

**JOINT FAO/WHO FOOD STANDARDS PROGRAMME
CODEX COMMITTEE ON FOOD ADDITIVES AND CONTAMINANTS**

**POSITION PAPER ON ARSENIC
(Prepared by Denmark)**

INTRODUCTION

1. Arsenic ranks 20th in abundance among the elements in the earth's crust. Arsenic is introduced into the environment from natural sources (*e.g.* volcanic activity and weathering of minerals) and from anthropogenic activity (*e.g.* ore smelting, burning of coal, pesticide use) and the ratio between the two types of sources has been estimated at 60:40¹. As a result of naturally occurring metabolic processes in the biosphere arsenic occurs as a large number of organic or inorganic chemical forms in food (species).

The different chemical and toxicological characteristics of the various molecular species and oxidation states occurring in food makes it necessary to distinguish between them in order to present a full picture of the content of arsenic in food and what impact the intake of arsenic in food has on the consumer.

2. In the marine environment the total arsenic concentrations which typically range from 0.5-50 mg/kg (wet weight) are found in animals and plants, including seaweed, fish, shellfish and crustaceans^{1,2}. The high concentration level of arsenic in seafood has been known since the beginning of the 20th century³. The study of the metabolic routes of arsenic in the marine environment has led to the understanding of some of the conversions of oceanic inorganic arsenic found in ocean water to the significantly higher concentration of organic forms of arsenic present in seafood². In fish from fresh waters arsenic is present at much lower concentrations in comparison with their oceanic counterparts, typically at less than 10 µg/kg⁴.

3. In the terrestrial environment arsenic is generally found at low concentrations in crop plants which typically range from 0-20 µg/kg with the exception of rice at 150-250 µg/kg and certain edible mushroom species which contain arsenic at several mg/kg from the soil⁵. Information is generally scarce regarding the molecular species of arsenic found in crop plants. In life stock the arsenic concentration level is similar to that in plants. A notable exception is arsenic in poultry which ranges from 0-100 µg/kg. The arsenic originates from arsenic-containing fish meal used in the poultry fodder or possibly arsenic-containing growth promoters which are used in some countries. Increased arsenic concentrations in plants (tobacco) have also been observed if dimethylarsinate was used as a pesticide. Levels and speciation of arsenic in drinking water

(including natural mineral and other bottled water) is a matter of concern in many countries as arsenic levels exceeding 200 mg/l have been reported⁶. Several reports in the literature of similar or even higher arsenic concentration levels in well and in ground water reflects this problem.

Atmospheric fall-out of arsenic has contaminated crop plants cultivated near industrial point sources. The amount of arsenic concentration found in such crops depends on a number of factors including the chemical form and bioavailability of arsenic in the soil and on the atmospheric deposition rate, and can therefore not be generalised. Finally, increased arsenic concentrations have been observed in crop plants when cultivated in soil with a naturally high arsenic content or in soil contaminated by spills after chromium, copper, arsenic (CCA)-wood impregnation⁷. No direct carry-over however, has been observed for e.g. potatoes stored in bins made from CCA impregnated wood⁸.

TOXICOLOGICAL EVALUATIONS

4. The most toxic forms of arsenic found in food and water are the inorganic arsenic (III) and (V)⁹ and the International Agency for Research on Cancer (IARC) has classified inorganic arsenic as a human carcinogen¹⁰. The inorganic arsenic trioxide has a well-known history as a poisonous compound, often used in cases of homicide. The methylated forms however, e.g. dimethylarsinate, are low in acute toxicity¹¹ while the principal arsenic species found in fish and crustaceans, arsenobetaine is considered non-toxic⁹. In shellfish, molluscs and seaweed the dimethylarsinylriboside derivatives, also known as "arsenosugars", are the quantitatively dominating arsenic species. Their possible toxicity to humans is not known in any detail. Whereas organic arsenicals generally dominate in food, only a few per cent of the total arsenic in fish is present as inorganic forms^{12,13}.

5. A provisional tolerable daily intake of inorganic arsenic via food and water was established by WHO at 2 µg/kg bodyweight in 1983¹⁴ and later changed to the equivalent provisional tolerable week intake (PTWI) at 15 µg/kg bodyweight in 1988¹⁵. The epidemiological data used for this risk assessment refer to inorganic arsenic in drinking water. However, a similar recommendation for organic arsenic species in food could not be established by WHO due to lack of appropriate toxicological data. This recommendation has been repeated and substantiated by the US Agency for Toxic Substances and Disease Registry¹⁶. The recommended WHO guideline level for inorganic arsenic in drinking water is 10 µg/l¹⁷ and according to these guidelines 20 % of the PTWI is allocated to drinking water.

