The Director General

Maisons-Alfort, 25 June 25 2018

OPINION
of the French Agency for Food, Environmental and Occupational Health & Safety

on the risk of excess iodine intake from the consumption of seaweed in foodstuffs[1]

ANSES undertakes independent and pluralistic scientific expert assessments.
ANSES's public health mission involves ensuring environmental, occupational and food safety as well as assessing the potential health risks they may entail.
It also contributes to the protection of the health and welfare of animals, the protection of plant health and the evaluation of the nutritional characteristics of food.

It provides the competent authorities with all necessary information concerning these risks as well as the requisite expertise and scientific and technical support for drafting legislative and statutory provisions and implementing risk management strategies (Article L.1313-1 of the French Public Health Code).

Its opinions are published on its website. This opinion is a translation of the original French version. In the event of any discrepancy or ambiguity the French language text dated 25 June 2018 shall prevail.

ANSES issued an internal request on 28 April 2017 to assess the risk of excess iodine intake from the consumption of seaweed in foodstuffs.

1. BACKGROUND AND PURPOSE OF THE REQUEST

■ Background

The Ministerial Order of 24 June 2014, hereafter referred to as the "Plants" Order, establishes the list of plants, other than fungi, authorised in food supplements as well as the conditions for their use. In 2016, given this new regulatory context, ANSES decided to create a Working Group (WG) on "Plants" whose missions include identifying the plants, listed in Annex I of this Order, potentially posing a risk to human health when consumed for nutritional or physiological purposes, especially in the form of food supplements. In this Order, "plants" are understood to mean whole plants including seaweed and microalgae.

The seaweeds included in the list in Annex I of the "Plants" Order are known as plant species capable of concentrating iodine that can be consumed as foods, condiments, food supplements or food ingredients. In 2005, ANSES assessed the nutritional impact of introducing iodine compounds into food products (AFSSA, 2005). Among other things, this report pointed out that the consumption of seaweed-based food supplements may pose a risk of excess iodine intake. At national level, the Ministerial Order of 9 May 2006, on nutrients that can be used in the manufacture of food supplements, sets a maximum daily intake (MDI) of 150 µg for iodine in food

[1] According to Article 2 of Regulation (EC) No 178/2002, "food" (or "foodstuff") means any substance or product, whether processed, partially processed or unprocessed, intended to be, or reasonably expected to be ingested by humans.

supplements. At European level, EFSA set a tolerable upper intake level (UL) of 600 µg of iodine per day for adults (EFSA, 2006).

The "Plants" Order lists 540 plants including around 30 seaweeds, microalgae (cyanobacteria and microscopic algae, considered as "seaweed" by the public) and halophytes (higher plants from sea areas) that can be used for the formulation of food supplements. Iodine levels in these various organisms can vary considerably and the risk of exceeding the regulatory limits for iodine when consuming them is not negligible.

Given this information and the adverse effects of seaweed consumption reported in the literature, the WG on "Plants" recommended that ANSES issue an internal request to conduct a review of knowledge relating to these products and, if necessary, issue recommendations to protect any at-risk populations that may be identified.

- **Purpose of the request**

ANSES issued an internal request to assess the risk of excess iodine intake from the consumption of seaweed in foodstuffs (foods, fortified foods and food supplements). This risk assessment takes into account iodine-containing seaweed likely to be consumed on the French market.

2. ORGANISATION OF THE EXPERT APPRAISAL

This expert appraisal was carried out in accordance with the French standard NF X 50-110 "Quality in Expertise – General Requirements of Competence for Expert Appraisals (May 2003)".

This expert appraisal falls within the scope of the Expert Committee (CES) on "Human Nutrition". ANSES entrusted the expert appraisal to the Working Group (WG) on "Plants". This WG fulfils part of the missions of the CES on "Human Nutrition", to which it reports, by providing it with specific scientific support in the area of pharmacognosy.

This work relied on the reports of four experts in the WG on "Plants" and on a hearing with an endocrinology professor-thyroid specialist. The methodological and scientific aspects of the work were presented to the CES on 12 January and 9 February 2018. It was adopted by the CES at its meeting on 14 March 2018.

ANSES's nutrivigilance scheme was called on to analyse reports of adverse effects in connection with the consumption of seaweed-based food supplements.

ANSES analyses interests declared by experts before they are appointed and throughout their work in order to prevent risks of conflicts of interest in relation to the points addressed in expert appraisals.

The experts' declarations of interests are made public via the ANSES website (www.anses.fr).

3. ANALYSIS AND CONCLUSIONS OF THE CES

The analysis and conclusions presented below summarise the expert reports of the rapporteurs in the WG on "Plants" and the review undertaken by the CES on "Human Nutrition".

3.1. Review of the physiological functions of iodine

Iodine is a halogen essential for the synthesis of the triiodothyronine (T3) and tetraiodothyronine (T4 or thyroxine) thyroid hormones, which play a key role in cell growth and maturation processes, thermogenesis, carbohydrate and lipid homeostasis, and the transcriptional modulation of protein synthesis. Iodine also plays a crucial role in foetal brain development in the first few months of pregnancy.

3.2. Iodine in food

Iodine can be found in drinking water and in food, primarily in the form of iodide, at highly variable concentrations. Iodide accumulates in marine organisms including seaweed, whereas on sea floors, small amounts of iodine are incorporated by plants and then later ingested by herbivores (Medrano-Macias *et al.,* 2016). In this Opinion, the generic term "iodine" encompasses all of the mineral and organic forms of iodine found in foods.

According to the results of the INCA 3 study (ANSES, 2017), meat, fish and egg (MFE) products account for 22% of iodine intakes in adults (including 9.2% for fish), followed by dairy products (excluding hot beverages), at 20%. The other major vectors of iodine are fruits and vegetables and fruit and vegetable products (12% including 6.9% for soups and broths), cereal products (12% including 6.4% for bread and dried bread products), hot beverages (7.7%) and condiments, herbs, spices and sauces (6.8%). In this study, seaweeds were considered as vegetables, in accordance with the European nomenclature.

According to the CIQUAL data[2] from CEVA[3], seaweed has high and varying iodine contents but a low level of consumption (CEVA, 2011-2013). In dry form, seaweed is the food with the highest average iodine concentration. This market is growing, especially among people on a vegan diet (Le Bras, Lesueur*, et al.,* 2015).

3.3. Dietary reference values for iodine

3.3.1. Adequate intakes

In its Opinion on the development of dietary reference values (ANSES, 2016b), ANSES selected an adequate intake (AI) of 150 µg of iodine per day for adults (aged 18-64). The adequate intake for pregnant and breastfeeding women is 200 µg of iodine per day. It is 90 to 130 µg/day for children depending on the age group (EFSA, 2017).

Table 1. Dietary reference values for iodine in the French population, expressed in µg/day.

