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

STATEMENT ON ARSENIC IN FOOD: RESULTS OF THE 1999 TOTAL DIET STUDY.

Introduction

1. The Food Standards Agency (FSA) has recently completed a Total Diet Study (TDS) of total and inorganic arsenic levels in food, which was carried out between 1999 and 2002. The Committee was asked to comment on the survey and assess if the levels of arsenic in the diet posed a risk to human health.

Toxicology of arsenic

2. Arsenic is a metal with complex chemistry that can form a number of inorganic and organic compounds. It can exist in many oxidation states, the most common being the tri- and pentavalent forms. A variety of inorganic arsenic compounds such as arsenates (AsO_4^{3-}, pentavalent arsenic) and arsenites (AsO_3^{3-}, trivalent arsenic) are found in water and at low levels in food.

3. Inorganic arsenic compounds (arsenite and arsenate) are well absorbed by the oral route in humans with absorption values reported to be from 50% to >95% [1]. They are metabolised by methylation and then excreted in the urine with a half-life of 3 to 5 days [1]. Inorganic arsenic is clastogenic in *in vitro* and *in vivo* assays and some evidence suggests clastogenicity in humans [2, 3, 4]. Arsenic in drinking-water (primarily inorganic, as arsenate and to a lesser extent arsenite) was evaluated as "carcinogenic to humans" (Group 1) on the basis of "sufficient evidence" for an increased risk for cancer of the urinary bladder, lung and skin [4]. Increased risks of lung and bladder cancer and of arsenic-associated skin lesions and other skin changes (such as hyperkeratosis and pigmentation changes) have been reported to be associated with ingestion of drinking-water at concentrations from approximately 30 µg arsenic/litre [5]. Chronic exposure to arsenic in drinking water has also been associated with peripheral vascular diseases such as blackfoot disease, cardiovascular diseases and possibly with diabetes and reproductive effects [5].

4. Organic arsenic compounds such as arsenobetaine and arsenocholine are found in fish and shellfish. Most arsenic in fish (>90%) is in the form of

arsenobetaine which is also the main form found in crustaceans and bi-valve molluscs [6], the remainder is arsenocholine and a small amount of inorganic arsenic (usually < 1%). Fish is the main source of arsenic in the diet; arsenobetaine is therefore the main form of arsenic present in food.

5. The fate of organic arsenic has not been clearly defined in experimental animals or in humans. In general organoarsenicals are thought to be less extensively metabolised than inorganic arsenic and more rapidly excreted [5]. Yamauchi *et al.*[7] calculated biological half-lives after administration of organoarsenicals to hamsters, reporting a 6.1 hour half-life for arsenobetaine. In humans, exposure to arsenobetaine through consumption of plaice resulted in 69 to 85% of the arsenobetaine being excreted unchanged in the urine within 5 days[8]. In a study of women volunteers who consumed fish containing arsenobetaine, Lehmann *et al.*[9] observed rapid elimination of the arsenobetaine from blood with a half-life of approximately 7.1 hours during the first 2 to 10 hours following ingestion. Between 10 and 48 hours elimination from the blood was slower with a half-life of approximately 63 hours.

6. There are no data on tissue distribution of arsenic in humans following ingestion of organic arsenic present in fish and seafood. Following intravenous administration of arsenobetaine, the highest tissue concentrations were found in kidney, liver and pancreas of mice and rats [7], and in the liver, kidney, spleen, muscle, skin and brain of rabbits and hamsters [7, 10]. Limited data indicate that organic arsenic compounds such as arsenobetaine and arsenocholine are not converted to inorganic arsenic *in vivo* [5].

7. Despite the limited database, the organic forms of arsenic are generally assumed to be less toxic than the inorganic compounds [1, 11]. There are no adequate studies of toxicity in man or animals from the consumption of organoarsenicals in seafood. In the one toxicity study available, weanling rats were fed diets containing fish, which provided a dose of approximately 3 mg/kg bw/day organic arsenic for 42 days. No treatment-related toxic effects were reported in the limited range of endpoints studied [12]. Limited data indicate that arsenobetaine and arsenocholine are not genotoxic in mammalian cells *in vitro* [5].