In contrast to its toxicity, the possible essential role of arsenic¹⁸ is a matter of controversy¹⁹. The underlying animal experiments however, do not allow for any conclusions regarding a possible essential function of arsenic to humans.

6. Inorganic arsenic (III) and (V) are well absorbed from the gastro-intestinal tract. The absorption rates of methylated arsenic and that of arsenobetaine are also high but tissue retention of the latter much lower as studied by excretion of radio-labelled arsenobetaine. Inorganic arsenicals are transported to the

liver where methylation may lead to the formation of monomethylarsonate and dimethylarsinate. However, a fraction of the inorganic arsenic may accumulate in hair, nails and skin²⁰. No transformation of arsenobetaine has been reported to take place in mammals but arsenocholine ingested via seafood can be oxidized to arsenobetaine. Elimination of inorganic and organic forms of arsenic mainly takes place via the urine. Only few studies exist regarding the fate of arsenobetaine in the human body. The question remains however, whether arsenobetaine is stable in the presence of anaerobic bacteria in the gastro-intestinal tract. In the marine environment such bacteria have been shown to metabolise arsenobetaine to lower molecular weight compounds. Obviously, this possible catabolic route in man needs investigation.

7. Epidemiological studies have shown human health effects after long-term oral exposure to inorganic arsenic species in drinking water from wells in areas where the soil is geochemically rich in arsenic. A long-term daily intake of inorganic arsenic at 10-50 µg/kg body weight contributed to vascular problems which may ultimately lead to necrosis and gangrene of hands and feet ("black foot disease")¹⁶. Inorganic arsenic may also cause skin lesions and skin cancer. Besides the risk of developing skin cancer, internal types of cancer have been reported in patients who already had developed arsenic-induced skin cancer.

8. The United States Environmental Protection Agency (US EPA) has estimated the excess skin cancer risk from life-time exposure to arsenic via water²¹ containing 1 µg per litre of inorganic arsenic at 7×10^{-5} . Therefore drinking water concentrations of arsenic exceeding this levels is a matter of concern. At the 10 µg/l WHO guideline level of arsenic in drinking water the estimated lifetime risk for arsenic-induced skin cancer has been estimated¹⁷ at 6×10^{-4} .

ANALYTICAL DATA

9. The analysis of total arsenic in food has up to date suffered from difficulties with respect to accuracy and precision. However, the situation has improved somewhat in recent years with the advent of modern analytical techniques such as atomic absorption spectrometry (AAS) with hydride generation or graphite furnace atomisation, and inductively coupled plasma mass spectrometry (ICP-MS).

However, it is generally advisable to disregard data older than approximately 10 years or reported data, the quality of which have not been justified by *e.g.* the use of certified reference materials. Especially data for arsenic in food at low concentration levels may be seriously biased because of possible interferences or because of other disturbances such as laboratory contamination or loss of analyte during sample work-up. Consequently, international intercomparison exercises are needed to test the proficiency of analytical laboratories, particularly for the analysis of arsenic in seafood.

10. The analytical difficulties encountered for arsenic are non-specific absorbance from matrix constituents in AAS or insufficient sample mineralization if hydride generation AAS has been used. In ICP-MS polyatomic interferences and matrix effects may hamper the accuracy of the analyses. For speciation work however, the ICP-MS is an excellent detector for coupling with separation techniques such as HPLC²².

11. Speciation data for arsenic are strongly needed because of the large difference in toxicity to humans of various chemical forms of arsenic. At least 25 different chemical forms of arsenic which are polar or ionic in molecular structure have been detected, particularly in seafood samples². Furthermore a number of non-polar (fat soluble) arsenolipids constitute 1-18% of the total arsenic content in seafood²³. Due to the different toxicology of these species a value for the total arsenic content in a food sample is of little value. First of all procedures that provide information on the content of the toxic inorganic arsenic species are needed. Secondly, data on the methylated species are of interest because they are the immediate conversion products of ingested inorganic arsenic. Finally, more sophisticated speciation procedures based on *e.g.* the HPLC-ICP-MS combination are needed in toxicological studies such as those suggested above for the arsenosugars and arsenobetaine.