Age group or population	*Iodine intake (µg/day)*	*Reference*
1-3 years	90	AI (EFSA, 2017)
4-6 years	90	
7-10 years	90	
11-14 years	120	
15-17 years	130	
Men and women (+18 years)	150	AI (ANSES, 2016b)
Pregnant and breastfeeding women	200	AI (EFSA, 2017)

[2] The French Information Centre on Food Quality (CIQUAL) is part of the ANSES Food Observatory Unit.
[3] Centre for the Study and Promotion of Algae (CEVA)

3.3.2. Tolerable upper intake levels (ULs)

EFSA proposed a tolerable upper intake level (UL) of 600 µg of iodine per day for adults (EFSA, 2006). This is the maximum amount of iodine that is not likely to cause adverse effects when ingested chronically. This maximum level has been adapted to each age group based on differences in body surface areas (Table 2).

Table 2. Tolerable upper intake levels for total iodine (µg/day).

Population	***UL for iodine***
Adults (men, women, pregnant women, breastfeeding women)	600 µg/day
Children	500 µg/day (15-17 years) 450 µg/day (11-14 years) 300 µg/day (7-10 years) 250 µg/day (4-6 years) 200 µg/day (1-3 years)

3.4. Clinical consequences of unsuitable iodine intakes

3.4.1. Inadequate iodine intake

The clinical effects of iodine deficiency are the result of an inadequate iodine intake causing thyroid dysfunction. These disorders can be found in all stages of development and are of particular concern during pregnancy and early childhood. Indeed, the human brain develops from the foetal period until the age of three years. Severe iodine deficiency induces a shortage of thyroid hormones and thus not only a slowing of the body's metabolic activities but also changes in brain development, resulting in irreversible mental retardation (WHO, 2004). Chronic iodine deficiency can also lead to thyroid hypertrophy with an enlarged thyroid gland, commonly referred to as goitre.

In addition, some foods such as those belonging to the *Brassicaceae* family (formerly *Cruciferae*) as well as cassava for example may reduce the incorporation of iodine into the biosynthetic pathway for thyroid hormones (Bruneton, 2016). The degradation products of secondary metabolites in these plants (some glucosinolates and isothiocyanates in *Brassicaceae* and cyanogenic heterosides in cassava) can reduce the bioavailability of iodine (Felker, Bunch, and Leung, 2016). Interactions involving iodine uptake have also been observed in the presence of soya isoflavones (Doerge and Sheehan, 2002).

3.4.2. Excess iodine intake

Cases of acute iodine poisoning, whether accidental or suicidal, are exceptional. Doses of 2 to 3 g of iodine (30-40 mg of iodine/kg bw) can be fatal in humans, even though cases of survival have been reported following the ingestion of 10 to 15 g of iodine (EFSA, 2006). Taking more than 10 mg of iodine per day is toxic for some individuals (WHO, 1988).

A healthy thyroid is capable of adapting to wide variations in iodine intake. Excess iodine in the body blocks further uptake for two or three days (acute Wolff-Chaikoff effect, triggered from 2000 µg/day). If excess iodine intake persists, adverse effects can be observed, such as diarrhoea and headaches, and less commonly dermatitis and even cardiac dysfunction, especially in subjects over the age of 50 (Leung and Braverman, 2012).

A subchronic study undertaken in female Wistar rats exposed by gavage to 7 and 350 mg/kg/day of potassium iodide for 60 days suggests that excess iodine intake (more than 100 times the recommended intake level) may also cause a decline in female fertility (Mahapatra and Chandra, 2017).

Chronic dietary exposure to excess iodine disrupts thyroid gland function, potentially leading to goitre, hypothyroidism or hyperthyroidism (Leung and Braverman, 2014).

Moreover, high iodine intakes are thought to promote the onset and progression of auto-immune thyroid diseases, as suggested by comparisons between populations with moderately high dietary iodine intakes and those with adequate or slightly low iodine intakes (Laurberg *et al.,* 1998).

The consumption of seaweed-based foods or food supplements can also be associated with hyperthyroidism (Müssig, 2009) or hypothyroidism. One of the causes is Hashimoto's thyroiditis, a chronic auto-immune disease ultimately leading to hypothyroidism. Some populations, such as that of Japan, are more affected due to a diet rich in iodine (related to the heavy consumption of raw fish and seaweed in particular). Chronic exposure to dietary iodine has typically been described in populations of Japan and Korea regularly introducing fresh or dried seaweed into their diet (Moon and Kim, 1999). The high prevalence of hypothyroidism in coastal regions of Japan has been associated with excess iodine intakes from the consumption of seaweed (Konno *et al.,* 1994). The risks associated with these high iodine intakes have been taken into account, leading the authorities of the countries concerned to regulate the use of certain iodine-rich products in the food industry or encourage manufacturers to self-regulate their use (Leung and Braverman, 2014).

3.5. Seaweed species considered for human consumption in France

3.5.1. Production and exposure data

The species considered have been identified as living in a marine biotope and are referred to as "seaweed" by the general public (Le Bras *et al.,* 2014). They comprise certain microalgae as well as macroalgae and halophytes. The generic term "seaweed" will be used in this Opinion.

Seaweed is used for a wide range of purposes in chemistry, microbiology and the food industry, which account for 75% of the market for macroalgae (produced and imported). Some seaweed species can be consumed as vegetables or processed (dried, salted, etc.). Since the 1960s, the technological properties of seaweed extracts have primarily been promoted by the food processing sector. Due to their varied rheological behaviours, they are widely used in processed foods as texturising additives. Seaweed-based food additives are not included in exposure data for seaweed. These products are not considered as seaweed-based foodstuffs.

Every year, France produces between 40,000 and 70,000 tonnes of fresh seaweed (14% of European production). In comparison, global production totals 20 million tonnes, of which 95% are produced through seaweed farming in Asia (FAO, 2014). The geographic origin of the seaweed and its production method are seldom included on the product label. Only 1% of French production is intended for human consumption (CEVA, 2014). Worldwide, seaweed intended for direct use in food by humans (as a vegetable) accounts for 20% to 45% of production.

Seaweed consumption is traditional in many Asian countries. In Japan, it is estimated that 1.5 kg to 2.5 kg of dried seaweed are consumed per person and per year (Zava and Zava, 2011). The consumption of edible seaweed is an emerging phenomenon in France and Europe, driven in particular by the growing popularity of Japanese food and the consumption of certain types of sushi. In this context, a national study on the consumption of edible seaweed was undertaken in 825 people across France (Le Bras *et al.,* 2014). The results of this study show that more than half of the population (58%) consumes edible seaweed at least once a year. However, only 20% consume it regularly (at least once a month), including a small proportion of consumers (9%) who have incorporated seaweed into their diet (consuming it at least once a week). A large share of consumers (91%) eat seaweed exclusively in the context of Japanese food. The IDEALG study (Le

Bras *et al.,* 2014) showed that 22% of consumers are not aware of consuming seaweed, especially from the consumption of Asian products.

The main edible seaweeds used for human nutrition in France (Le Bras *et al.,* 2014) are as follows:

- thongweed or sea spaghetti (*Himanthalia elongata*);
- sea lettuce or ulva (*Ulva* spp.);
- dulse (*Palmaria palmata*);
- nori (*Porphyra* spp.);
- wakame (*Undaria pinnatifida*);
- sugar kelp (*Saccharina latissima*, formerly *Laminaria saccharina*).