Arsenic in fish

8. There does not appear to be any particular type of fish that contains higher levels of arsenic and bio-magnification in aquatic food chains has not been observed [5]. In the last multi-element survey of fish (1998), levels of total arsenic in the most commonly consumed fish (cod, haddock, salmon, tuna) in the UK were in the range of 1.9 mg/kg - 8.4 mg/kg fresh weight, with a mean of 4.6 mg/kg [13].

Previous Evaluations

JECFA

9. In 1983 the Joint FAO/WHO Expert Committee on Food Additives (JECFA) proposed a Provisional Maximum Tolerable Daily Intake (PMTDI) for inorganic arsenic of 2 μg/kg body-weight (bw) per day [14]. JECFA noted the epidemiological evidence of an association between overexposure of humans to inorganic arsenic from drinking-water and an increased cancer risk; 0.2 mg As/L was associated with a 5% increase in the lifetime risk of skin cancer. At that time JECFA also noted that skin cancer did not occur in the absence of other toxic effects of arsenic. The available epidemiological evidence allowed the tentative conclusion that arsenicism could be associated with water supplies containing an upper arsenic concentration of 1 mg/L or greater, and that a concentration of 0.1 mg/L may give rise to presumptive signs of toxicity. The chemical species of arsenic present in the drinking-water were not clearly determined but JECFA concluded it was reasonable to consider them to be inorganic arsenic. Assuming a daily water consumption of 1.5 litres, JECFA concluded that intakes of 1.5 mg/day of inorganic arsenic were likely to result in chronic arsenic toxicity and daily intakes of 0.15 mg may also be toxic in the long term to some individuals. However, the rationale for the PMTDI was unclear.

10. JECFA reviewed its evaluation in 1989, and established a Provisional Tolerable Weekly Intake (PTWI) for inorganic arsenic of 15 μg/kg bw/week based on the previous PMTDI of 2 μg/kg bw/day [11]. JECFA acknowledged that there was a narrow margin between the PTWI and intakes reported to have toxic effects in epidemiological studies, but again did not provide clear justification for the value of the PTWI.

11. In 1989 JECFA also considered organic arsenic present in seafood, and commented that further investigations of the type and levels of organic arsenic compounds naturally occurring in marine products and further animal studies on these specific compounds would be highly desirable [11]. The available data were not sufficient to set a PTWI for organic arsenic. JECFA noted reports of populations who consume large quantities of fish resulting in intakes of organic arsenic of about 50 μg/kg bw/day, with no subsequent reports of ill health effects [11]. However no information was provided on what possible effects were investigated in these fish eating populations, and there have been no specific epidemiological studies to determine if there are any health effects associated with this level of organic arsenic intake.

WHO drinking water guidelines

12. In 1993 the WHO established a provisional guideline value for arsenic in drinking water of 10 μg/L [15], which was described as the 'practical quantification limit'. This concentration was considered to be associated with an estimated excess lifetime skin cancer risk of 6×10^{-4} (or 6 additional cases per 10000 people). WHO noted that a similar value could be derived by

assigning a 20% allocation of the JECFA PTWI to drinking water. The drinking water guideline value is currently under review. The draft text, which is open for consultation, proposes that the guideline value of 10 μg/L should be retained, whilst noting the uncertainty in the risk assessment and the practical difficulties in removing arsenic from drinking water [16].

COT

13. The COT last considered arsenic in food in 1995 when it reviewed the results of the 1991 TDS [17]. The estimated upper bound dietary intake of total arsenic from the 1991 TDS was 0.067 mg/day, approximately 1 μg/kg bw/day in a 70 kg adult. The Committee concluded that "since almost all of the estimated dietary intake of arsenic is expected to consist of organic compounds which are of low toxicity compared to inorganic arsenic compounds, it is unlikely to constitute a hazard to health. We would like, however, to see specific estimates of intakes of inorganic and organic compounds of arsenic, both for the general population and for particular groups with greater than average intakes of arsenic, such as adults consuming relatively large amounts of fish and shellfish."

