SCIENTIFIC OPINION

# Scientific Opinion on Arsenic in Food[1]

**EFSA Panel on Contaminants in the Food Chain (CONTAM)**[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

## SUMMARY

Arsenic is a metalloid that occurs in different inorganic and organic forms, which are found in the environment both from natural occurrence and from anthropogenic activity. The inorganic forms of arsenic are more toxic as compared to the organic arsenic but so far most of the occurrence data in food collected in the framework of official food control are still reported as total arsenic without differentiating the various arsenic species. The need for speciation data is evident because several investigations have shown that especially in seafood most of the arsenic is present in organic forms that are less toxic. Consequently, a risk assessment not taking into account the different species but considering total arsenic as being present exclusively as inorganic arsenic would lead to a considerable overestimation of the health risk related to dietary arsenic exposure.

Following a call for data, 15 European countries submitted more than 100,000 results on arsenic concentrations in various food commodities. Two thirds of the samples were below the limit of detection. Approximately 98 % of the results were reported as total arsenic, and only a few investigations differentiated between the various arsenic species. The highest total arsenic levels were measured in the following food commodities: fish and seafood, food products or supplements based on algae, especially hijiki, and cereal and cereal products, with particularly high concentrations in rice grains and rice-based products, and bran and germ. Depending on the type of food processing, temperature and time, changes in total arsenic concentration and arsenic species may occur. The arsenic content in cooking water seems to be of special importance because it determines whether the arsenic concentrations in the prepared food may be higher or lower compared to the raw product.

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As representative speciation data are scarce, the EFSA Panel on Contaminants in the food chain (CONTAM Panel) was not able to assess the typical ratios between inorganic and organic arsenic in different groups of foodstuffs. Consequently, the CONTAM Panel had to make a number of assumptions for the estimation of the contribution of inorganic arsenic to total arsenic in the exposure assessment based on the few data on inorganic arsenic submitted by the reporting European countries, as well as on key literature data. Thus, the proportion of inorganic arsenic was assumed to vary from 50 to 100 % of the total arsenic reported in food commodities other than fish and seafood, with 70 % considered as best reflecting an overall average. In fish and seafood the relative proportion of inorganic arsenic is small and tends to decrease as the total arsenic content increases, and the ratio may vary depending on the seafood type. Based on the limited data on inorganic arsenic in the present dataset and on published data, fixed values for inorganic arsenic of 0.03 mg/kg in fish and 0.1 mg/kg in seafood were considered realistic for calculating human dietary exposure.

Given the above assumptions, the national inorganic arsenic exposures from food and water across 19 European countries, using lower bound and upper bound concentrations, have been estimated to range from 0.13 to 0.56 μg/kg body weight (b.w.) per day for average consumers, and from 0.37 to 1.22 μg/kg b.w. per day for 95$^{th}$ percentile consumers. The minimum and maximum dietary exposure varied by a factor of 2 to 3 across the 19 European countries, based on different dietary habits rather than different occurrence data. Extrapolating from the main food categories of the EFSA Concise Food Consumption Database the food subclasses of cereal grains and cereal based products, followed by food for special dietary uses, bottled water, coffee and beer, rice grains and rice based products, fish and vegetables were identified as largely contributing to the inorganic arsenic daily exposure in the general European population.

High consumers of rice in Europe, such as certain ethnic groups, are estimated to have a daily dietary exposure of inorganic arsenic of about 1 μg/kg b.w. per day, and high consumers of algae-based products can have dietary exposure of inorganic arsenic of about 4 μg/kg b.w. per day. The limited available evidence does not indicate a different dietary exposure for vegetarians from that of the general population, unless they consume a large amount of algae-based products.

Children under three years of age are the most exposed to inorganic arsenic. Exposure estimates reported in two different studies show an inorganic arsenic intake ranging from 0.50 to 2.66 μg/kg b.w. per day. Dietary exposure to inorganic arsenic for children under three years old, including from rice-based foods, is in general estimated to be about 2 to 3-fold that of adults. These estimates do not include milk intolerant children substituting rice-drinks for formula or cows' milk.

Compared to dietary exposure, non-dietary exposure to arsenic is likely to be of minor importance for the general population in the European Union (EU).

High inter-species, inter-population and inter-individual variability was reported for arsenic metabolism and toxicokinetics. Because experimental animals differ considerably from humans with regard to arsenic metabolism and other aspects of toxicokinetics, the results of toxicity studies in animals do not provide a suitable basis for risk characterisation.

In humans, soluble inorganic arsenic is rapidly and nearly completely absorbed after ingestion. Absorption of different organic arsenic compounds is generally greater than 70 %. After being absorbed, arsenic is widely distributed to almost all organs and readily crosses the placental barrier. Biotransformation of inorganic arsenic in mammals includes reduction of pentavalent arsenic to trivalent arsenic and methylation of trivalent arsenic.

The CONTAM Panel noted that, since the provisional tolerable weekly intake (PTWI) of 15 μg/kg b.w. was established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), new data had established that inorganic arsenic causes cancer of the lung and urinary tract in addition to skin, and that a range of adverse effects had been reported at exposures lower than those reviewed by the JECFA. Therefore the CONTAM Panel concluded that the JECFA PTWI of 15 μg/kg b.w. is no longer appropriate and, in its assessment, focussed on more recent data showing effects at lower doses of inorganic arsenic than those considered by the JECFA.

