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DE SÉCURITÉ SANITAIRE
DES ALIMENTS

Maisons-Alfort, 17 April 2009

Opinion[1]

of the French Food Safety Agency on the recommended maximum inorganic arsenic content of laminaria and consumption of these seaweeds in light of their high iodine content

THE DIRECTOR GENERAL

1- CONTEXT OF THE REQUEST

On 5 January 2007, the French Food Safety Agency (AFSSA) received a request from the Directorate General for Competition, Consumer Affairs and Fraud Control (DGCCRF) for an opinion on the maximum recommended inorganic arsenic content of laminaria (kelp) and consumption of these seaweeds given their high iodine content.

2- BACKGROUND AND QUESTIONS

After alerts were issued by the RASFF[2] reporting high levels of arsenic and/or iodine in dried kelp (Kombu: *Laminaria digitata*), the Agency was requested to:

1) re-examine the maximum recommended mineral arsenic content of laminaria intended for human consumption, given that excess inorganic As levels were observed in over 50% of the analysed seaweed samples (*concentrations higher than the maximum mineral As level of 3 mg/kg dry weight recommended by the French High Council for Public Hygiene (CSHPF) in 1997*);

2) assess the risk of consuming kelp as a vegetable, in light of its high iodine content, and examine the possibility of retaining the iodine recommendations relating to consumption and maximum content (6g/kg dry weight) that were published by AFSSA in 2002 and that are not adhered to in practice.

The literature's toxicological data on arsenic and iodine were therefore reviewed in conjunction with: i) a critical analysis of the Toxicological Reference Values (TRVs) that may be used to assess risk and define maximum levels in seaweeds and ii) the 16 May 2007 hearing of the European Research Center for Algae (CEVA).
After consulting with the Scientific Panel on Human Nutrition on 27 and 28 March 2008 and the Scientific Panel on Physical and Chemical Contaminants and Residues on 2 July 2008, AFSSA is issuing the following opinion.

3- ARSENIC'S TOXICITY AFTER CHRONIC ORAL EXPOSURE

3-1 Introduction

Arsenic is a metalloid that is widespread in the Earth's crust and can be found in over 245 minerals. Its average concentration in the soil is approximately 2 mg/kg. There are various forms (organic and inorganic) of arsenic and it has a valence of -3, 0, +3 or +5. Arsenic's speciation determines its behaviour in the environment, its bioavailability and its toxicity.
Rock erosion, soil leaching and oxidation-reduction reactions cause arsenic to be redistributed in the aquatic and atmospheric compartments. Arsenic in the atmosphere comes from natural

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[1] This opinion incorporates the modifications made by the 20 July 2009 Erratum, in the 5th paragraph of Part 7, "Conclusions and Recommendations", on average child and adult exposure to iAs

[2] RASFF: Rapid Alert System for Food and Feed

sources such as volcanic activity and from anthropogenic sources such as the production of arsenic trioxide and the combustion of fossil fuels (coal, petroleum, oil) containing significant levels of arsenic. Arsenic trioxide is used in a wide variety of industrial processes, and arsenic derivatives were previously used in agriculture. This helps explain why it has accumulated in the environment.

3.2 Toxicological-kinetic data after oral exposure

3.2.1 Absorption

Inorganic arsenic (iAs):
In animals and humans, inorganic compounds (arsenates: AsV and arsenites: AsIII) are rapidly absorbed after ingestion. The bioavailability of ingested arsenic varies however according to the food matrix (foods, beverages) and the solubility of the ingested arsenic compounds. Absorption rates ranging from 65% to 90% have been observed with drinking water; however, little information is available about the bioavailability of iAs found in various foods (NRC, 1999).

Organic arsenic (oAs):
In humans, the gastro-intestinal absorption of monomethylarsonic acid (MMA)[3], dimethylarsinic acid (DMA)[1] and arsenobetaine (the main form of organic arsenic found in crustaceans and molluscs) is rapid (IPCS, 2001). However, there are no consolidated data that enable absorption in humans to be quantified.

3.2.2 Distribution

Inorganic arsenic (iAs):
Ingested iAs passes into the blood pool where it binds closely to the plasma proteins and haemoglobin since it has a strong affinity for sulfhydryl groups. It is rapidly eliminated from the blood (its half-life is around one hour). The distribution of iAs in the body is widespread, as it reaches the liver, kidneys, lungs, muscles, skin, skin appendages and bones. Retention is greatest in the hair and nails (0.02 to 1 mg/kg dry weight), skin and lungs (0.01 to 1 mg/kg dry weight). In tissues, arsenic is found primarily in inorganic form and to a lesser extent in the form of DMA. MMA has been detected in the liver and kidneys (NRC, 1999; IPCS, 2001). Inorganic arsenic derivatives cross the placental barrier in animals and humans (NRC, 1999; IPCS, 2001).

Organic arsenic (oAs):
Organic arsenic, like iAs, is rapidly eliminated from the blood pool. Arsenobetaine spreads widely through the soft tissues and is eliminated in the urine in unchanged form within 24 hours. No data are available on any potential crossing of the placental barrier (IPCS, 2001).

3.2.3 Metabolism

Inorganic arsenic (iAs):
In numerous species, iAs metabolism depends on the reduction from pentavalent form to trivalent form, and then on oxidative methylation leading to the formation of organic compounds: MMA and DMA (Cohen *et al.*, 2006).
Methylation takes place mainly in the liver, although most organs are capable of methylating iAs. The enzyme responsible for methylation in humans is not isolated, but in rats, a methyltransferase has been identified that is the counterpart of human CYT-19 (Lin *et al.*, 2002). However, arsenic metabolism varies significantly (quantitatively and qualitatively) among species, as some species such as chimpanzees and guinea pigs have very limited methylation capacities. To date, there are no animal models which can be used to study the metabolism and toxicity of iAs in humans (Vahter M, 2000; Vahter M *et al.*, 1995).