Contaminated land guideline values

14. In 2001, the Committee endorsed a toxicological approach to setting guideline values for hazardous chemicals in contaminated soil. This approach defines the possibility of establishing an "Index Dose" for a genotoxic carcinogen, based on an accepted exposure standard, such as a drinking water standard. The Index Dose is applied to a single source of contaminant and is defined as a level at which the risk is considered minimal, but there is a requirement that exposure from each individual source should be as low as reasonably practicable. An Index Dose of 0.3 μg/kg bw/day was recommended for inorganic arsenic [1], based on the EU/WHO drinking water guideline of 10 μg/L, assuming consumption of 2L water per day.

The 1999 Total Diet Study (TDS)

15. In response to the previous request of the COT, analysis of samples from the 1999 TDS was carried out to investigate levels of both inorganic and total arsenic in foods. One hundred and nineteen different categories of food were collected from 24 towns throughout the UK and made into 20 composite food groups. The proportion of each food in a food group reflects its importance in the average UK diet (largely based on an average of three years previous consumption data from the National Food Survey).

16. Each of the 24 samples of the 20 food groups were analysed in duplicate for total and inorganic arsenic using both direct nebulisation inductively coupled plasma-mass spectrometry (ICP-MS) and hydride generation ICP-MS for total arsenic, and high resolution ICP-MS for inorganic arsenic. The limits of detection were 0.01mg/kg for inorganic arsenic in all food groups and ranged from 0.0005 to 0.004 mg/kg for total arsenic in

different food groups. Specific organic arsenic compounds were not measured.

Results of the Total Diet Study

17. The full survey results are published in a Food Surveillance Information Sheet [18]. Total arsenic was detected in all samples of the carcass meat, offal, fish and "other vegetables" food groups and in some samples of each the other food groups. In approximately one quarter of all the samples analysed, the concentration of total arsenic was below the limit of detection. The highest levels of total arsenic were found in fish (mean 3214 μg/kg, range 1106-8423 μg/kg), poultry (mean 73.1 μg/kg, range <2.1-167 μg/kg) and the miscellaneous cereals food groups (mean 13 μg/kg, range <2.1-26 μg/kg). The mean total arsenic concentrations in all the other food groups were below 10 μg/kg. These data are similar to those from the 1994 and 1997 TDS [19, 20].

18. Inorganic arsenic was detected in 20 of the 24 fish samples, 10 of the 24 miscellaneous cereals samples and 3 of the 24 poultry samples. The upper bound mean concentrations of inorganic arsenic in fish, poultry and miscellaneous cereals were 15.9, 12.5 and 11.6 μg/kg, respectively. The mean concentration of inorganic arsenic in fish was less than 0.5% of total arsenic. The concentrations of total arsenic in all other food groups were below the limit of detection for inorganic arsenic (i.e. < 10 μg/kg) and therefore inorganic arsenic was not measured because it was assumed that it would not be detectable.

19. Estimates of dietary exposure to arsenic (total and inorganic) for consumers of all age groups (toddlers to elderly) are summarised in Table 1, expressed as a range from lower bound to upper bound. For adult consumers the mean and high level estimates of dietary exposure to total arsenic were 1.3 and 4.4 μg/kg bw/day, respectively. The mean total arsenic level was lower than that of the previous TDS [19] (2.0 μg/kg bw/day), but the 97.5 percentile was the same (4.4 μg/kg bw/day). Intake estimates for children were higher than those for adults, as would be expected from their higher food consumption expressed relative to body weight. Intake data from previous surveys are not available for population groups other than the adults. The data indicate that fish was the major contributor to dietary exposure to total arsenic providing 4.6 μg/kg bw/day for the high level adult consumers of fish.