In France, 12 macroalgae species and one microalgae species have received favourable opinions from the French High Council for Public Health (CSHP, 1997) for use in human food as a vegetable or condiment. Other seaweeds have received favourable opinions from AFSSA and been authorised according to Regulation (EC) No 258/97 (EU, 1997). The other species considered have been taken from the list of plants authorised in food supplements from the Ministerial Order of 24 June 2014, broadened to include the list from the Belfrit project[4] as well as the DGCCRF[5] list of eligible plants under Article 15 of Decree No 2006-352 of 20 March 2006 relating to food supplements[6]. All of the macroalgae, microalgae and halophytes likely to be consumed in France are listed in the following table.

Table 3. List of macroalgae, microalgae and halophytes likely to be consumed in France.

Scientific name	Common name	Seaweed type	Iodine content* (µg/g)				Status**
			min	max	avg	n[7]	
Macroalgae							
Alaria esculenta (L.) Grev.	Dabberlocks	brown	99	1110	346	15	Edible seaweed "Plants" Order
Ascophyllum nodosum (L.) Le Jolis	Knotted wrack	brown	148	1770	682	43	Edible seaweed "Plants" Order
Chondrus crispus Stackhouse	Irish moss, carrageen	red	193	550	346	5	Edible seaweed "Plants" Order
Corallina officinalis L.	-	red	-	-	-	-	Belfrit Art-15
Enteromorpha spp.	Green laver	green	27	251	94	7	Edible seaweed
Fucus serratus L.	Toothed wrack	brown	212	884	400	46	Edible seaweed "Plants" Order
Fucus vesiculosus L.	Bladder wrack	brown					Edible seaweed "Plants" Order
Gelidium corneum (Hudson) J.V.Lamouroux	Agar-agar	red	-	-	-	-	"Plants" Order
G. amansii J.V.Lamouroux	-	red	-	-	-	-	"Plants" Order
G. sesquipedale (Clemente) Thuret	-	red	-	-	-	-	"Plants" Order
Gracilaria gracilis (Stackhouse) Steentoft, L.M. Irvine & Farnham	Ogonori	red	-	-	-	-	"Plants" Order
Gracilaria verrucosa (Hudson) Papenfuss	Gracilaria, ogo, ogonori	red	227	7770	4943	13	Edible seaweed
Himanthalia elongata (L.) S.F.Gray	Thongweed, sea spaghetti	brown	74	248	144	8	Edible seaweed "Plants" Order
Hizikia fusiformis (Harvey) Okamura	-	brown	-	-	-	-	Belfrit
Laminaria digitata (L.) J.V. Lamouroux	Laminaria	brown	1891	10415	4855	42	Edible seaweed "Plants" Order
Laminaria hyperborea (Gunnerus) Foslie	-	brown	-	-	-	-	"Plants" Order

[4] Harmonised list of 1025 plants identified in Belgium, France and Italy as being eligible for use in food supplements.
[5] Directorate General for Competition Policy, Consumer Affairs and Fraud Control.
[6] https://www.economie.gouv.fr/files/files/directions_services/dgccrf/securite/teleicare/Table-Plantes.pdf
[7] "n" is the number of analysed batches.

Laminaria palmata Bory	-	brown	-	-	-	-	Belfrit Art-15
Macrocystis pyrifera (L.) C.Agardh	Kelp	brown	-	-	-	-	"Plants" Order
Mastocarpus stellatus (Stackh.) Guiry	False Irish moss	red	-	-	-	-	"Plants" Order
Padina pavonica (L.) Thivy	-	brown	-	-	-	-	Edible seaweed
Palmaria palmata (L.) F.Weber & D.Mohr	Dulse	red	67	1119	325	17	Edible seaweed "Plants" Order
Phymatolithon calcareum (Pallas) W.H.Adey & D.L.McKibbin ex Woelkering & L.M.Irvine Syn.[8] *Lithothamnium calcareum*	-	red	-	-	-	-	"Plants" Order, Belfrit and Art-15 Edible seaweed
Porphyra dioica J.Brodie & L.M.Irvine	Nori	red	5	215	51	18	Edible seaweed
Porphyra laciniata (Lightfoot) C.Agardh	Nori	red					Edible seaweed
Porphyra leucosticta Thuret	Nori	red					Edible seaweed
Porphyra purpurea (Roth) C.Agardh	Nori	red					Edible seaweed
Poryphora tenera (Kjellman) N.Kikuchi, M.Miyata, M.S.Hwang & H.G.Choi	Nori	red					Edible seaweed
Poryphora umbilicalis Kützing	Nori	red					Edible seaweed "Plants" Order
Poryphora yezoensis (Ueda) M.S.Hwang & H.G.Choi	Nori	red	-	-	-	-	Edible seaweed
Pyropia tenera (Kjellman) N.Kikuchi, M.Miyata, M.S.Hwang & H.G.Choi	Nori	red	-	-	-	-	Belfrit Art-15
Saccharina latissima (L.) C.E.Lane, C.Mayes, Druehl & G.W.Saunders Syn. *Laminaria saccharina*	Sugar kelp, sea belt, Devil's apron	brown	36	6396	3407	37	Edible seaweed "Plants" Order
Saccharina japonica (Areschoug) C.E.Lane, C.Mayes, Druehl & G.W.Saunders Syn. *Laminaria japonica*	Kombu	brown	1828	3140	2359	6	Edible seaweed "Plants" Order
Sargassum fusiforme (Harvey) Setchell	Hijiki	brown	-	-	-	-	"Plants" Order
Ulva lactuca L.	Sea lettuce, ulva	green	70	267	92	34	Edible seaweed "Plants" Order
Undaria pinnatifida (Harvey) Suringar	Wakame	brown	20	1437	191	23	Edible seaweed "Plants" Order
Halophytes							
Crambe maritima L.	Sea kale	halophyte	-	-	-	-	Belfrit
Crithmum maritimum L.	Rock samphire Sea fennel	halophyte	-	-	-	-	"Plants" Order
Salicornia spp.	Glasswort	halophyte	-	-	-	-	Halophytes
Microalgae							
Dunaliella salina (Dunal) Teodoresco	-	microalga	-	-	-	-	"Plants" Order
Haematococcus pluvialis Flotow, syn. *Haematococcus lacustris* (Girod-Chantrans) Rostafinski	-	microalga	-	-	-	-	"Plants" Order
Odontella aurita (Lyngbye) C.Agardh	-	microalga	-	-	-	-	Edible seaweed
Parachlorella kessleri (Fott & Nováková) Krienitz, E.H.Hegewald, Hepperle, V.Huss, T.Rohr & M.Wolf	-	microalga	-	-	-	-	Art-15
Aphanizomenon flos-aquae Ralfs ex Bornet & Flahault	Blue-green Klamath Lake alga, AFA	microalga	-	-	-	-	"Plants" Order