[3] MMA and DMA are products of inorganic Arsenic metabolism in humans

Organic arsenic (oAs):
Arsenic's organic compounds (MMA and DMA) are only minimally transformed in the body (IPCS, 2001). Compounds such as arsenoribosides found in marine organisms are biotransformed into over a dozen metabolites including DMA, dimethylarsinoylethanol and trimethylarsine oxide (Francesconi *et al.*, 2002).
Recent studies on DMA metabolism in animals (US EPA, 2006; Cohen *et al.*, 2006) showed in particular that DMA^{V} is reduced in the form of DMA^{III}, whose toxicity is extremely high for the urinary tract cells (*in vitro* tests: Stylbo *et al.*, 2000). A dose-dependent increase in the quantity of DMA^{III} in urine, secondary to ingestion of DMA^{V}, has been reported in rats (Cohen *et al.*, 2006). Other *in vitro* and *in vivo* observations (Cohen *et al.*, 2001, 2002) show that DMA^{III} is considerably more toxic than DMA^{V} in the cell lines of humans and rodents. In humans, it is probable that DMA^{V} can also be transformed into DMA^{III} (Le *et al.*, 2000).

3.2.4 Elimination

Inorganic arsenic (iAs):
Inorganic arsenic is primarily eliminated through the urine in the form of DMA (55-75%), MMA (10-20%) and iAs (10-30%), with a half-life of around four days. The distribution of excreted forms varies according to genetic factors (low excretion of MMA in some subjects, related to a polymorphism of methyltransferase), the absorbed chemical species of iAs (acute or chronic, low or high), nutritional factors and pathologies. Little iAs is excreted through milk (IPCS, 2001).

Organic arsenic (oAs):
Arsenic's organic compounds (MMA and DMA) are rapidly eliminated in the urine in unchanged form (IPCS, 2001).

3.3 Toxicological studies in animals and humans

*3.3.1- Experimental data (*in vitro *and* in vivo*)*

In animals, adverse effects vary according to arsenic's form and degree of oxidation: it is generally accepted that inorganic derivatives are more toxic than organic derivatives and that derivatives of As III are more toxic than those of As V, at least at high doses. Recent data however suggest that this hypothesis may not be valid (Petrick *et al.*, 2000; Stylbo *et al.*, 2000).

3.3.1.1 Non-carcinogenic effects

According to data from animal experimentation, the target organs of repeated administration of arsenic compounds are the liver and kidneys. Effects have also been observed on the spleen, body weight and various haematological and biochemical parameters. Toxic effects have been reported in rats and mice at doses lower than or equal to 1.5 mg/kg b.w./day, when arsenic is administered in drinking water[4] (growth retardation, reduced litter sizes and histological alterations to the liver, kidneys, spleen and skin) (Byron *et al.*, 1967; Schroeder and Balassa, 1967; Schroeder and Mitchener, 1971; Ishinishi *et al.*, 1980).

3.3.1.2 Effects on development and reproduction

In a three-generational study in mice, slightly smaller litter sizes and modified sex ratios were reported after administration of 1 mg sodium arsenite/kg b.w./day in drinking water (Schroeder and Mitchener, 1971).

Exencephaly and facial anomalies were observed in mice and hamsters after administration of maternotoxic doses of arsenite (40-45 mg/kg in mice, 20-25 mg/kg in hamsters) (Baxley *et al.*, 1981; Hood and Harrison, 1982).

[4] In water, inorganic arsenic is the primary form of As.

Furthermore, oral administration of arsenite during gestation in mice (7.5 to 48 mg/kg b.w.) and rabbits (0.19 to 3 mg/kg b.w.) brings about foetal-toxic effects (spontaneous abortions, reduced foetal weight) at maternotoxic doses.

3.3.1.3 Mutagenicity and experimental carcinogenicity

- ***Mutagenic effects***

Derivatives of inorganic and organic arsenic are genotoxic *in vivo* and *in vitro* (formation of micronuclei, chromosome aberrations, exchanges of sister chromatids *(*Basu *et al.*, 2001)).

Several recent studies (Soriano C *et al.*, 2007; Colognato R *et al.*, 2007; Klein *et al.*, 2007) suggest that methylated forms of arsenic (MMA and DMA) are less genotoxic than inorganic forms and that in general, trivalent forms are more genotoxic than pentavalent forms.

- ***Carcinogenic effects observed in animals***

The carcinogenic effects of arsenic and its derivatives have been tested in rats, mice and dogs after oral exposure. All of these earlier studies were carried out under unsatisfactory experimental conditions (choice of model, protocol, etc.) and their conclusions were both negative and positive. It is generally accepted that no animal model can be used to study the metabolism and toxicity of arsenic for humans (Vahter M, 2000; Vahter M *et al.*, 1995).

However, based on animal carcinogenicity data, the IARC concluded in 2004 that proof was:

- sufficient for dimethylarsinic acid (DMA);
- limited for sodium arsenite, calcium arsenate and arsenic trioxide;
- insufficient for sodium arsenate and arsenic trisulfide.

- ***Carcinogenic mechanisms or mode of action***

The carcinogenic effect could result from an **indirect genotoxic action** involving several mechanisms including interaction with protein sulfhydryl groups, formation of free radicals, glutathione depletion, inhibition of DNA repair, etc. or an alteration of DNA methylation profiles (Kitchin, 2001).

3.3.2 – Effects observed in humans

Numerous epidemiological studies carried out in populations exposed to drinking water from wells contaminated with inorganic As have shown a relationship between ingestion of arsenic and the onset of non-carcinogenic or carcinogenic effects.

3.3.2.1 Non-carcinogenic effects

- Acute oral exposure to high doses (greater than 0.04 mg/kg b.w./day) of inorganic arsenic[4] causes non-specific gastrointestinal disorders (diarrhoea described as arsenic poisoning, causing dehydration and severe hydroelectrolytic disturbances), haematological disorders (anaemia, leukopenia, widespread intravascular coagulation) and neurological disorders (peripheral polyneuropathy sometimes combined with axonal degeneration (Feinglass, 1973; Wagner *et al.*, 1979).

