted by Raquel Soler-Blasco. The original format of this attachment was an Excel document.

The content of the attachment:

Association between prenatal As and its metabolite concentrations and children's neuropsychological development assessed by the McCarthy test scores at 4–5 years of age. INMA Project (Valencia and Gipuzkoa. Spain. 2003–2008).

This data corresponds to the results of figure 2 from the study:

Soler-Blasco, R., Murcia, M., Lozano, M., Sarzo, B., Esplugues, A., Riutort-mayol, G., Vioque, J., Lertxundi, N., Santa, L., Lertxundi, A., Irizar, A., Braeuer, S., Ballester, F., & Llop, S. (2022). Prenatal arsenic exposure, arsenic methylation efficiency, and neuropsychological development among preschool children in a Spanish birth cohort. Environmental Research, 207, 112208. https://doi.org/10.1016/j.envres.2021.112208

Covariates and confounders included in each main model

Soler-Blasco, R., Murcia, M., Lozano, M., Sarzo, B., Esplugues, A., Riutort-mayol, G., Vioque, J., Lertxundi, N., Santa, L., Lertxundi, A., Irizar, A., Braeuer, S., Ballester, F., & Llop, S. (2022). Prenatal arsenic exposure, arsenic methylation efficiency, and neuropsychological development among preschool children in a Spanish birth cohort. Environmental Research, 207, 112208. https://doi.org/10.1016/j.envres.2021.112208

General scale core additionally adjusted for covariates: maternal and paternal educational level, parity, child's sex, attendance at nursery, maternal verbal intelligence quotient.

Additionally, each exposure model adjusted for different confounders:

- **Total As:** season of sample collectio+A5:P103n, maternal age, maternal place of birth, and rice and seafood consumption during the first trimester of pregnancy.
- **ΣAs:** season of sample collection and rice and seafood consumption during the first trimester of pregnancy.
- **DMA:** season of sample collection, and vegetables, rice and seafood consumption at first trimester of pregnancy.
- **MMA:** season of sample collection, maternal place of birth, and vegetables consumption at first trimester of pregnancy.

- **iAs:** maternal place of birth, and rice consumption at first trimester of pregnancy.

Verbal scale core additionally adjusted for covariates: maternal age, maternal body mass index (BMI) before pregnancy, maternal place of birth, maternal and paternal educational level, maternal working status during pregnancy, type of area of residence, parity and child's sex.

Additionally, each exposure model adjusted for different confounders:

- **Total As:** season of sample collection, and seafood consumption at first trimester of pregnancy.
- **∑As:** season of sample collection, and vegetables and seafood consumption at first trimester of pregnancy.
- **DMA:** season of sample collection, parental social class, and vegetables and seafood consumption at first trimester of pregnancy.
- **MMA:** proximity of residence to agricultural area, and vegetables and rice consumption at first trimester of pregnancy.
- **iAs:** non-adjusted for other confounders.

Quantitative scale core additionally adjusted for covariates: maternal place of birth, maternal and paternal educational level, maternal working status at the third trimester of pregnancy, paternal tobacco consumption during pregnancy, child's sex and attendance at nursery,

Additionally, each exposure model adjusted for different confounders:

- **Total As:** season of sample collection, and rice and seafood consumption at first trimester of pregnancy.
- **∑As:** season of sample collection, and rice, vegetables and seafood consumption at first trimester of pregnancy.
- **DMA:** season of sample collection, and rice, vegetables and seafood consumption at first trimester of pregnancy.
- **MMA:** maternal BMI before pregnancy, proximity of residence to agricultural area, and vegetables, meat and rice consumption at first trimester of pregnancy.
- **iAs:** legumes and rice consumption at first trimester of pregnancy.

Perceptual-performance scale core additionally adjusted for covariates: maternal educational level, child's sex, attendance at nursery, maternal verbal intelligence quotient and maternal tobacco consumption at 5 years of age.

Additionally, each exposure model adjusted for different confounders:

- **Total As:** season of sample collection and seafood consumption at first trimester of pregnancy.
- **ΣAs:** season of sample collection and seafood consumption at first trimester of pregnancy.
- **DMA:** season of sample collection, and seafood consumption at first trimester of pregnancy.
- **MMA:** season of sample collection, maternal BMI before pregnancy and meat consumption at first trimester of pregnancy.
- **iAs:** maternal BMI before pregnancy.

Memory scale core additionally adjusted for covariates: maternal education level, parity, child's sex, attendance at nursery, maternal verbal intelligence quotient.