[8] Syn.: corresponds to an obsolete previous name

Auxenochlorella protothecoides (Krüger) Kalina & Puncochárová	-	microalga	-	-	-	-	Art-15
Auxenochlorella pyrenoidosa (H.Chick) Molinari & Calvo-Pérez	-	microalga	-	-	-	-	Art-15
Chlorella vulgaris Beijerinck	Chlorella	microalga	-	-	-	-	"Plants" Order
Chlorella sorokiniana Shihira & R.W.Krauss	-	microalga	-	-	-	-	Art-15
Scenedesmus vacuolatus Shihira & Krauss	-	microalga	-	-	-	-	Art-15
Arthrospira major (Kützing ex Gomont*)* W.B.Crow Syn.: *Spirulina major* Kützing ex Gomont	Spirulina	microalga					Edible seaweed "Plants" Order
Arthrospira maxima Setchell & N.L.Gardner Syn.: *Spirulina maxima* (Setchell & N.L.Gardner) Geitler	Spirulina	microalga	-	-	-	-	Edible seaweed "Plants" Order
Arthrospira fusiformis (Voronikhin) Komarek & J.W.G.Lund*)* Syn.: *Spirulina platensis* (Gomont) Geitler	Spirulina	microalga					Edible seaweed "Plants" Order
Spirulina P.J.F.Turpin ex M.Gomont	Spirulina	microalga					Art-15

* Iodine levels in dehydrated seaweed taken from the nutritional sheets of the CEVA website (dated from 2011 to 2015). Not determined for all seaweed.
** The status of seaweed, microalgae and halophytes:
- edible according to the CEVA, based on the consumption history or on CSHP or ANSES opinions;
- seaweed included in the list of the "Plants" Order, the Belfrit list or the DGCCRF "Article 15" (Art-15) list.

3.5.2. Microalgae

Freshwater, terrestrial and marine microalgae are unicellular organisms belonging to the groups of cyanobacteria and microscopic algae.

Spirulina, whose name refers to the cyanobacteria of the *Arthrospira* (formerly *Spirulina)* genus, is the microalga most commonly used as a food ingredient or supplement due to its consumption history in third countries and its nutritional potential. In France, spirulina is marketed in bulk, as a powder or a food supplement in the form of capsules or tablets (Cornillier, Korsia-Meffre, and Senart, 2008). Since it contains almost no iodine, the risk of excess iodine intake from this microalga seems negligible. Furthermore, aside from the risk of contamination, spirulina does not pose any health risks at the doses usually used (ANSES, 2016a).

Of the other microalgae likely to be consumed in France, only the *Dunaliella salina* species contains iodine. This species can be cultivated in open ponds using seawater (Enzing *et al.,* 2014). However, *Dunaliella salina* is primarily cultivated in bioreactors for the production of biodiesel, xanthophylls and phytosterols. Its consumption through food can therefore be considered negligible (Matos *et al.,* 2017).

3.5.3. Macroalgae

Marine macroalgae are multicellular plant-like organisms. Unlike microalgae, most of these seaweeds are sedentary in nature. They can cover large areas forming fields or forests, often compared to those of the terrestrial system. However, due to a need for light, colonisation of seawater by most macroalgae has a depth limit of around 30 metres. Marine macroalgae vary widely in colour and have a wide variety of biological structures ranging from simple filaments just a few centimetres long to thalli with lengths of several tens of metres (Kornprobst, 2005).

Macroalgae are divided into three groups (phyla) based on their pigmentation: green seaweed (close to the surface), brown seaweed (intermediate depths) and red seaweed (maximum depth of 200 metres).

They are known for their ability to concentrate heavy metals and iodine (Besada *et al.,* 2009). Laminaria are those that concentrate the most iodine. This iodine-concentrating capacity depends on the species, location, farming conditions and development cycle (Teas *et al.,* 2004).

3.5.4. Halophytes

Halophytes are higher plants that grow in salty environments such as coastal soils and saline inland soils. Three species are likely to be consumed in France: *Crambe maritima* (common name: sea kale), *Crithmum maritimum* (common names: sea fennel and rock samphire) and *Salicornia* spp. (common name: glasswort).

3.5.5. Iodine levels in the seaweed in question and regulatory limits

Brown seaweeds are the species that have the highest concentrations of iodine, with levels that can exceed 10,000 µg/g dry weight. In comparison, iodine levels described in red seaweeds are below 1000 µg/g dry weight and those in green seaweeds are below 100 µg/g dry weight (CEVA, 2011-2013). The microalgae and halophytes likely to be consumed have negligible iodine levels.

Given the high iodine levels in seaweed, especially dried seaweed, its consumption can lead to potentially hazardous iodine intakes for the exposed populations (EFSA, 2006). When authorising seaweed in human food, the CSHP set maximum iodine levels of 6000 mg/kg dry weight for laminaria and 5000 mg/kg dry weight for other species. It should be noted that these maximum levels were set assuming the consumption of edible seaweed mainly in condiment form, i.e. for very low exposure levels.

Due to changes in consumption habits and patterns, exposure to seaweed in vegetable form was taken into account to assess the risk of excess iodine intake (AFSSA, 2002). In this context, the maximum level of iodine in seaweed was revised with a threshold value of 2000 mg/kg dry weight only for certain species (AFSSA, 2002). This value was then recommended for all species of edible seaweed (AFSSA, 2009). In comparison, the German legislation has set this threshold at 20 mg of iodine per kg fresh weight in food products, corresponding to around 400 mg of iodine per kg dry weight (BfR, 2004).

It can be noted that the average iodine levels from the nutritional sheets on the CEVA website for *Gracilaria verrucosa*, *Laminaria digitata*, *Laminaria japonica (*syn. *Saccharina japonica*) and *Saccharina latissima* largely exceed the recommended value in France of 2000 mg/kg dry weight. Considering that iodine levels in seaweed, regardless of the species, can vary considerably depending on the production conditions and locations, other seaweed species may have very high levels of iodine. However, these values were likely obtained through analyses of raw materials (raw seaweed), not of products directly intended for consumers.

In Japan, where the consumption of seaweed is high, seaweed "de-iodation" practices (wilting on sand followed by washing) have traditionally been used (Nisizawa *et al.,* 1987). Simple industrial processes such as cooking and brining can also cause significant losses of iodine in processed products, of 20% for frying, 23% for grilling, and 58% for steaming and boiling (WHO, 1988). It is therefore advisable to determine and mention the iodine content for processed products intended for consumers.

These limits on iodine levels take into account its relatively good bioavailability. The intestinal absorption of iodine is considered to be high (> 90%) (EFSA, 2017). The bioavailability of the iodine contained in *Gracilaria verrucosa* (a red seaweed) and *Laminaria hyperborea* (a brown seaweed) was measured in adults. It was significantly higher with *Gracilaria verrucosa* (Aquaron *et al.* 2002). These results show that the bioavailability of iodine depends on the species in question and especially the forms of iodine (organic or inorganic) it contains. When iodine was supplied in the form of a seaweed-based food supplement (containing *Ascophyllum nodosum*), lower bioavailability (33%) was observed than with iodine intake in the form of potassium iodide (59%) in adults (Combet *et al.,* 2014).

3.6. Seaweed in food supplements

3.6.1. Uses of seaweed-based food supplements

The use of food supplements in Europe is regulated by Directive 2002/46/EC[9], transposed into French law by Decree No 2006-352 of 20 March 2006 relating to food supplements, clarified in particular by the Ministerial Order of 9 May 2006, on nutrients that can be used in the manufacture of food supplements, as well as the "Plants" Order.