- Skin disorders, in the form of hyperkeratosis combined with hyper- or hypo-pigmentation, have been observed in populations living in regions (southwest Taiwan, northern Chile and Bangladesh) where there are several hundred micrograms of inorganic As per litre of water. The higher the levels of arsenic the population is exposed to, the earlier these cutaneous symptoms appear (after six months to three years if ingesting 0.04 mg/kg/day and after five to fifteen years if ingesting 0.01 mg/kg/day). Such symptoms are a sensitive indicator of exposure.

Cardiovascular effects are associated with chronic ingestion of inorganic arsenic derivatives. These primarily include conduction disturbances and cardiac repolarisation modifications (Joye *et al.*, 1999). Vascular system disorders have mainly been recorded in Taiwan, where blackfoot disease became endemic after the ingestion of drinking water with high arsenic concentrations ranging from 0.014 to 0.065 mg As/kg/day (Albernathy *et al.*, 1989). This disease is characterised by a gradual alteration of the peripheral circulation in the lower extremities, with ulcers, black pigmentation of skin and progressive dry gangrene (Chen *et al.*, 1988; Tseng 1989). This kind of disorder has been observed only in Taiwan. Peripheral vascular disorders have also been observed in other contexts, such as in Chile, in the form of an increased incidence of Raynaud's disease and finger and nail cyanosis in connection with the intake of inorganic arsenic in drinking water (Zaldivar and Guillier, 1977).
As there have been few studies on the links between arsenic exposure and high blood pressure, no definitive conclusion can be drawn (Chen *et al.*, 1985; Rahman *et al.*, 1999).

Numerous studies report the occurrence of haematological disorders such as anaemia and leukopenia following ingestion of inorganic arsenic derivatives (Guha Mazunder, 1992; Lerman and Green, 1980).

A correlation between arsenic exposure and diabetes has been suggested by several studies (Lai *et al.*, 1994; Tsai *et al.*, 1999). However, while such a correlation seems possible given arsenic's effects on gluconeogenesis and the transport of glucose across the membranes, recently published data (Navas-Acien *et al.*, 2006) do not show any causal relationship between arsenic and diabetes.

Liver disease has been reported further to oral intake of inorganic arsenic derivatives. The primary diseases observed have been hepatomegaly and more rarely portal fibrosis (Cowlishaw *et al.*, 1979; Mazumder *et al.*, 1988).
Sensory-motor peripheral neuropathy is a condition that has been described at length in epidemiological studies (Huang *et al.*, 1985; Franzblau and Lilis, 1989).

- Developmental effects (spontaneous abortions, premature births, neonatal and perinatal mortality) have been described in animals at doses causing high maternal toxicity; such effects have not been reported by epidemiological surveys, but since there are methodological weaknesses in the latter, no definitive conclusion can be drawn.

3.3.2.2 Carcinogenic effects

The IARC has classified arsenic and its compounds as proven human carcinogens (Group 1); arsenic is in the United States Environmental Protection Agency's Class A (carcinogenic substance for humans, 1988). Furthermore, the European Union has classified arsenic pentoxide, arsenic trioxide and lead arsenate as Category 1 substances.
Skin, lung, liver and bladder cancers have been observed in subjects exposed to iAs through food/water or air (occupational exposure). Moreover, the various epidemiological studies that have been carried out over the past twenty years or so among contaminated populations in Taiwan, Chile and Argentina have generally agreed that long-term exposure to arsenic in drinking water causes a dose-dependent increase in the incidence of bladder, kidney, skin and lung cancers and of liver, colon and prostate cancers to a lesser extent [Chen *et al.*, 1985, 1986; Wu *et al.*, 1989; Chen and Wang, 1990].
The study undertaken by Tseng *et al.* (1968 and 1977) included 40,421 subjects exposed to extremely high concentrations of As in water (50% of the water samples had As concentrations of between 400 and 700 µg/L) and 7,500 unexposed subjects. This study showed a relationship between exposure to arsenic in water and skin cancer prevalence in the three age ranges it examined: 20-39, 40-59 and over 60 years (weak exposure-risk relationship for arsenic concentrations < 300 µg/L, average for arsenic concentrations between 300 and 600 µg/L and strong for arsenic concentrations > 600 µg/L). No skin cancers were observed in the control group, which was exposed to As concentrations in water that were lower than 17 µg/L.

As for the risk of lung and bladder cancers, epidemiological studies have revealed a dose-response relationship for high exposure levels (> 50 µg/L).

For lower exposure levels (< 50 µg/L), the results are contradictory. Two studies support the increased risk of bladder and lung cancers with a statistically significant exposure-risk relationship (Chiou *et al.*, 2001; Ferreccio *et al.*, 2000) while three others show negative or contradictory results (Bates *et al.*, 1995; Lewis *et al.*, 1999 and Kurttio *et al.*, 1999). It is therefore difficult to quantitatively determine the dose-response relationship for As concentration levels in water < 50 µg/L.

However, two recent studies carried out in the United States showed:

1. no increase in deaths from bladder cancer attributable to arsenic in 2.5 million white males (from 1950 to 1979) for exposure levels ranging from 3 to 60 µg/L in drinking water in 26 North American states. Eighty-two percent of this study's population was exposed to concentrations between 3 and 5 µg/L (Lamm *et al.*, 2004);
2. a similar study undertaken by the US EPA and AWWA (2004) in 11 US states based on data collected between 1950 and 1999 showed no relationship between arsenic concentrations in drinking water (average concentrations were 10 µg/L or more) and the incidence of bladder and lung cancers or deaths related to these cancers.

In each of these studies, the authors do mention the limits of these cancer risk assessments based on mortality data on bladder cancer, which generally is not lethal.

4. Arsenic and Toxicological Reference Values

Based on all of the data that are available on animals and humans, international organisations have proposed various Toxicological Reference Values (TRVs) for non-carcinogenic and carcinogenic effects.