The main adverse effects reported to be associated with long term ingestion of inorganic arsenic in humans are skin lesions, cancer, developmental toxicity, neurotoxicity, cardiovascular diseases, abnormal glucose metabolism, and diabetes. Neurotoxicity is mainly reported with acute exposure from deliberate poisoning or suicide, or at high concentrations in drinking water. Evidence of cardiovascular disease (Blackfoot disease, peripheral vascular disease, coronary heart disease, myocardial infarction and stroke) and diabetes in areas with relatively low levels of inorganic arsenic exposure is inconclusive. There is emerging evidence of negative impacts on foetal and infant development, particularly reduced birth weight, and there is a need for further evidence regarding the dose-response relationships and critical exposure times for these outcomes.

Therefore the data for cancers of the urinary bladder, lung and skin, which are causally associated with oral exposure to inorganic arsenic, and skin lesions were considered by the CONTAM Panel as possibly providing an appropriate reference point. A limitation in all of the available studies is that total dietary exposure to inorganic arsenic was not measured. In most studies, the concentration of arsenic in drinking water was used as the exposure metric. Urinary or toenail arsenic has been used in a smaller number of studies. In order to provide an opinion on the risks to health related to the presence of inorganic arsenic in foodstuffs, it is necessary to make assumptions about the total dietary exposure of the populations in which the respective health endpoints were studied. The CONTAM Panel noted that underestimating the total dietary exposure in the study populations will lead to an underestimation of the reference point and, consequently, to an overestimation of the risk when considering the total dietary exposure of EU countries in this opinion, and *vice versa*, and concluded that it would be appropriate to identify a range of possible total dietary exposures in the key epidemiological studies.

The CONTAM Panel modelled the dose-response data from the key epidemiological studies and also noted other reported dose-response modelling results. A benchmark response of 1 % extra risk was selected because it could be within the range of the observed data. Because of the uncertainties in the exposure in the key epidemiological studies, the CONTAM Panel identified a range of values for the 95 % lower confidence limit of the benchmark dose of 1 % extra risk ($BMDL_{01}$) for each endpoint. The lowest $BMDL_{01}$ values are for lung cancer. These data are from a study that is relatively small but has the advantage that the population is likely to have a nutritional and genetic background that is more similar to that of EU populations than those of the rural Asian populations, for which most of the epidemiological data are available. In contrast, the data for skin lesions are from larger populations and show a high degree of consistency between studies. Arsenic exposure is considered to be a necessary but not sufficient cause of dermal lesions and given that the observations of dermal lesions mainly originate from rural Asian communities with high levels of arsenic in the water, it is possible that the findings were influenced by other factors such as nutritional status. The CONTAM Panel therefore concluded that the overall range of $BMDL_{01}$ values of 0.3 to 8 μg/kg b.w. per day should be used instead of a single reference point in the risk characterisation for inorganic arsenic.

The CONTAM Panel noted that inorganic arsenic is not directly DNA-reactive and there are a number of proposed mechanisms of carcinogenicity such as oxidative damage, epigenetic effects and interference with DNA damage repair, for each of which a threshold mechanism could be postulated. However, taking into account the uncertainty with respect to the shape of the dose-response relationships, it was not considered appropriate to identify from the human data a dose of inorganic arsenic with no appreciable health risk, i.e. a tolerable daily or weekly intake. Therefore an assessment should be made of the margins of exposure (MOEs) between the identified reference points from the human data and the estimated dietary exposure to inorganic arsenic in the EU population.

The estimated dietary exposures to inorganic arsenic for average and high level consumers in Europe are within the range of the $BMDL_{01}$ values identified by the CONTAM Panel, and therefore there is little or no MOE and the possibility of a risk to some consumers cannot be excluded. Consumer groups with higher exposure levels include high consumers of rice, such as certain ethnic groups, and high consumers of algae-based products. The estimated dietary exposures of these groups are also within the range of the $BMDL_{01}$ values. Infants below 6 months of age fed on only breast-milk, or on cows' milk formula reconstituted with water containing arsenic at the average European concentration, have the lowest estimated dietary exposure to inorganic arsenic. The estimated dietary exposures of children are higher than those of adults, due to their greater food consumption relative to their body weight. However, this does not necessarily indicate that children are at greater risk because the effects are due to long term exposure and the exposure estimates are also within the range of $BMDL_{01}$ values.

Of the organic forms of arsenic, arsenobetaine, which is the major form in fish and most seafood, is widely assumed to be of no toxicological concern. Arsenosugars and arsenolipids are mainly metabolised in humans to dimethylarsinate, but no specific information is available regarding their toxicity. For other organoarsenic compounds no human toxicity data are available. Because of the lack of data, arsenosugars, arsenolipids, methylarsonate and dimethylarsinate could not be considered in the risk characterisation.

The CONTAM Panel recommended that dietary exposure to inorganic arsenic should be reduced. In order to refine risk assessment of inorganic arsenic there is a need to produce speciation data for different food commodities to support dietary exposure assessment and dose-response data for the possible health effects.

**KEY WORDS**

total arsenic, inorganic arsenic, organic arsenic, analysis, food, occurrence, dietary exposure, risk assessment, toxicity, bench mark dose (BMD), margin of exposure (MOE)