20. The upper bound estimate of intake of inorganic arsenic was calculated assuming that all the arsenic was inorganic in those food groups where the total arsenic content was below the limit of detection for inorganic arsenic. The upper bound mean estimates of inorganic arsenic intake ranged from 0.07 to 0.2 μg/kg bw/day for different consumer groups, upper bound high level estimates were 0.13 to 0.34 μg/kg bw/day. The miscellaneous cereals food group was the major contributor to inorganic arsenic, providing up to 0.064 μg/kg bw/day for the high level adult consumer.

21. Population mean exposures were calculated using the mean concentrations of arsenic in each food group and the average consumption of each food group based on data from the National Food Survey (NFS) of household food purchases. The upper bound population mean exposure to total arsenic was 0.83 µg/kg bw/day, which is slightly lower than for the 1991, 1994 and 1997 TDS (1.0 –1.1 µg/kg bw/day) [19,20,21]. The upper bound population mean exposure to inorganic arsenic was 0.09 µg/kg bw/day. No previous data are available for dietary exposure to inorganic arsenic.

Table 1: Estimated dietary exposure to arsenic (total and inorganic) for mean and high level consumers.

Survey Population Group	Estimated total dietary exposure to arsenic (mg/kg body-weight/day)			
	Mean		97.5th Percentile	
	Total arsenic [a]	Inorganic arsenic [b]	Total arsenic [a]	Inorganic arsenic [b]
Adults [c]	1.33	0.018 – 0.082	4.37	0.043 – 0.14
Toddlers (1.5 - 4.5 years) [d]	2.43 – 2.46	0.049 – 0.2	11.31 – 11.34	0.11 – 0.34
Young people aged 4-18 [e]	1.60 – 1.61	0.033 – 0.13	6.65 – 6.66	0.076 – 0.25
Elderly (free living) [f]	1.60 – 1.61	0.017 – 0.073	5.33 – 5.34	0.041 – 0.13
Elderly (institutionalised) [f]	1.44 – 1.46	0.022 – 0.089	4.62 – 4.64	0.047 – 0.15
"Vegetarians" [g] (including fish eaters)	1.24 – 1.25	0.019 – 0.071	6.98 – 6.99	0.047 – 0.13

Notes:

a. Exposures to total arsenic have been estimated from the upper and lower bound mean concentrations, which assume non-detectable concentrations were the limit of detection and zero, respectively. Where the difference between the lower bound and upper bound mean concentrations is very small, rounding of the data leads to a single value.

b. The upper end of the range for inorganic arsenic was calculated assuming that all the arsenic was inorganic in food groups where the total arsenic was below the limit of detection for inorganic arsenic. The lower end of the range was calculated using the lower bound mean concentrations of inorganic arsenic in fish, poultry and miscellaneous cereals. For those food groups where the total arsenic level was lower than the limit of detection for inorganic arsenic, it was assumed that none of the arsenic was inorganic.

c. Dietary and Nutritional Surveys of British Adults. (1990) [22]

d. National Diet and Nutrition Surveys Children Aged 11/2-41/2 years. (1995) [23]

e. National Diet and Nutrition Survey: young people aged 4-18 years. (2000) [24]

f. National Diet and Nutrition Survey: People aged 65 years and over. (1998) [25]

g. Vegetarians Dietary Survey: Technical Report on Weighed Intake Diary Data. (1990) (individuals describing themselves as vegetarians, some of whom ate fish):[26]