According to the INCA 3 study (ANSES, 2017), the consumption of food supplements in France was higher than in the period previously assessed: the percentage of French adults reporting that they use them, based on a broader definition including medicinal products that are sources of nutrients (definition used in the INCA studies), had risen from 20% to 29%. In 2015, food supplements for slimming purposes accounted for 10% of sales in France, behind the digestive transit (14%), sleep (14%) and vitality (17%) segments (ANSES, 2017).

Seaweed-based food supplements are positioned in the "digestive transit" and "slimming" segments, which accounted for almost a quarter of food-supplement sales in 2016. Women (35% consumption rate) are more likely to consume these food supplements than men (Synadiet, 2016).

Seaweed-based food supplements are commonly used as adjuvants to weight-loss diets. Seaweed contains large amounts of polysaccharides (such as alginates and carrageenans), which fulfil the definition of dietary fibres. It is used as an appetite suppressant in this context on account of its thickening properties. Only the following generic claims are authorised according to Article 1 of Commission Regulation (EU) No 432/2012:

- Iodine contributes to normal energy-yielding metabolism;
- Iodine contributes to normal cognitive function;
- Iodine contributes to normal functioning of the nervous system;
- Iodine contributes to the maintenance of normal skin;
- Iodine contributes to the normal production of thyroid hormones and normal thyroid function.

3.6.2. Maximum daily intake (MDI)

The Ministerial Order of 9 May 2006 on nutrients that can be used in the manufacture of food supplements sets a maximum daily intake (MDI) of 150 µg for iodine in food supplements.

3.6.3. Current recommendations and restrictions on use

No recommendations or restrictions on use are given in the list of the "Plants" Order for the macroalgae, microalgae and halophytes included. A restriction on use is mentioned in the list of the Belfrit project for the *Fucus serratus* and *Fucus vesiculosus* species: "*Not recommended for people taking anticoagulants*". It is related to platelet aggregation activity demonstrated *in vitro* as well as anti-thrombotic activity demonstrated *in vivo* (Kwak *et al.,* 2010). Considering that these results were observed after an intraperitoneal injection in mice, this restriction does not seem relevant for *Fucus vesiculosus* contained in a food supplement for oral use only.

[9] Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements.

3.7. Seaweed in medicinal products

3.7.1. Traditional uses of seaweed

Traditional plant-based medicinal products benefit from a special simplified marketing authorisation procedure. Decrees Nos 2008-841 and 2008-839 enabled 148 plants listed in the pharmacopoeia to be released from the pharmaceutical monopoly, including some seaweeds included in the "Plants" Order for use in food supplements.

Traditional use as adjuvant therapy for weight-loss diets is mentioned in the notice to manufacturers by the French National Agency for Medicines and Health Products Safety (ANSM) (Cahier de l'agence n°3: Médicaments à base de plantes, 1997), for the dried thallus of *Ascophyllum nodosum*, *Fucus vesiculosus and Fucus serratus*, and by the European Medicines Agency (EMA) for the powdered thallus of *Fucus vesiculosus* (oral route).

Other traditional uses have been identified without being recognised by the health authorities, such as the treatment of constipation, use for healing and gastric-protection properties, and the prevention and treatment of goitre (Mendis and Kim, 2011). Uses for hypolipidaemic, antiplatelet, fibrinolytic, antioxidant and antiviral activity have also been described (Philpott and Bradford, 2006).

3.7.2. Maximum doses and dosages

The ANSM's notice to manufacturers sets a maximum dose of 120 µg of iodine per day (Cahier de l'agence n°3: Médicaments à base de plantes, 1997). The EMA (EMA, 2014b) has set a maximum dose of 400 µg of iodine per day for *Fucus*-based medicinal products (*Fucus* spp.). Currently, only *Fucus* (*Fucus* spp.) is marketed in France in seaweed-based medicinal products.

The EMA Committee on Herbal Medicinal Products (HMPC) has only validated one indication for traditional seaweed-based medicinal products. It involves dried, powdered *Fucus vesiculosus* thallus used as an "adjuvant to reduced calorie diets to help weight loss in overweight adults, after serious conditions have been excluded by a medical doctor" (EMA, 2014b). The corresponding dosage is 260 mg/day for a duration of use that should not exceed 10 weeks without a medical opinion. Given the average level of iodine in *Fucus* (400 µg/g), the doses of iodine corresponding to the indicated dosages are around 100 µg/day.

Furthermore, there is a product currently marketed in France that contains a dry aqueous extract of *Fucus* thallus and is recommended for the short-term treatment of occasional constipation in adults.

Lastly, there are herbal teas containing *Fucus* thallus that are marketed in France (non-bulk) with the indication "traditionally used by adults as an adjuvant to weight-loss diets". The dosage of *Fucus* from these herbal teas is 200 to 900 mg/day.

3.8. The risk of excess iodine intake from the consumption of seaweed

3.8.1. For the general public

Despite the recommendation for a maximum iodine level of 2000 µg/g dry weight in edible seaweed (AFSSA, 2009), there is a risk of exceeding the tolerable upper intake level (UL) set at 600 µg/day (EFSA, 2006). Chronic consumption of 500 mg of dried seaweed per day, within the limit of 2000 µg/g dry weight, would cause the UL set for iodine to be exceeded with the occurrence of side effects. However, this seaweed consumption does not take into account iodine losses of around 20% to 60% related to the final preparation of the seaweed (such as cooking, especially via boiling).

In France, the level of seaweed consumption is currently far below those observed in Asia and, on a closer level, in Norway (Le Bras *et al.,* 2014). According to the INCA 3 study, average iodine intakes in the French population are 148 µg/day for adults (about the same as the AI value), 115.7 µg/day for children aged 0 to 10, and 135 µg/day for adolescents aged 11 to 17 (greater than or approximately equal to the dietary reference values established for children of various ages and adolescents) (ANSES, 2017).

ANSES reiterates that the use of seaweed, consumed fresh or in extract form in food supplements, is not appropriate for correcting the iodine deficiencies observed in France for certain populations, due to the very occasional nature of this consumption and the extremely variable concentrations of iodine in this seaweed (AFSSA, 2008).

The French eating habits observed in the IDEALG study (Le Bras *et al.,* 2014) indicate that the risk of hyperiodemia, from the chronic consumption of seaweed, can be ruled out for the majority of the French population. However, the market for seaweed-based products is steadily growing, with a wide variety of product types (canned food, tartares, condiments, herbal teas, biscuits, beverages, etc.) facilitating current consumption and enabling new consumers to be reached (Le Bras, Ritter*, et al.,* 2015).

Therefore, regular consumers of seaweed-based food products should be advised to favour foodstuffs with low levels of iodine, e.g. brined products or those subject to heat treatment such as canning (cans and jars) (WHO, 1988).

Consumers of seaweed-based food supplements can also be exposed to high quantities of iodine. Indeed, the plant substance is often not clearly defined for seaweed-based food supplements (the scientific name, origin and production method are often missing), nor is the level of iodine in the product. Based on the maximum theoretical iodine level (worst-case scenario) in certain seaweed species, it can be noted that the daily doses recommended by the operator can cause the maximum daily intake, set at 150 µg of iodine per day for food supplements, to be exceeded. In addition, as part of their use as adjuvants to weight-loss diets, these food supplements are often misused, i.e. used on a regular basis at a level that exceeds the recommended dose. If this happens, adverse effects may be observed.