INTAKE DATA

12. Humans are mainly exposed to arsenic via the diet and drinking water while a small group of the population additionally is occupationally exposed. The arsenic level in these individuals must be specifically monitored in order to prevent a possible health risk. The highest average arsenic concentration is found in seafood products followed by poultry and cereal products. Combined with data on food consumption the average adult intake has been estimated in Denmark at 118 mg per day with a 90th percentile intake of 233 $\mu\text{g}/\text{day}$ ⁵. Seafood contributes to the average arsenic intake by 86 $\mu\text{g}/\text{day}$ (72% of the total intake) in spite the fact that fish only accounts for a small fraction of the daily food consumption. The mean adult dietary intake for UK consumers is 63 $\mu\text{g}/\text{day}$ and fish constitute 56 $\mu\text{g}/\text{day}$ or 89 % of this value²⁴. In Canada the mean daily intake was 49 $\mu\text{g}/\text{day}$ and the contribution from fish constituted 32 $\mu\text{g}/\text{day}$ or 64% of the total²⁵. In Australia, the mean adult dietary intake of arsenic has been estimated at 63 $\mu\text{g}/\text{day}$ with seafood contributing 63% of the total while the 95th percentile intake of total arsenic was 119 $\mu\text{g}/\text{day}$ ²⁶. An estimate of the mean adult dietary intake of inorganic arsenic in Australia was 0.77 $\mu\text{g}/\text{day}$ or 0.5% of the PTWI value. The equivalent 95th percentile value was 1.25 $\mu\text{g}/\text{day}$ for inorganic arsenic²⁶. Finally, in the USA the total intake of arsenic has been estimated at 57 $\mu\text{g}/\text{day}$ and seafood contributed 52 $\mu\text{g}/\text{day}$ or 92 % of the total intake²⁷. The reported data reflect that the total arsenic intake in a given population is largely determined by the amount of seafood consumed. In Japan where the arsenic-rich seafood, seaweed and rice traditionally constitutes a large part of the diet the daily arsenic intake via the diet has been estimated at 985 $\mu\text{g}/\text{day}$ ²⁸.

13. In order to arrive at a meaningful estimate of the intake which can be evaluated using the existing toxicological standards, arsenic species information is strongly needed. However, such results for market foods are rarely available in the literature. Furthermore, with the increasing consumption of dietary supplements, particularly those of marine origin, arsenic species contained herein may need to be monitored and considered.

POTENTIAL HEALTH RISKS

14. If it is (erroneously) assumed that all arsenic in the food is inorganic the average arsenic intake as given in paragraph 12 for the Danes would amount to 79% of the PTWI value for inorganic arsenic which is 1050 µg for a person of 70 kg bodyweight. This high value is however not of immediate relevance because it is well known that arsenic does not occur as inorganic arsenic in the diet, except in low amounts. A more relevant estimate is therefore based on the assumption that a maximum of 5% of the arsenic ingested via seafood is inorganic¹³. The Australian estimate of the inorganic arsenic intake (paragraph 12) at 1% of the total arsenic intake confirms the generally low content of inorganic arsenic in food including seafood.

Conservatively based on the assumption that arsenic in all other foods items of the diet and in water is present as inorganic species, the weekly intake of inorganic arsenic amounts to 250 µg based on data from the Danish investigation⁵. This is equivalent to 24 % of the PTWI value. Results of similar magnitude would be obtained based upon the UK and Canadian intake data (paragraph 12) whereas the situation in Japan would merit a closer investigation of the intake of the occurring arsenic species *via* the traditional diet.

This estimated intake of inorganic arsenic implies that a large majority of consumers should not be in any danger of exceeding the PTWI, unless inorganic arsenic in their drinking water is present at an elevated concentration level or if individuals have been exposed to arsenic via other sources, such as inhalation of arsenic-containing particles in air. In such cases measures must be taken to reduce the risk by *e.g.* improved processing of the water or if possible by removal of the source of arsenic.

However, if the diet contains an appreciable amount of seaweed, which is customary in some countries, the intake of inorganic arsenic from this source may increase strongly, and the risk of exceeding the PTWI value for inorganic arsenic must be considered²⁹. In such cases, a risk assessment aimed at the relevant population groups must be carried out.