Additionally, each exposure model adjusted for different confounders:

- **Total As:** maternal age, season of sample collection, seafood consumption at first trimester of pregnancy.
- **ΣAs:** vegetables and seafood consumption at first trimester of pregnancy.
- **DMA:** vegetables and seafood consumption at first trimester of pregnancy.
- **MMA:** maternal BMI before pregnancy, vegetables consumption at first trimester of pregnancy.
- **iAs:** maternal place of birth.

Motor scale core additionally adjusted for covariates: maternal education level, maternal BMI before pregnancy, attendance at nursery.

Additionally, each exposure model adjusted for different confounders:

- **Total As:** non-adjusted for other confounders.
- **ΣAs:** vegetables and rice consumption at first trimester of pregnancy.
- **DMA:** vegetables and rice consumption at first trimester of pregnancy.
- **MMA:** vegetables consumption at first trimester of pregnancy.

- **iAs:** legumes consumption at first trimester of pregnancy.

Gross motor scale core additionally adjusted for covariates: alcohol consumption during pregnancy, maternal tobacco consumption until 32 weeks of gestation, child's sex.

Additionally, each exposure model adjusted for different confounders:

- **Total As:** seafood consumption at first trimester of pregnancy.
- **∑As:** vegetables and seafood consumption at first trimester of pregnancy.
- **DMA:** vegetables, rice and seafood consumption at first trimester of pregnancy.
- **MMA:** maternal BMI before pregnancy, vegetables and meat consumption at first trimester of pregnancy.
- **iAs**: maternal BMI before pregnancy.

Fine motor scale core additionally adjusted for covariates: maternal education level, maternal BMI before pregnancy, child's sex, maternal tobacco consumption at 5 years of age, attendance at nursery.

Additionally, each exposure model adjusted for different confounders:

- **Total As:** season of sample collection, maternal place of birth, seafood consumption at first trimester of pregnancy.
- **∑As:** season of sample collection, vegetables and seafood consumption at first trimester of pregnancy.
- **DMA:** season of sample collection, vegetables and seafood consumption at first trimester of pregnancy.
- **MMA:** vegetables consumption at first trimester of pregnancy.
- **iAs:** maternal place of birth.

Executive function scale core additionally adjusted for covariates: maternal and paternal educational level, maternal place of birth, parity, maternal BMI before pregnancy, child's sex, attendance at nursery, maternal verbal intelligence quotient.

Additionally, each exposure model adjusted for different confounders:

- **Total As:** maternal age, season of sample collection, rice and seafood consumption at first trimester of pregnancy.

- **ΣAs:** season of sample collection, rice, vegetables and seafood consumption at first trimester of pregnancy.
- **DMA:** season of sample collection, vegetables, rice and seafood consumption at first trimester of pregnancy.
- **MMA:** vegetables, rice and meat consumption at first trimester of pregnancy.
- **iAs:** legumes consumption at first trimester of pregnancy."

Working memory scale core additionally adjusted for covariates: maternal place of birth, maternal educational level, parity, parental social class, paternal smoking habit during pregnancy, attendance at nursery, main care provider at 4–5 years old.

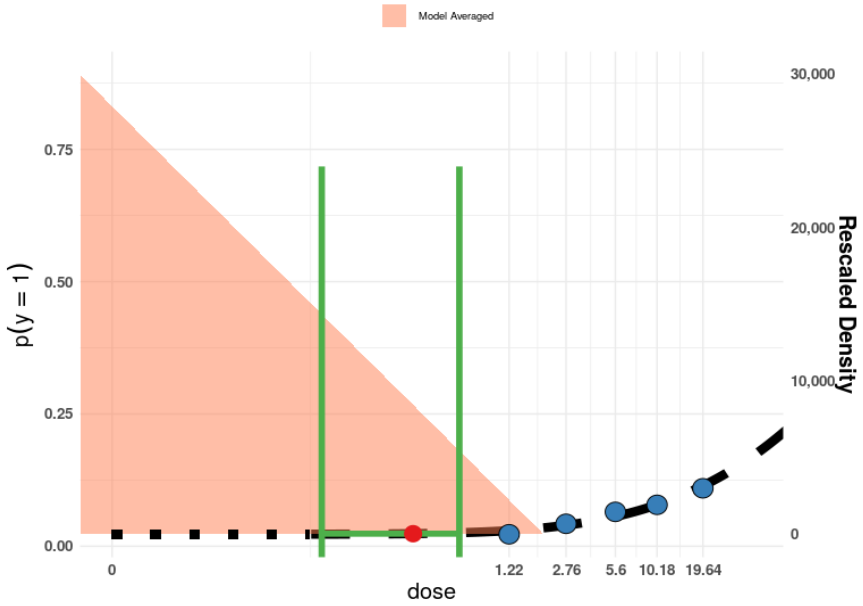
Additionally, each exposure model adjusted for different confounders:

- **Total As:** season of sample collection, and seafood consumption at first trimester of pregnancy.
- **ΣAs:** season of sample collection, rice and seafood consumption at first trimester of pregnancy.
- **DMA:** season of sample collection, rice and seafood consumption at first trimester of pregnancy.
- **MMA:** maternal BMI before pregnancy, proximity to agricultural area and meat consumption at first trimester of pregnancy.
- **iAs:** legumes consumption at first trimester of pregnancy.