3.8.2. For pregnant women

Iodine supplementation before or during pregnancy remains a recommendation helping to prevent impaired mental development of the newborn (Zimmermann and Delange, 2004). The recommended iodine intake for pregnant women is 200 µg/day (EFSA, 2017). However, for non-deficient women with excess iodine intakes, there is a risk of thyroid disorders for both the mother and newborn (Connelly *et al.,* 2012). Urine concentrations of iodine exceeding 500 µg/l are associated with a high risk of hypothyroidism for the mother. Subclinical disorders have even been observed with values slightly above 250 µg/l (Shi *et al.,* 2015). Moreover, very high iodine intakes (estimated at 1000-1500 µg/day) from seaweed consumption in Japanese pregnant women have been associated with cases of congenital hypothyroidism (Nishiyama *et al.,* 2004).

3.8.3. For infants and breastfeeding women

The dietary reference value for iodine in infants varies depending on the country. The WHO set a value of 15 µg/kg/day for breastfed infants. Iodine concentrations in the breast milk of women with adequate iodine intakes range from 150 to 180 µg/l.

Much higher concentrations have been observed in the milk of women from Korea and Northern China, traditionally consuming high quantities of seaweed, especially in wakame (*Undaria pinnatifida*) soups, with the aim of increasing their milk production. This consumption corresponds to iodine intakes of 1200 to 4000 µg/day and can lead to iodine concentrations in breast milk of 900 to 2200 µg/l (Leung *et al.,* 2012).

Several cases of congenital hypothyroidism have been associated with this practice in Korea (Chung *et al.,* 2009), as well as in the United States and Australia in newborns of women having maintained their food traditions (Emder and Jack, 2011).

3.8.4. For children

Iodine intakes higher than the dietary reference values for children have been associated with cases of hypothyroidism and hyperthyroidism. Such intake levels have been observed following campaigns of iodine supplementation through salt (Delange, de Benoist, and Alnwick, 1999) as well as in children consuming large quantities of seaweed in coastal regions of Japan (Suzuki *et al.,* 1965). The review prepared by Zimmerman in 2013 regarding inadequate and excess iodine intakes in children in 128 countries confirmed the benefits of iodine supplementation in most of the countries. It also pointed out the risks associated with excess iodine intakes, especially from the consumption of seaweed (Zimmermann, 2013).

3.9. Other identified risks

3.9.1. Drug interactions related to iodine

The HMPC assessment report on *Fucus* (EMA, 2014a) states that it has interactions with medications used for thyroid disease (methimazole), as well as with lithium treatments, anticoagulants and medications causing functional kidney failure (diuretics, non-steroidal anti-inflammatory drugs, converting enzyme inhibitors).

Dietary iodine intakes can influence the type of thyroidal adverse effect related to the use of amiodarone. For example, cases of hyperthyroidism have been observed in regions with inadequate intakes, in contrast with hypothyroidism being observed in zones with adequate iodine intakes (Martino *et al.,* 1984).

A low-iodine diet (< 50 µg/day) is recommended by most practitioners for one to three weeks before the administration of radioactive iodine (I^{131}) for a thyroid scan or thyroid removal (Sawka *et al.,* 2010).

Iodinated contrast agents contain between 320 and 370 mg of iodine per ml. Administration of these agents leads to high urine concentrations of iodine (of up to 866 µg/l) (Lee *et al.,* 2015). Urine concentrations of iodine return to normal after one month, but the authors recommend a waiting period of two months before using another iodinated contrast agent.

3.9.2. Non-thyroidal adverse effects of iodine

Cardiovascular effects

Hyperthyroidism induced by excess iodine can have severe clinical manifestations (thyrotoxicosis) with cardiac repercussions (arrhythmia and heart failure). Thus, the consumption of seaweed rich in iodine should be monitored in patients with heart abnormalities (Dunn, Semigran, and Delange, 1998).

Renal effects

A case of acute renal failure was described for a 37-year-old woman exposed to povidone iodine as part of a hysteroscopy (Beji *et al.,* 2006). The article mentions 12 other cases of acute renal failure occurring in patients treated with povidone iodine. Most of them already had chronic renal failure.

3.9.3. Non-thyroidal adverse effects of seaweed

Powdered *Fucus vesiculosus* thallus is contraindicated in the event of hypersensitivity to *Fucus* (EMA, 2014a). Iodine allergy does not exist as a pathophysiological entity. Recent reviews have confirmed that the iodine atom is not responsible for reactions of immediate or delayed hypersensitivity to medicinal products or foods containing iodine (Dewachter and Mouton-Faivre, 2015). In fact, the iodine atom, due to its size, cannot generate the production of specific IgE via an immunological sensitisation mechanism. Immediate hypersensitivity reactions (involving specific IgE) related to the consumption of seaweed have only been observed for spirulina, a particular form of cyanobacteria. The identified molecular allergen in spirulina is phycocyanin, a phycobiliprotein. In the event of a demonstrated allergy, further consumption of spirulina, or of any seaweed/microalgae containing this same allergen or a homologous allergen, is contraindicated.

3.9.4. Seaweed contaminants

Trace metal elements (cadmium, arsenic, mercury, lead and tin), residues of plant protection products, marine toxins and cyanotoxins are contaminants that can be found in seaweed and microalgae (ANSES, 2016a). Seaweed intended for human consumption, like any foodstuff, is regulated by European and national regulations setting a maximum level for each type of contaminant in marketed products. Microbiological criteria are also defined to ensure the safety of edible seaweed.

Edible seaweed must fulfil the criteria given in the following tables (CEVA, 2014).

Table 4. Microbiological criteria for dried seaweed.

Tested bacteria	***Maximum levels (unit/g)***
Mesophilic aerobic bacteria	< 100,000/g
Faecal coliforms	< 10/g
Sulphite-reducing anaerobic bacteria	< 100/g
Staphylococcus aureus	< 100/g
Clostridium perfringens	< 1/g
Salmonella	Absence in 25 g of dried product

Table 5. Maximum levels of trace metal elements and iodine in dried products (seaweed in vegetable or condiment form).

Element	***Maximum level (mg/kg)***
Mineral arsenic	3
Cadmium	0.5
Mercury	0.1
Lead	5
Tin	5
Iodine	2000

As part of a DGCCRF request, ANSES is currently assessing whether to maintain the maximum level for cadmium in edible seaweed at 0.5 mg/kg dry weight, as set in the conclusions of the CSHP[10] in 1988 and 1990.

[10] Conclusions of the French High Council for Public Health, issued during the sessions of 14 June 1988 and 9 January 1990.

In addition, Commission Regulation (EC) No 629/2008, amending Regulation (EC) No 1881/2006 setting maximum levels for certain contaminants in foodstuffs, provides a maximum level for cadmium of 3 mg/kg in food supplements consisting exclusively or mainly of dried seaweed or of products derived from seaweed.