4.1 TRVs and non-carcinogenic effects used for assessing risk

Concerning non-carcinogenic cutaneous effects (hyperpigmentation, keratosis) with possible vascular complications:

- the United States Environmental Protection Agency (US EPA) proposed an RfD[5] of 0.3 µg/kg b.w./day (1993). This TRV was defined by considering the general population's two primary sources of exposure to iAs: water (intended for drinking and food preparation) and food. It was estimated in light of the critical effects (hyperpigmentation, keratosis and blackfoot disease) identified in two epidemiological studies (Tseng, 1977; Tseng *et al.*, 1968 in ATSDR 2000).
Knowing that there were no symptoms in the population that had consumed water with arsenic concentrations of between 1 and 17 µg/L, the US EPA proposed an NOAEL[6] of 9 µg/L (arithmetical mean of arsenic concentrations) for chronic exposure through drinking water. In order to have an NOAEL that would take into account arsenic intake through drinking water and food and specific "local" characteristics, the US EPA developed an exposure scenario, referring to the data published by Abernathy *et al.* in 1989. Water consumption was estimated to be 4.5 L/day for an average individual weighing 55 kg and average daily arsenic intake through food (rice and sweet potatoes) was evaluated to be 0.002 mg. The NOAEL that was calculated as a result was 0.0008 mg/kg/day (0.8 µg/kg/day). The TRV was established using a safety factor of 3 to account for the fact that there are not enough data to exclude the possibility that arsenic may affect reproduction and that there are uncertainties related to variations in the population's susceptibility.

- In 2000, the Agency for Toxic Substances and Disease Registry (ATSDR) proposed an MRL[7] of 0.3 µg/kg b.w./day for chronic oral exposure. This value was established based on the same studies as those used by the US EPA (Tseng 1977; Tseng *et al.*, 1968 in ATSDR 2000), after an uncertainty factor of 3 was applied to account for intra-species variability.
The ATSDR therefore proceeded in the same way as the EPA, but specified that the NOAEL of 0.8 µg/kg/day has a limited scope, because the majority of the population under study is under 20 years old, the incidence of skin lesions increases with age and arsenic concentrations measured in water or estimated in food are unconfirmed.
As far as arsenic intake through food is concerned, an estimate based on food measurements taken in Taiwan between 1993 and 1995 indicates that the quantity of arsenic ingested through food is between 15 and 211 µg/day with an average of 61 µg/day (Schoof *et al.*, 1998), which is significantly higher than the average daily intake identified by the US EPA (see Abernathy *et al.*, 1989).
Such data illustrate the critical importance of selecting an appropriate exposure level to calculate the TRV.

If all of the available studies are taken into consideration, a TRV of 0.3 µg iAs/kg/day can be agreed upon for non-carcinogenic effects based on clearly defined critical effects such as cutaneous hyperpigmentation, keratosis and blackfoot disease.

[5] RfD: Reference Dose

[6] NOAEL: No Observed Adverse Effect Level

[7] MRL: Maximal Risk Level

4.2 TRVs and carcinogenic effects used for assessing risk

As far as carcinogenic effects are concerned, in 1988, the US EPA established a TRV based on the data in the Tseng *et al.* studies published in 1968 and 1977, which examined 40,421 exposed subjects and 7,500 unexposed subjects. To establish this TRV, the US EPA used a multi-stage mathematical model intended to predict skin cancer prevalence according to the dose of iAs ingested through drinking water and acknowledged, lacking precise knowledge of iAs' carcinogenic mechanisms of action, that there is a linear relationship between the ingested dose of iAs and the risk of cancer.
This TRV was expressed in the form of a slope factor of $1.5.10^{-3}$ (µg/kg-day)-1, which gives, for consumption of 2 L/day of water containing 10 µg arsenic/L, an estimated related risk of skin cancer of 6.10^{-4}.
In its June 2004 report[8], AFSSA stated that such an excess cancer risk is significant and that as a result, ingestion of water with an arsenic concentration greater than 10 µg/L is not acceptable.
However, given that:

1. the studies undertaken by Tseng *et al.* are old and were conducted among populations likely to have specific genetic predispositions and nutritional deficiencies;
2. other studies (mentioned in 3.3.2.2) show that the risk level associated with bladder and lung cancers in the American population exposed to water containing no more than 10 µg arsenic/L was estimated to be 12 and 18 per 10,000 respectively for the female population and 23 and 14 per 10,000 for the male population,

it may be useful and relevant to define maximum arsenic levels in drinking water based on risk of lung and bladder cancers rather than the onset of skin cancers.

Based on the studies carried out by Tseng *et al.* and using a conservative calculation (linear no-threshold extrapolation model), the EPA estimated a slope factor of $1.5.10^{-3}$. Using this estimate and acknowledging a skin cancer risk of 1.10^{-4}, we obtain a Virtually Safe Dose (VSD) of 0.05 µg iAs/kg b.w./day.

4.3 Other TRVs

- In 1983, the JECFA[9] proposed a Provisional Tolerable Maximum Daily Intake (PTMDI) of 2 µg/kg b.w./day, which was confirmed in 1988 in the form of a Provisional Tolerable Weekly Intake (PTWI) of 15 µg/kg/week. To establish this PTWI, the JECFA considered that the specific symptoms of arsenic exposure (skin disorders) appear at concentrations in water greater than 1 mg/L (it did not, however, indicate the pivotal studies used). No toxicity is observed for a concentration of 0.1 mg/L. Using a daily intake of 1.5 L per day, the committee set 0.15 mg iAs/day as the dose above which toxicity may appear. Considering that intake through food is negligible in comparison with intake through drinking water and that an average adult weighs 70 kg, the Acceptable Daily Intake (ADI) is estimated to be $2.1\ 10^{-3}$ mg/kg/day. An uncertainty factor of 2 is applied to account for the limitations of epidemiological studies.

- In 2001, the Dutch Institute for Public Health and the Environment (RIVM) proposed an ADI of 1 µg/kg b.w./day for chronic oral exposure to arsenic, emphasising that a consensus had been reached acknowledging that iAs' carcinogenic action is based on a non-genotoxic mechanism of action.
To establish the NOAEL, the RIVM referred to the JECFA's proposals (1983 and 1988), according to which the specific symptoms of arsenic exposure (skin disorders) appear at concentrations in water higher than 1 mg/L.