15. Further research is needed to clarify the fate of organic arsenic, including arsenosugars and arsenobetaine, in humans, particularly with the aim to elucidate whether any arsenic species of toxicological concern are formed during human metabolism of the compounds ingested *via* seafood. Furthermore, such studies should also illustrate if these arsenic species are accumulated in any given tissue.

16. Further research is needed to clarify whether arsenic in processed seafood products (canned or frozen) are converted to more toxic compounds during processing or storage.

FAIR TRADE CONSIDERATIONS

17. Several countries have established maximum levels (MLs) for arsenic in food

commodities. There are a number of Codex MLs for arsenic which however, do not cover the whole range of national MLs. The foods for which Codex MLs have been established are fats, oil, juice, nectar, sugar, cocoa and chocolate (reference).

18. In general trade problems are not prevalent. On some markets however, the accepted upper limits of arsenic in seafood products are set at relatively low values. It is highly likely that such import regulations are erroneously based on the assumption that a substantial amount of the arsenic in seafood is present as toxic forms such as inorganic arsenic.

19. Until maximum limits for specific toxic arsenic compounds in food are laid down by the Codex Alimentarius Commission it is suggested that foods moving in international trade that risk rejection on the grounds of existing general maximum limits for arsenic in the importing countries are analysed and assessed on a case by case basis in the light of the information presented in this paper.

CONCLUSIONS AND RECOMMENDATIONS

20. The industrial uses of arsenic-containing preparations such as those used for wood preservation should be phased out in society and replaced by other less toxic agents. Similarly, the arsenic emissions from burning fossil fuels should also be reduced by improving the efficiency of smoke cleaning.

21. There is no apparent risk of exceeding the PTWI value for inorganic arsenic from food and water, except in regions with high arsenic levels in drinking water and/or extreme seafood and seaweed consumption. The levels of inorganic arsenic reported in some drinking and in some bottled waters, however, may cause concern.

22. The contribution by organo-arsenic compounds dominates the total intake of arsenic from food (with the exception of water). These food items are primarily of marine origin. This can not be changed because of the natural bio-geochemical cycles of this element in nature, including raw food products. Until further knowledge regarding the content of the naturally occurring arsenic species in a wide range of foods and the toxicity of these species has been established, and until methodologies have been developed for their control, there seems not to be sufficient basis to decide whether Codex MLs are needed for these species. The information available, however, indicates that such MLs should not be necessary.

23. It is however, recommended that further studies on the analytical methodology with special emphasis on the arsenic species of known or suspected toxicological concern is undertaken. To make analytical methods readily available to other laboratories than expert laboratories, such analytical development should ideally be based on inexpensive instrumentation. Furthermore, the absorption rate, bioavailability and possible toxic effects of arsenic species needs further study. This applies particularly to the arsenosugars.

24. Water is a special case that may cause concern because of possible high levels of inor-

ganic arsenic that may contribute to the risk of skin cancer. For packaged water (including spring, well, surface and ground water) moving in international trade it is recommended that the Codex Alimentarius considers to replace the current Codex ML of 50 µg/l for total arsenic by the WHO guideline level of 10 µg/l for inorganic arsenic in drinking water.

25. The current Codex Alimentarius MLs in some foods are based on total arsenic and do not take into consideration which chemical forms of arsenic are present. Consequently, they do not cover the situation adequately, but it is suggested that they should continue until reliable methods of analysis are available to routinely test for inorganic arsenic or other toxic arsenicals. Such future methods will provide control over foods which naturally contain toxic arsenicals, or have been contaminated deliberately.

26. The PTWI value was established by WHO saying that sufficient knowledge was unavailable to set a similar tolerable intake value for organic forms of arsenic. Arsenobetaine and the group of arsenosugars which originate from various marine food products represent the quantitatively important organic arsenic species and their fate and possible toxicological effects to man must be elucidated. We now have laboratory methods and instrumentation at hand that allow such investigations to be carried out. Ultimately, the calculation of the dietary intake of arsenic species may constitute the basis for human health risk evaluation.

27. Future legislative limits for arsenic must be based on those arsenic species which are of toxicological concern, such as As(III), As(V) and possibly certain organoarsenicals. As a result of the suggested research topics the need for more detailed legislation regarding arsenic species will emerge and it is recommended that any legislation should be focused on commodities which have potential to cause health concern.