3.10. Vigilance data

3.10.1. Nutrivigilance at the national and international levels

The Australian authorities reported a case of thyroid dysfunction related to the consumption of a soya-based drink containing kombu (*Laminaria japonica*) that had a very high iodine content. This report resulted in it being withdrawn from the market in the United Kingdom, Germany, Spain and Ireland. The product was not available on the French market but the DGCCRF issued a statement warning against possible purchases of this product on the Internet[11].

Between 2009 and 2015, ANSES's Nutrivigilance unit identified 31 reports of adverse effects attributable to food supplements containing marine macroalgae, among other things. These reports mainly involved women between the ages of 30 and 56. Twelve of them were considered sufficiently documented to be analysed for causality. These reported poisoning cases primarily involved the liver (seven hepatitis cases) and kidneys (two cases of acute renal failure). Only one case of thyroid impairment (congenital hypothyroidism) was reported. However, the analysed level of intrinsic causality, as described in the method defined in the ANSES Opinion of 11 May 2011 (ANSES, 2011), only provides for an assessment of the link between the consumption of a product (and not each of its ingredients) and the observed effects.

In Croatia, 44 cases of thyroid disorders have been reported following the consumption of kombu (*Laminaria japonica*). In order to limit excess iodine intakes and the related risks, the Croatian authorities recommend including the following statement on these products: *"Do not consume more than 0.3 g of kombu per day"*.

In Germany, between 2008 and 2017, six cases of adverse effects were reported involving the consumption of food supplements containing seaweed. Four of them were allergic reactions, while the other two respectively involved abdominal pain and an increase in TSH levels. As with the cases identified by ANSES's Nutrivigilance unit, the analysis of these reports showed that these effects could not be attributed exclusively to the presence of seaweed or to the iodine content of the product (which was not precisely known).

In general, when cases of adverse effects related to the consumption of seaweed or seaweed-based food supplements are identified, it is not possible to consider that these reports are attributable – with a fairly high level of probability – to the presence of seaweed or iodine in the consumed product.

3.10.2. Pharmacovigilance

According to the EMA's Assessment Report on *Fucus vesiculosus*, there are "no alarming signals from pharmacovigilance" (EMA, 2014a).

[11] http://invs.santepubliquefrance.fr//display/?doc=presse/2010/communiques/lait_soja_bonsoy/index.html

4. THE CONCLUSIONS OF THE WG ON "PLANTS" AND THE CES ON "HUMAN NUTRITION"

The WG on "Plants" and the CES on "Human Nutrition" identified seaweed species particularly rich in iodine such as the brown kelp *Laminaria* spp. and *Saccharina* spp., and the red algae *Gracilaria verrucosa.* However, the conditions under which the seaweed is produced can cause iodine levels to vary considerably, regardless of the species. Moreover, the type of seaweed-based preparation (powder, extract) used in food supplements as well as the method used to process the ingredient or food can affect iodine levels in foodstuffs.

Therefore, the WG on "Plants" and the CES on "Human Nutrition" conclude that it appears necessary to:

- clearly define the botanical identity of the seaweed as well as its processing method;
- systematically include the level of iodine per daily dose in the product's registration statement, compared to the MDI of 150 µg/day for food supplements. In addition, mentioning iodine levels would be very useful to allow consumers to monitor their total iodine intakes.

Furthermore, the WG and CES advise regular consumers of seaweed-based products to favour products with moderate levels of iodine, in particular brined products or those subject to heat treatment such as canning.

In order to protect at-risk populations, the WG on "Plants" and the CES on "Human Nutrition" consider that foodstuffs containing seaweed should not be consumed by the following groups:

- people with thyroid dysfunction, heart disease or kidney failure, or those taking medication containing iodine or lithium;
- pregnant or breastfeeding women, without seeking medical advice.

Due to a lack of sufficient data to characterise the risks for children, their consumption of seaweed-based products should be monitored.

In addition, it should be noted that the use of seaweed, consumed fresh, dried or in extract form in food supplements, is not appropriate for correcting iodine deficiencies (AFSSA, 2008).

Lastly, the WG on "Plants" and the CES on "Human Nutrition" underline that there is a risk of the tolerable upper intake levels for iodine being exceeded when seaweed is consumed, *a fortiori* in combination with seaweed-based food supplements or iodine-containing medications.

5. AGENCY CONCLUSIONS AND RECOMMENDATIONS

The French Agency for Food, Environmental and Occupational Health & Safety (ANSES) adopts the recommendations of the Working Group on "Plants" and the Expert Committee on "Human Nutrition".

The Agency recommends that consumers should favour supply channels with the best oversight by the public authorities (compliance with French regulations, traceability and identification of the manufacturer) for all seaweed-based foods and food supplements.

Considering the iodine levels in seaweed and the reported adverse effects, ANSES advises against the consumption of foods or food supplements containing seaweed for people with thyroid dysfunction, heart disease or kidney failure, those taking medication containing iodine or lithium, as well as pregnant or breastfeeding women, without seeking medical advice.

Moreover, ANSES reiterates that, as specified in its Opinion of 16 May 2008, the use of seaweed, consumed fresh, dried or in extract form in food supplements, is not appropriate for correcting iodine deficiencies.

Note, however, that since the conditions under which seaweed is produced can cause iodine levels to vary considerably, regardless of the seaweed species in question, a request for information was submitted to the DGCCRF in order to document iodine levels in the food supplements available on the market, as well as the characterisation and safety of the plant preparations used by operators. The results of this investigation will enable the actual level of iodine exposure in populations consuming seaweed-based food supplements to be estimated.

In light of changes in the dietary habits of French consumers, ANSES considers it necessary to undertake an investigation to precisely determine the frequency and patterns of seaweed consumption other than through food supplements. Furthermore, ANSES would also like to obtain results on the determination of iodine levels in seaweed when consumed[12] in addition to information for each seaweed regarding its botanical identity, processing method and preparation method. These data will enable iodine exposure related to the various types of seaweed consumption to be estimated more precisely for the populations concerned. They will also enable the limit value for iodine levels in edible seaweed to be reassessed if necessary.

In conclusion, ANSES reminds healthcare professionals of the need to report to its nutrivigilance scheme any adverse effects likely to be associated with the consumption of food supplements of which they become aware.

Dr Roger Genet

[12] Commission Recommendation (EU) published on 19 March 2018 in the Official Journal of the European Union requests the monitoring of iodine in seaweed-based food supplements in the years 2018, 2019 and 2020.

KEYWORDS

Iode, algues, effets indésirables, compléments alimentaires, nutrition, plantes.

Iodine, algae, seaweed, adverse effects, food supplements, nutrition, plants.

REFERENCES

Afssa. 2002. "Avis de l'Agence française de sécurité sanitaire des aliments relatif à une demande d'évalaution sur la teneur maximale en iode acceptable pour les algues alimentaires faisant suite à un message d'alerte des autorités allemandes concernant le retrait du marché d'algues séchées d'origine chinoises et contenant 4988 et 5655 mg d'iode par kg de poids sec . Saisine n° 2002-SA-0144.".

Afssa. 2005. "Rapport de l'Agence nationale de sécurité sanitaire des aliments relatif à l'évaluation de l'impact nutritionnel de l'introduction de composés iodés dans les produits agroalimentaires."