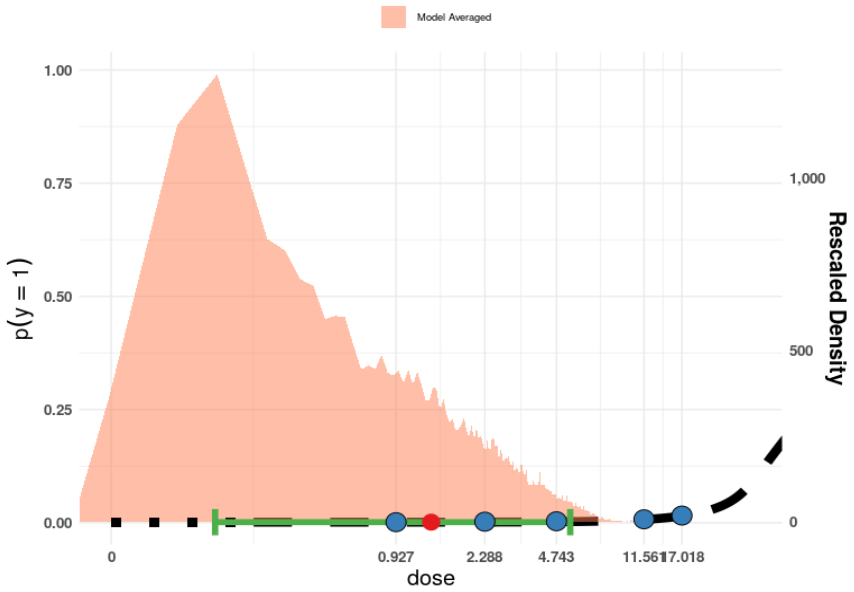
Appendix B Attachment to Public Consultation comment number 93

This appendix contains the attachment for Public Consultation comment number 93, submitted by RIVM.

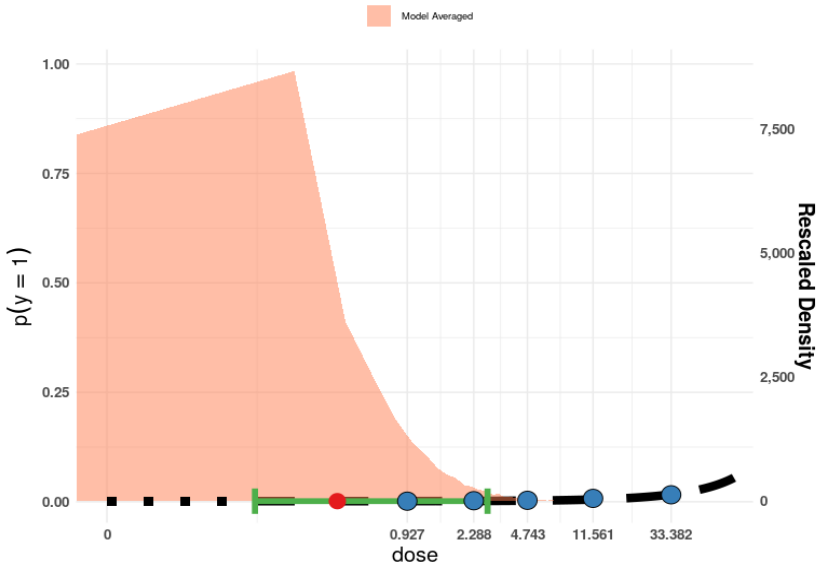
Figures copied from Annex E1.