Knowing, as was already stated in a previous report published by the French Institute for Public Health Surveillance (InVS)[10], that the JECFA's method for establishing the PTWI is very

[8] refer to the arsenic sheet from AFSSA's June 2004 report: "Assessment of the health risks from non-compliance with drinking water parametric values"

[9] Joint FAO/WHO Expert Committee on Food Additives

[10] Chronic exposure to arsenic in water and health risks: Review of epidemiological data, quantitative assessment of health risks in Auvergne, InVS October 2002

concisely described and that the critical effect used is not specified, this TRV was not selected for the risk assessment process.

5. IODINE'S TOXICITY AND TOLERABLE UPPER INTAKE LEVEL

In its 2005 report assessing the nutritional impact of introducing iodine compounds into agri-food products, for adult subjects, AFSSA applied the tolerable upper intake level (UL) of 600 µg/24 hours proposed by the SCF (Scientific Committee on Food, 2002). This level was then calculated based on the ratio of calculated body surface areas specific to each age range (see Table 2).

Table 2. Tolerable upper intake levels for total iodine intake (µg/24 hours) defined by the SCF (2002)

Age (years)	SCF
1-3	200
4-6	250
7-10	300
11-14	450
15-17	500
> 18	600

For information, the tolerable upper intake level for iodine is 1100 µg/24 hours in the United States, Australia and New Zealand, and 1000 µg/24 hours according to the WHO and the WHO/FAO/IAEA expert panel (WHO, 1996).

6. CHARACTERISTICS OF EXPOSURE TO ARSENIC AND IODINE IN THE GENERAL POPULATION

6.1 Exposure to total arsenic and inorganic arsenic[11]

For an individual not occupationally exposed, the primary route of exposure to As is ingestion through food or drinking water.

In water, As is the primary form of As. The pH and oxidation-reduction conditions are two factors that determine iAs chemical form (trivalent or pentavalent). Non-negligible quantities of organic As may also be found in surface water (up to 20% of total As) due to microbial activity. Concentrations of total As are generally lower than 10 µg/L, but can reach high levels in proximity to natural and/or anthropogenic sources of environmental contamination.

In laminaria, the analysis results submitted by the CEVA and the data in the literature show that concentrations of total As can vary from 39 to 116 mg/kg dry matter and concentrations of iAs can range from 0.1 to 3.6 mg/kg dry matter (giving levels that are generally lower than the maximum limit of 3 mg/kg dry matter proposed by the CSHPF).
With the exception of a study carried out specifically in a vegetarian population in 1997 indicating that average seaweed consumption (all types of seaweed combined) can vary from 2.5 to 70 g/day, there are no data currently available on seaweed consumption and more specifically consumption of laminaria (kelp) in the general population. In the absence of such data, seaweed's contribution to total arsenic intake cannot currently be estimated.
In foods, variable proportions of organic and inorganic As are found depending on the food. Seafood and fish have the highest levels of total As. The results of the first Total Diet Study (TDS) reveal average total As levels of 2.237 µg/g fresh weight in fish and 1.93 µg/g in molluscs and crustaceans (Leblanc *et al.*, 2005).

Exposure to total As in France: in the general population and considering all foods with the exception of kelp (Leblanc *et al.*, 2005), adults' exposure to total arsenic has been estimated to be 62 µg/day (P97.5 = 31 µg/kg b.w./week) and for children it has been estimated to be 43

[11] for a review of the food analysis methodology, refer to Appendix 1

µg/day (P97.5 = 42 µg/kg b.w./week) with a significant contribution from seafood and fish (58% in adults and 62% in children) and fruit (15% in adults and 17% in children).
As a measure of comparison, in the southwest region of Taiwan, where exposure to As in water is extremely high, daily ingestion of total As has been estimated to be approximately 1,000 µg/day.

Exposure to iAs: in France, intake of iAs through food was evaluated considering[12] that in meats and dairy products, 75% of the arsenic was inorganic. This figure was 65% in poultry and cereals, 10% in fruit and 5% in vegetables and seafood/fish (Leblanc *et al.*, 2005 and 2006). One hundred percent of the arsenic in beverages was considered as inorganic (US EPA, 2001). It was therefore estimated that, for adults, 10.5 µg of iAs were ingested daily through food and drinking water. For children, this figure was 9 µg iAs (for more details, refer to Appendix 2).

6.2 Exposure to iodine according to age and sex (Source: AFSSA, 2005)

Two French food consumption studies assessed dietary iodine intake:

- the food consumption survey carried out by INSEE (French Institute of Statistics and Economic Research) (1991)
- the INCA (Individual and National Study of Food Consumption) survey (1998-1999).

In the INSEE food consumption survey, the iodine intakes of adults aged 25 to 60 were estimated to be 109 and 89 µg/24 hours respectively in men and women, or 72.6% and 59.3% of the Dietary Reference Intake[13] (DRI). In subjects over 60 years, these figures were 80 and 68 µg/24 hours respectively in men and women, or 53.3% and 45.3% of the DRI.
In the INCA survey on adults' and children's individual food consumption in France (Volatier, 2000), average (± standard deviation) dietary iodine intakes and their distribution (median, 25th and 75th percentiles) are given separately for children, men and women (Table 6). This same Table 6 shows the percentage of subjects in each age range exceeding the upper intake levels.

[12] The percentage of iAs in food is based on WHO's estimates, the results of the TDS study and the CALIPSO study (Study on the dietary consumption of seafood and fish, 2006)

[13] DRI: Dietary Reference Intake = 150 µg Iodine/24 hours for adults

Table 6. Daily iodine intake (average, standard deviation (S.D.), median) according to sex and age (salt iodised at 12.5 µg/g included) and percentage of subjects exceeding the tolerable upper intake level (UL) – (AFSSA, 2005)