REFERENCES

1. Cullen, W.R., and Reimer, K.J., *Chem. Rev.*, 1989, **89**, 713.
2. Francesconi, K.A., and Edmonds, J.S., *Oceanogr. Mar.-Biol. Annu. Rev.*, 1993, **31**, 111.
3. Chapman, A.C., and Linden, H., *Analyst*, 1926, **51**, 563.
4. Danish Veterinary and Food Administration. *Danish Fresh Water Fish. Contents of Trace Elements, PCB and Chlorinated Pesticides*. Publication No. 138. Soborg, 1986.
5. National Food Agency of Denmark. *Food Monitoring in Denmark. Nutrients and Contaminants 1983-1987*. Publication No. 195, Soborg, 1990.
6. Farmer, J.G., and Johnson L.R., *Env. Geochem. Health*, 1985, **7**, 124.
7. Larsen, E.H., Moseholm, L., and Møller, M.M., *Sci. Tot. Environm.*, 1992, **126**, 263.
8. Jorhem, L. and Nilsson, K. *Lagring af potatis i impregnerada trälådor*. SLV- rapport nr. 1, 1992. National Food Administration, Uppsala
9. World Health Organisation (WHO). Arsenic. *Environmental Health Criteria 18*. Geneva, 1981.
10. IARC Monographs, 1987, *Suppl. 7*, 100-106.
11. ICPS, International Programme on Chemical Safety, *Dimethylarsinic acid, methanearsonic acid, and salts*. Health and safety guide No. 69, World Health Organisation, Geneva, 1992.
12. Buchet, J.P., Lauwerys, R., and Roels, H., *Int. Arch. of Occup. and Environm. Health*, 1981, **48**, 71.
13. Edmonds, J.S., and Francesconi, K.A., *Mar. Poll. Bull.*, 1993, **26**, 665.
14. Food and Agriculture Organisation (FAO), World Health Organisation (WHO), 1983, *WHO Food Addit. Ser., No. 18*.
15. Food and Agriculture Organisation (FAO), World Health Organisation (WHO), 1989, *WHO Food Addit. Ser., No. 24*.
16. *Toxicological Profile for Arsenic*. U.S. Department of Health And Human Services, Agency for Toxic Substances and Disease Registry, Atlanta, 1991.
17. World Health Organisation (WHO), *Guidelines for drinking water quality*, Geneva, 1993.
18. Uthus, E.O., *Environmental Geochemistry and Health*, 1992, **14**, 55.
19. Department of Health, *Report on Health and Social Subjects*, **41**, London, 1991.
20. Vahter, M., and Marafante, E., *In vivo Methylation and Detoxication of Arsenic*. In: *The Biological Alkylation of Heavy Elements*. Ed.: Craig, P.J., and Glocking, F. Special Publication No. 66, Royal Society of Chemistry, London, 1988, p. 105.
21. United States Environmental Protection Agency, *Special Report on Ingested Inorganic Arsenic. Skin Cancer; Nutritional Essentiality*, EPA-625/3-87-013, Washington D.C., 1988.
22. Larsen, E.H., *Spectrochim. Acta*, 1998, **53B**, 253.
23. Larsen, E.H., Pritzl, G., and Hansen, S.H., *J. Anal. At. Spectrom.*, 1993, **8**, 1075.
24. Ministry of Agriculture, Fisheries and Food, *1994 Total Diet Study: Metals and Other Elements*. Food Surveillance Information Sheet No. 131, London, 1997.
25. Dabeka, R.W., McKenzie, A.D., Lacroix, G.M.A., Cleroux, C., Bowe, S., Graham, R.A., Conacher, H.B.S., and Verder, P., *J. AOAC International*, 1993, **76**, 14.
26. Australian Quarantine and Inspection Service *1994 Diet Survey*, Canberra
27. Tao, S-H, and Bolger, P.M., *Dietary intakes of arsenic in the Unites States*. Third International

Conference on Arsenic Exposure and Health Effects, 1998.

28. Shinichiro, S., Hayase, A., Murakami, M., Hatai, I., Higashigawa, K., Moon, C.S., Zhang, Z.-W., Watanabe, T., Igushi, H., and Ikeda, M., *Fd. Addit. Contamin.*, 1996, **13**, 775.
29. Gezondheidsraad, *Arsenic; Advisory Report Issued by the Committee on Risk Assessment of Substances of Health Council of the Netherlands*, Report No. 1993/02, The Hague, 1993.