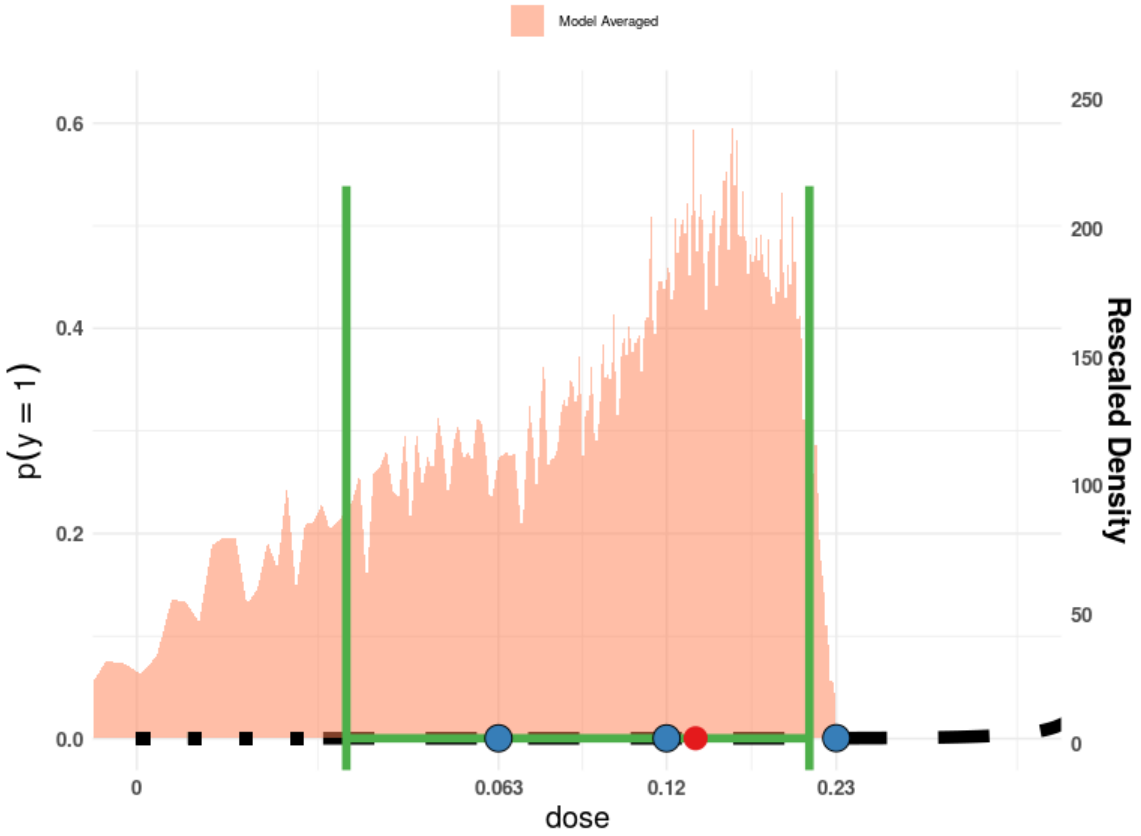
Ahsan et al. (2006) skin lesions relative BMR 5%;



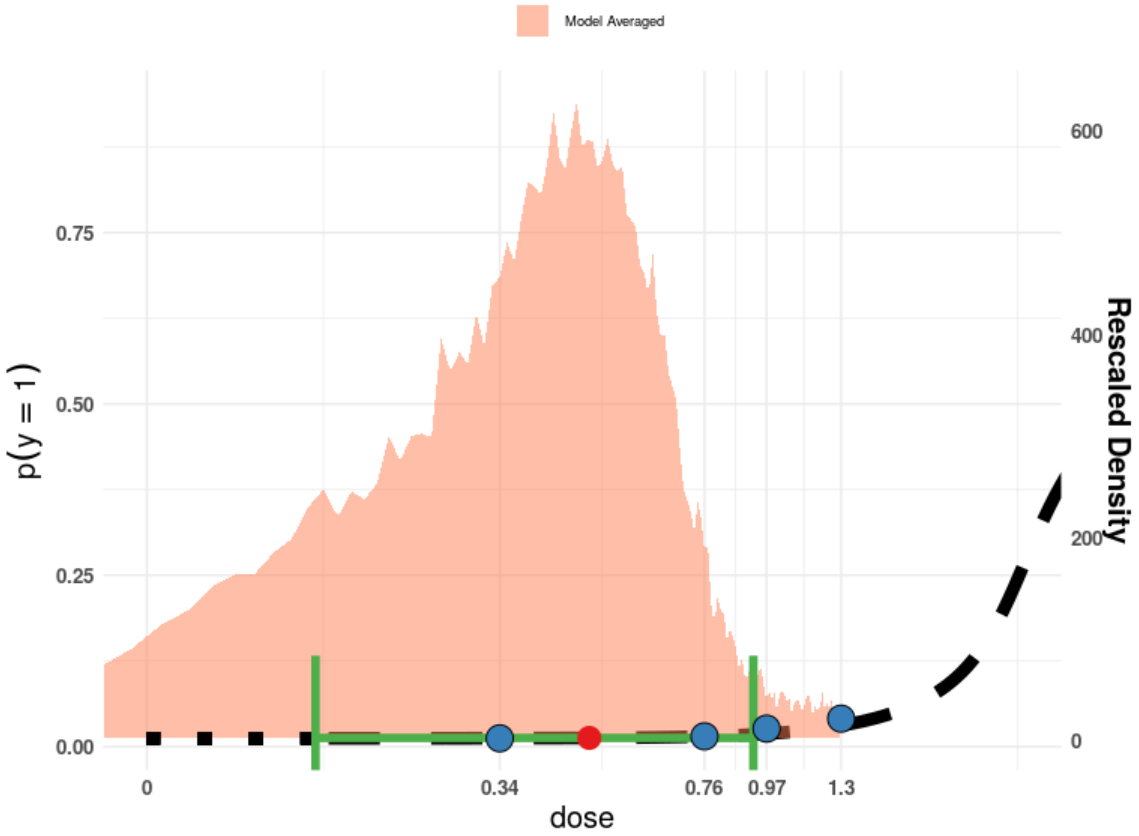
Chen et al. (2010b) bladder cancer relative BMR 5%;