Age (years)	*n*	Iodine (µg/24 hours)					
		average	S.D.	25th	median	75th	% > UL
Children							
3	*85*	131.5	59.4	105.7	121.7	142.1	5.9
4-6	*256*	126.6	34.0	106.3	125.8	147.5	1.2
7-9	*252*	131.4	37.9	106.0	130.4	153.5	0.4
Men							
10-14	*216*	143.0	51.9	108.7	132.4	173.7	0.0
15-19	*71*	142.0	44.8	109.3	139.1	176.8	0.0
20-34	*160*	157.0	48.4	121.3	149.3	187.6	0.0
35-44	*146*	146.1	44.0	111.5	143.1	172.4	0.0
45-59	*142*	152.6	54.0	118.8	140.5	171.7	0.0
60-69	*91*	146.8	47.5	113.1	144.2	173.4	0.0
> 70	*62*	132.7	44.4	104.5	126.7	155.0	0.0
Women							
10-14	*209*	126.6	42.0	100.1	123.9	148.2	0.0
15-19	*85*	126.0	44.5	98.1	127.0	151.0	0.0
20-34	*209*	132.3	43.4	100.7	125.2	155.1	0.0
35-44	*136*	136.0	48.7	109.3	127.0	149.8	0.0
45-59	*171*	127.8	41.2	98.3	123.5	148.3	0.0
60-69	*83*	126.7	42.7	93.9	122.8	149.0	0.0
> 70	*84*	124.0	45.0	94.5	110.0	148.1	0.0

These data show that the adult French population is at risk of a slight iodine deficiency, with women being more exposed than men.
In children, requirements are met in all age ranges, but young children run the risk of exceeding the upper limit.

6.3 Impact of laminaria consumption on exposure to iodine and arsenic

6.3.1 Impact of laminaria consumption on iAs intakes

The CSHPF proposed maximum levels (3 mg/kg dry weight) of iAs in laminaria in France (CSHPF, 1997).
In 2002, in response to a request concerning the acceptable iodine content of edible seaweed, AFSSA proposed maintaining special labelling on laminaria (*Laminaria digitata* and *Laminaria saccharina)* stating that their consumption should not exceed 30 mg/day for adults and 15 mg/day for children under 4, and that they should be consumed exclusively in the form of condiments (AFSSA, 2002).
Considering firstly these consumption recommendations and secondly the maximum iAs content of these seaweeds proposed by the CSHPF, intake of iAs through laminaria would be 0.09 µg/day in adults and 0.045 µg/day in children. According to these hypotheses, kelp consumed in the form of condiments do not contribute significantly to iAs exposure (<1%).
However, in light of the information reported by the DGCCRF on possible kelp consumption in the form of vegetables, the impact of consuming these seaweeds on iAs intake should be reconsidered when fresh or dried seaweed are consumed in the form of broths or soups or in extract form in food supplements.

6.3.2 Impact of laminaria consumption on iodine intakes

The CSHPF proposed maximum iodine levels in seaweeds in France (CSHPF, 1999): 5000 mg/kg dry weight for species authorised for human consumption, with the exception of laminaria, for which 6000 mg/kg dry weight are tolerated. This exception was justified since higher iodine concentrations have been observed in laminaria than in other species.

Considering firstly the consumption recommendations proposed in 2002 (AFSSA, 2002), which were 15 mg/day in children and 30 mg/day in adults, when laminaria is consumed in the form of condiments, and secondly the maximum tolerated iodine concentration in laminaria (CSHPF, 1999), the corresponding exposure would be:

- for an adult: 30 mg/day x 6000 mg Iodine/mg = **180 µg/day** (the DRI of iodine for this population is 15 µg/day);
- for a child: 15 mg/day x 6000 mg Iodine = **90 µg/day** (the DRI of iodine for this population is 80 µg/day).

AFSSA's 2005 assessment of daily iodine intakes (see Table 6) shows that average daily iodine intake (excluding seaweed consumption) is approximately 130 µg in children and 150 µg in adult men. Under these conditions, additional iodine intake related to the consumption of laminaria in the form of condiments would mean that the DRIs of iodine in adults and children would be exceeded and would increase the risk of exceeding the upper intake levels for young children (200-300 µg/24 hours for children aged 1 to 10).[14]

According to the data submitted by the DGCCRF in connection with this request, it seems that kelp is also consumed in the form of fresh and dried vegetables. However, no information about consumption levels and habits is available in France. All that is specified is that dried seaweeds are generally packaged in 25 to 200 g sachets, which represents an intake that is 800 to 3,000 times higher than the daily quantity proposed in 2002. Moreover, the iodine content of these seaweeds is extremely variable and can be as high as 8500 mg/kg dry weight.

6.3.3 Impact of technological processes on iodine concentrations in products made from kelp

According to the data submitted by the CEVA, the impact that processing seaweeds has on their iodine content and the bioavailability of this iodine is currently documented.
Drying kelp at 60°C after washing it in freshwater reduces its iodine content by approximately 27% (Ofimer, 2000). The degree to which drying reduces iodine content is confirmed by a study conducted on sun-dried and freshly harvested seaweed (Teas *et al.*, 2004). The average iodine content of seaweeds wilted on sand (*Laminaria pallida)* is 514 mg/kg whereas fresh fronds have concentrations as high as 6570 mg/kg.
In Japan, these deiodination practices (wilting on sand then washing) are traditionally used. As a result, the product marketed by the name of Kombu (dried kelp cut into strips) contains 2500 mg iodine/kg on average (Nisizawa *et al.*, 1987).

Bleaching reduces iodine content by 22% and 41% for *Laminaria saccharina* and *Laminaria digitata* respectively.

Salting seaweed also lowers its iodine content by 33% to 41% according to the seaweed/salt ratio.

Studies undertaken at the CEVA show that the application of various production processes can lead to iodine levels of approximately 1000 mg/kg dry matter. Seaweed's use of iodine, as part of its defence processes, explains that only one part of this compound is labile and can be eliminated through technological treatments.

Considering:

[14] Note that AFSSA considered that the use of kelp (consumed fresh, dried or in extract form in food supplements) is not an appropriate way of correcting moderate iodine deficiencies observed in adults in France. See AFSSA's 16 May 2008 opinion on a request to evaluate a draft order on the use of substances intended for nutritional or physiological purposes and plants and plant preparations in the production of food supplements

that iodine levels in raw materials cannot reflect those in processed seaweeds as they are consumed, and that some processing processes such as washing, canning, brining and cooking can significantly lower seaweed's iodine concentrations,

AFSSA is proposing a maximum threshold of 2000 mg iodine per kg dry matter, regardless of the edible seaweed species considered.