Arsenic in drinking water

22. A significant proportion of inorganic arsenic intake comes from drinking water. The current statutory limit for arsenic in drinking water is 50 μg/L, although this will be reduced to 10 μg/L in December 2003. Information provided by the Drinking Water Inspectorate for England and Wales (DWI), Department for Environment Northern Ireland (DOENI) and the Drinking Water Quality Regulator for Scotland (DWQRfS) suggests that the level of arsenic in drinking water for the majority of the population in the UK does not exceed the incoming standard of 10 μg/L. A consumption level of 2 L/day is commonly assumed for drinking water, this would contribute up to 20 μg/day or (0.28 μg/kg bw/day for a 70kg adult) to total arsenic exposure. Data available from a 1995 national survey of tap water consumption indicate that children aged 0-5 years consume an average of about 0.5 L/day, which would contribute 0.34 μg/kg bw/day for a 14.5 kg toddler aged 1.5-4.5 years [27]. However, for a significant proportion of the population, arsenic levels in water are considerably lower than the incoming standard of 10 μg/L, therefore exposure from drinking water would be far less.

COT evaluation

23. Having reviewed the previous evaluations of arsenic, the Committee concluded that there are no relevant tolerable intakes or reference doses by which to assess the safety of either inorganic or organic arsenic in the diet. The JECFA PTWI for inorganic arsenic was established in 1989 using an approach that would not now be considered appropriate in view of the evidence of genotoxicity and carcinogenicity. The index dose was proposed as a risk management tool in support of guideline values for hazardous chemicals in contaminated land, and is also not appropriate for evaluation of dietary exposure. The Committee therefore concluded that exposure to inorganic arsenic from all sources should be as low as reasonably practicable (ALARP).

24. Very few data are available on clearance and toxicity in animals and humans of the forms of organic arsenic found in fish. The general assumption that organic arsenic is less toxic than inorganic arsenic is therefore based on an extremely limited database, which is not adequate to establish tolerable intakes.

25. Interpretation of the data is restricted by the limited sensitivity of the analyses, particularly for inorganic arsenic. Nevertheless, the data confirm that fish is the major contributor to arsenic in the diet, and the predominant form of arsenic in fish is organic, most of which is likely to be arsenobetaine. Overall, inorganic arsenic contributed less that 10% of the total dietary exposure to arsenic. Whilst the low analytical sensitivity results in considerable uncertainty in the estimates of dietary exposure to inorganic arsenic, the large number of food samples with inorganic arsenic concentration below the limit of detection appears to be consistent with dietary exposure being ALARP.

26. It has previously been noted that some fish eating populations are exposed to organic arsenic at levels up to 50 μg/kg bw/day and there is no evidence to suggest that these populations suffer ill-effects as a result. In the absence of information on the toxicological properties of organic arsenic in fish, it is not possible to define the nature of potential ill-effects that should be investigated in such populations.

27. The adult consumer and population mean exposures to total arsenic appeared slightly lower than for previous surveys. Although this decrease may be due to refinements in the methodology used to measure total arsenic over the years, it offers reassurance that the level of arsenic in food is not increasing.

Conclusions

28. We *consider* that there are no relevant tolerable intakes or reference doses by which to assess safety of either inorganic or organic arsenic in the diet. Inorganic arsenic is genotoxic and a known human carcinogen. We therefore *conclude* that exposure to inorganic arsenic should be as low as reasonably practicable (ALARP).

29. We *note* the low sensitivity of the method used to measure inorganic arsenic. The large number of food samples with inorganic arsenic concentration below the limit of detection appears to be consistent with dietary exposure being ALARP. However we would welcome any refinements to the methodology that would increase the sensitivity of the analysis.

30. We *note* that fish is the major contributor to dietary exposure to arsenic, and the predominant form of arsenic in fish is organic.

31. We *note* that the general assumption that organic arsenic is less toxic than inorganic arsenic is based on an extremely limited database. However there is no evidence that exposure to organic arsenic through high levels of fish consumption has resulted in harmful effects, which indicates that the dietary exposure to organic arsenic identified in this survey is unlikely to constitute a hazard to health.

32. We *note* that the average population dietary exposure to total arsenic is lower than that estimated for previous years providing reassurance that exposure to total arsenic through food is not increasing. No data are available on trends in dietary exposure to inorganic arsenic.

May 2003
COT/2003/01

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