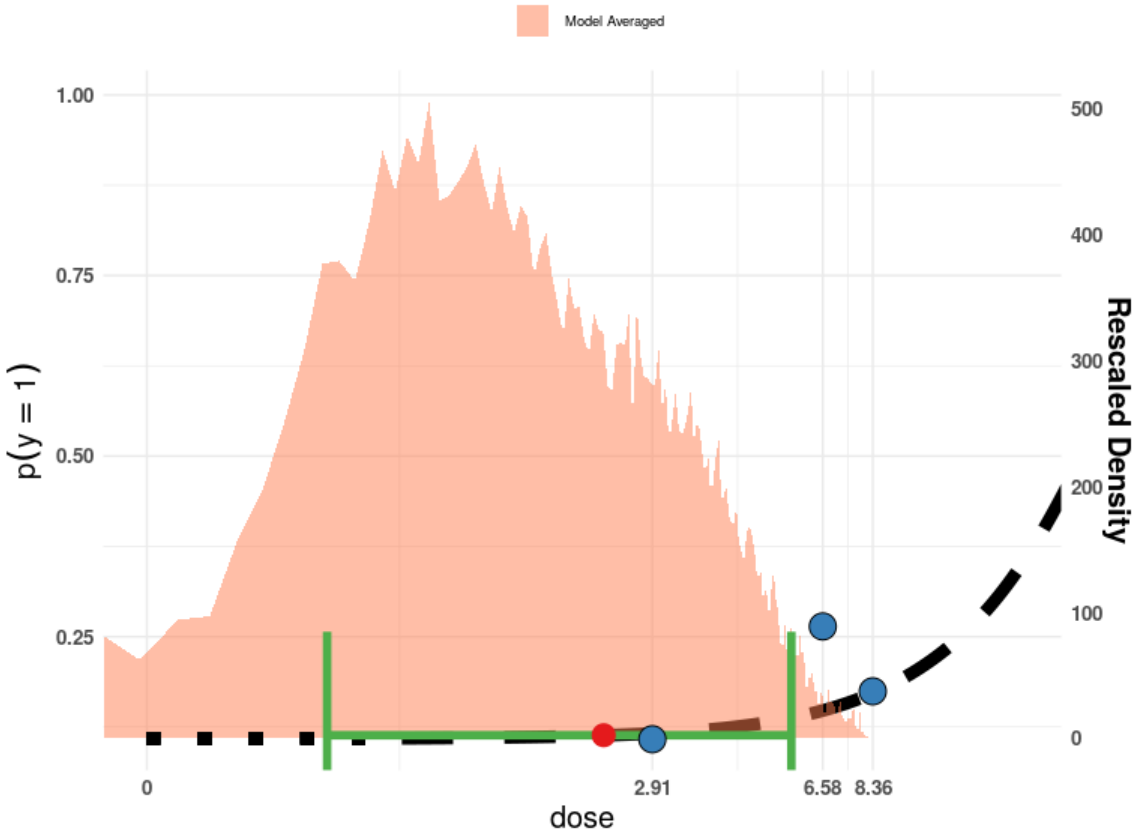
Chen et al. (2010b) bladder cancer, relative BMR 5% (Sensitivity analysis: The highest exposure point estimate doubled);



Gilbert-Diamond et al. (2013) skin cancer, relative BMR 5% (Without an informative background prior (included only in the uncertainty analysis));



James et al. (2015) ischemic heart disease, relative BMR 5%



Milton et al. (2005) neonatal death, relative BMR 5%

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