7. CONCLUSIONS AND RECOMMENDATIONS

For arsenic

Considering that the currently available toxicological and particularly cancer-related data on arsenic and its inorganic derivatives (iAs) show that:

- based on the slope factor proposed by the EPA (*conservative calculation based on a linear no-threshold extrapolation model*) and considering a skin cancer risk level of 1.10^{-4}, the Virtually Safe Dose (VSD) is 0.05 µg iAs/kg b.w./day;

- arsenic and its inorganic derivatives do not affect DNA using a direct mechanism of action;

- the epidemiological studies carried out in Taiwan did not reveal an excess risk of skin cancer in the reference populations exposed to 0.5 µg iAs/kg b.w./day through drinking water;

- the recent epidemiological studies carried out in the United States did not reveal an excess risk of lung or bladder cancer in the populations exposed to 0.3 µg iAs/kg b.w./day through drinking water;

- in France, average exposure to iAs is estimated to be 9 µg/day for children (or 0.30 µg/kg b.w./day for a 30 kg child) and 10.5 µg/day for adults (or 0.15 µg/kg b.w./day for a 70 kg adult),

AFSSA considers that:

- average daily dietary intake of iAs is considerably higher than the VSD of 0.05 µg iAs/kg b.w./day taken from the EPA,

- intake of iAs through kelp, consumed in the form of condiments, appears to be negligible in comparison with the estimated contribution of other more common dietary vectors,

- when these seaweeds are consumed in the form of vegetables, the contribution to estimated intake of total As and iAs would need to be reconsidered based on precise food consumption data.

As a result, AFSSA considers that, pending more precise information on edible seaweed consumption, the maximum iAs content of laminaria set at 3 mg/kg dry weight (see CSHPF recommendations from 14 October 1997) can be maintained but must not be exceeded in any case, and recommends monitoring developments in knowledge on the effects of low doses of inorganic arsenic and on organic arsenic's toxicity and particularly its genotoxic and carcinogenic potential.

For iodine

AFSSA considers that:

- the contribution of laminaria (consumed solely in the form of condiments) to the general population's total iodine intake could be non-negligible and possibly even higher than the main contributor, which is milk, and could therefore increase the risk of exceeding the upper intake level in young children;

- from a nutritional point of view, consumption of laminaria (consumed fresh, dried or in extract form in food supplements) is not an appropriate way of correcting minor iodine deficiencies observed in adults in France, given: i) the extreme variability of iodine concentrations in these seaweeds and the fact that they are consumed very occasionally; ii) the variety of forms in which these seaweeds may be consumed in France;

- the technological processes used to process seaweed enable iodine levels to be lowered to 2000 mg iodine/kg dry matter, regardless of the edible seaweed species considered,

As a result, AFSSA considers that the recommendations on kelp consumption in the form of condiments that were established in 2002 with the hypothesis of a maximum iodine level of 6g/kg dry weight cannot be maintained, and recommends that a maximum threshold of 2000 mg iodine per kg dry matter be used for all edible seaweed species.

Furthermore, for both iodine and arsenic

AFSSA recommends that data on seaweed uses in the food industry be collected in order to more accurately estimate the French population's iodine and arsenic intake related to seaweed consumption and, if necessary, to draw up new recommendations on seaweed consumption.

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9. KEYWORDS

Algae, Laminaria, Arsenic, Iodine, Toxicological Reference Value

The Director General of the French
Food Safety Agency

Pascale BRIAND

Appendix 1

Determining levels of arsenic in foods

To date, there is only one method that is the subject of a standard (in the US and Japan) for human consumption. This is the method described in the American Food Chemicals Codex (III), which still appears in version V of the FCC. This method has been used for many years in Japan, a country with one of the world's highest levels of edible seaweed consumption.

When French recommendations on edible seaweed were drawn up in 1989, the CHSPR adopted the FCC's protocol for the analysis of mineral arsenic in seaweed.

Technically, this method is divided into two stages: the first consists in extracting the mineral part of arsenic contained in the sample through distillation in the presence of $FeCl_2$ and HCI. The As^V forms of mineral arsenic are reduced to As^{III}, which when combined with existing As^{III}, form volatile $AsCl_3$ carried into the gaseous phase of distillation. The distillate is recovered and treated by a reducing mixture made from $SnCl_2$ and KI in an acidic environment in order to form the volatile arsine AsH_3 which reacts with a silver diethyldithiocarbamate/pyridine mixture to form a coloured compound. Absorbance of the compound at 525 nm compared to that of the standards makes it possible to determine the quantity of arsenic in the sample.

Keep in mind however that while the method described in the Food Chemicals Codex for the analysis of mineral arsenic is a standard in the US and Japan, there is no standardised method in France or in Europe. However, progress to that end was recently made with the publication in the July 2006 Official Journal (N.151) of a proposed draft standard entitled "Foodstuffs - Determination of trace elements - Determination of inorganic arsenic in seaweed by hydride generation atomic absorption spectrometry (HG AAS)" prEN 15517.

This draft standard is currently in the trial stage pending the method's validation by various national agencies (comparison of results obtained with the new method and those generated by the Food Chemicals Codex method).

This new analysis methodology is based on a mild acid extraction by 0.07M HCI at 37°C, followed by contact - still in an acidic environment - with various reducing agents (iodide then borohydride) to generate AsH_3 gas analysed by atomic absorption spectrometry.

According to the authors, the recommended extraction and analysis conditions make it possible to quantitatively determine, without distinction, the inorganic forms As, As^V et As^{III} and the organic forms monomethylarsonic acid and dimethylarsinic acid.

Arsenic's non-toxic organic compounds such as arsenobetaine, arsenocholine and arseno-sugars do not react to form volatile hydrides and therefore are not quantified.

Appendix 2

VECTORS OF EXPOSURE TO TOTAL ARSENIC AND INORGANIC ARSENIC

Table 1: Contribution of various vectors of arsenic exposure (total and mineral) in adults (µg/day)

	Total As, av.	Total As, P95	Total As, % exp.	Inorg. As, av.	Inorg. As, P95
Bread, packaged toast	0.80	1.99	1.28	0.52	1.30
Breakfast cereals	0.01	0.11	0.02	0.01	0.07
Pasta	0.09	0.25	0.14	0.06	0.16
Rice and semolina	0.08	0.26	0.12	0.05	0.17
Other cereals	0.00	0.00	0.01	0.00	0.00
Sweet breads	0.05	0.22	0.08	0.03	0.14
Biscuits	0.03	0.12	0.04	0.02	0.08
Pastries	0.07	0.26	0.11	0.05	0.17
Milk	0.30	0.88	0.48	0.22	0.66
Ultra-fresh dairy	0.10	0.40	0.16	0.07	0.30
Cheeses	0.06	0.19	0.10	0.05	0.14
Eggs and by-products	0.13	0.52	0.21	0.03	0.13
Butter	0.37	1.37	0.60	0.28	1.03
Oils	0.05	0.16	0.08	0.01	0.04
Meat	0.45	1.29	0.73	0.34	0.97
Poultry and game	0.58	1.90	0.94	0.38	1.23
Offal	0.00	0.04	0.01	0.00	0.03
Cooked meats	0.76	2.14	1.22	0.57	1.60
Fish	30.6	110	49.2	1.53	5.51
Crustaceans and molluscs	7.99	53.2	12.9	0.40	2.66
Vegetables (excl. potatoes)	0.85	2.29	1.37	0.04	0.11
Potatoes and similar species	0.85	2.21	1.37	0.04	0.11
Dried vegetables	0.04	0.21	0.07	0.00	0.01
Fruits	10.4	33.7	16.7	1.04	3.37
Dried fruits and oilseeds	0.38	2.56	0.61	0.04	0.26
Ice creams	0.31	1.57	0.50	0.23	1.18
Chocolate	0.01	0.08	0.02	0.00	0.02
Sugars and by-products	0.33	1.02	0.53	0.08	0.25
Water	0.88	2.63	1.42	0.88	2.63
Soft drinks	1.50	6.13	2.42	1.50	6.13
Alcoholic beverages	0.26	1.23	0.42	0.26	1.23
Coffee	0.99	2.95	1.60	0.99	2.95
Hot beverages	0.18	1.00	0.29	0.18	1.00
Pizzas, quiches, etc.	0.17	0.86	0.28	0.04	0.21
Sandwiches, etc.	0.01	0.10	0.02	0.00	0.02
Soups	0.37	1.47	0.60	0.02	0.07
Dishes with multiple ingredients	1.93	15.3	3.11	0.48	3.82
Starters	0.05	0.23	0.07	0.01	0.06
Desserts	0.05	0.21	0.07	0.01	0.05
Compotes and stewed fruits	0.03	0.14	0.04	0.00	0.01
Condiments and sauces	0.01	0.05	0.02	0.00	0.01
TOTAL	62.1	163	100	10.5	

It is considered that an average adult weighs 70 kg.

Table 2: Contribution of various vectors of arsenic exposure (total and mineral) in children (µg/day)

	Total As, av.	Total As, P95	Total As, % exp.	Inorg. As, av.	Inorg. As, P95
Bread, packaged toast	0.42	1.27	0.98	0.27	0.83
Breakfast cereals	0.06	0.21	0.13	0.04	0.14
Pasta	0.09	0.25	0.21	0.06	0.16
Rice and semolina	0.07	0.23	0.18	0.05	0.15
Other cereals	0.01	0.03	0.01	0.00	0.02
Sweet breads	0.07	0.23	0.15	0.04	0.15
Biscuits	0.06	0.20	0.14	0.04	0.13
Pastries	0.06	0.24	0.13	0.04	0.15
Milk	0.55	1.13	1.28	0.41	0.85
Ultra-fresh dairy	0.10	0.33	0.24	0.08	0.25
Cheeses	0.03	0.11	0.07	0.02	0.08
Eggs and by-products	0.09	0.36	0.20	0.02	0.09
Butter	0.24	0.91	0.56	0.18	0.68
Oils	0.01	0.00	0.02	0.00	0.00
Meat	0.32	0.92	0.74	0.24	0.69
Poultry and game	0.46	1.46	1.08	0.30	0.95
Offal	0.00	0.02	0.01	0.00	0.01
Cooked meats	0.61	1.73	1.43	0.46	1.30
Fish	21.6	73.7	50.6	1.08	3.68
Crustaceans and molluscs	3.34	23.7	7.81	0.17	1.19
Vegetables (excl. potatoes)	0.51	1.38	1.19	0.03	0.07
Potatoes and similar species	0.86	2.11	2.01	0.04	0.11
Dried vegetables	0.03	0.15	0.06	0.00	0.01
Fruits	6.33	19.9	14.8	0.63	1.99
Dried fruits and oilseeds	0.22	1.19	0.51	0.02	0.12
Ice creams	0.44	2.09	1.03	0.33	1.57
Chocolate	0.03	0.16	0.07	0.01	0.04
Sugars and by-products	0.45	1.65	1.04	0.11	0.41
Water	0.75	1.92	1.75	0.75	1.92
Soft drinks	3.06	8.29	7.15	3.06	8.29
Alcoholic beverages	0.00	0.00	0.01	0.00	0.00
Coffee	0.05	0.31	0.11	0.05	0.31
Hot beverages	0.05	0.17	0.11	0.05	0.17
Pizzas, quiches, etc.	0.10	0.55	0.24	0.03	0.14
Sandwiches, etc.	0.02	0.07	0.04	0.00	0.02
Soups	0.18	0.76	0.42	0.01	0.04
Dishes with multiple ingredients	1.35	8.84	3.15	0.34	2.21
Starters	0.03	0.07	0.06	0.01	0.02
Desserts	0.07	0.27	0.16	0.02	0.07
Compotes and stewed fruits	0.03	0.11	0.06	0.00	0.01
Condiments and sauces	0.01	0.04	0.02	0.00	0.01
TOTAL	42.7	102.9	100	8.97	

It is considered that an average child weighs 30 kg.