Afssa. 2008. "Avis de l'Agence française de sécurité sanitaire des aliments relatif à une demande d'évaluation d'un projet d'arrêté relatif à l'emploi de substances à but nutritionnel ou physiologique et de plantes et préparations de plantes dans la fabrication de compléments alimentaires. Saisine n° 2007-SA-0231."

Afssa. 2009. "Avis de l'Agence française de sécurité sanitaire des aliments relatif à la teneur maximale en arsenic inorganique recommandée pour les algues laminaires et aux modalités de consommation de ces algues compte tenu de leur teneur élevée en iode. Saisine n° 2007-SA-0007.".

Anses. 2011. "Avis de l'Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail relatif à la construction d'une méthode d'imputabilité des signalements d'effets indésirables de nutrivigilance. Saisine 2010-SA-0195.".

Anses. 2016a. "Avis de l'Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail relatif aux risques liés à la consommation de compléments alimentaires contenant de la spiruline. Saisine n°2014-SA-0096.".

Anses. 2016b. "Rapport de l'Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail relatif à l'actualisation des repères du PNNS : élaboration des références nutritionnelles. Saisine n° 2012-SA-0103.".

Anses. 2017. "Rapport de l'Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail relatif à l'étude individuelle des consommations alimentaires 3 (INCA 3). Saisine n° 2014-SA-0234.".

Aquaron, R., F. Delange, P. Marchal, V. Lognone, et L. Ninane. 2002. "Bioavailability of seaweed iodine in human beings." *Cell Mol Biol (Noisy-le-grand)* 48 (5):563-9.

Beji, S., H. Kaaroud, F. Ben Moussa, E. Abderrahim, S. Zghidi, F. Ben Hamida, H. Ben Maiz, et A. Kheder. 2006. "[Acute renal failure following mucosal administration of povidone iodine]." *Presse Med* 35 (1 Pt 1):61-3.

Besada, V., J. M. Andrade, F. Shultze, et J. J. Gonzàlez. 2009. "Heavy metals in edible seaweeds commercialised for human consumption." *Journal of Marine Systems* 75 (1-2):305-313.

BfR. 2004. "Health risks linked to high iodine levels in dried algae. BfR Opinion No. 026/2007." *BfR Opinion No. 026/2007*.

Bruneton, J. 2016. "Pharmacognosie. Phytochimie. Plantes médicinales. ." *Lavoisier. Tec & Doc.*

Ceva. 2011-2013. "Centre d'étude et de valorisation des algues : Fiches nutritionnelles des algues alimentaires." *www.ceva.fr*.

Ceva. 2014. "Synthèse du centre d'étude et de valorisation des algues : Réglementation algues alimentaires."

Chung, H. R., C. H. Shin, S. W. Yang, C. W. Choi, et B. I. Kim. 2009. "Subclinical hypothyroidism in Korean preterm infants associated with high levels of iodine in breast milk." *J Clin Endocrinol Metab* 94 (11):4444-7. doi: 10.1210/jc.2009-0632.

Combet, E., Z. F. Ma, F. Cousins, B. Thompson, et M. E. Lean. 2014. "Low-level seaweed supplementation improves iodine status in iodine-insufficient women." *Br J Nutr* 112 (5):753-61. doi: 10.1017/S0007114514001573.

Connelly, K. J., B. A. Boston, E. N. Pearce, D. Sesser, D. Snyder, L. E. Braverman, S. Pino, et S. H. LaFranchi. 2012. "Congenital hypothyroidism caused by excess prenatal maternal iodine ingestion." *J Pediatr* 161 (4):760-2. doi: 10.1016/j.jpeds.2012.05.057.

Cornillier, Y., S. Korsia-Meffre, et S. Senart. 2008. "Les ingrédients de A à Z - Spiruline." Dans *Le guide des compléments alimentaires*, edité par Vidal.

CSHP. 1997. "Avis du Conseil Supérieur d'Hygiène Publique émis lors des séances du 14 juin 1988, du 13 décembre 1988, du 9 janvier 1990 et du 14 octobre 1997 publié dans le Bulletin Officiel du Ministère de la Santé (n°90/45, p. 103), B.I.D n°2/98-030 et BID n° 4/99-079." *Bulletin Officiel du Ministère de la Santé* n°90/45 (B.I.D n°2/98-030):103.

Delange, F., B. de Benoist, et D. Alnwick. 1999. "Risks of iodine-induced hyperthyroidism after correction of iodine deficiency by iodized salt." *Thyroid* 9 (6):545-56. doi: 10.1089/thy.1999.9.545.

Dewachter, P., et C. Mouton-Faivre. 2015. "[Allergy to iodinated drugs and to foods rich in iodine: Iodine is not the allergenic determinant]." *Presse Med* 44 (11):1136-45. doi: 10.1016/j.lpm.2014.12.008.

Doerge, D. R., et D. M. Sheehan. 2002. "Goitrogenic and estrogenic activity of soy isoflavones." *Environ Health Perspect* 110 Suppl 3:349-53.

Dunn, J. T., M. J. Semigran, et F. Delange. 1998. "The prevention and management of iodine-induced hyperthyroidism and its cardiac features." *Thyroid* 8 (1):101-6. doi: 10.1089/thy.1998.8.101.

Efsa. 2006. "Scientific report of European Food Safety Authority : Tolerabble upper intake levels for vitamins and minerals." *Scientific Report*.

Efsa. 2017. "Technical report of European Food Safety Authority : Dietary reference values for nutrients."

EMA, HMPC. 2014a. "European Medicines Agency : Assessment report on Fucus vesiculosus L., thallus." *EMA/HMPC/313675/2012*.

EMA, HMPC. 2014b. "European Medicines Agency : Community herbal monograph on Fucus vesiculosus L., thallus." *EMA/HMPC/313674/2012*.

Emder, P. J., et M. M. Jack. 2011. "Iodine-induced neonatal hypothyroidism secondary to maternal seaweed consumption: a common practice in some Asian cultures to promote breast milk supply." *J Paediatr Child Health* 47 (10):750-2. doi: 10.1111/j.1440-1754.2010.01972.x.

Enzing, C., M. Ploeg, M. C. Barbosa, et L. Sijtsma. 2014. "Microalgae-based products for the food and feed sector: an outlook for Europe. Report EUR 26255 EN." *European Commission. Joint Research Centre. Scientific and Policy reports.* doi: 10.2791/3339.

FAO. 2014. "Food and Agriculture Organization of the United Nations : The state of world Fisheries and Aquaculture. Opportunities and challenges."

Felker, P., R. Bunch, et A. M. Leung. 2016. "Concentrations of thiocyanate and goitrin in human plasma, their precursor concentrations in brassica vegetables, and associated potential risk for hypothyroidism." *Nutr Rev* 74 (4):248-58. doi: 10.1093/nutrit/nuv110.

Konno, N., H. Makita, K. Yuri, N. Iizuka, et K. Kawasaki. 1994. "Association between dietary iodine intake and prevalence of subclinical hypothyroidism in the coastal regions of Japan." *J Clin Endocrinol Metab* 78 (2):393-7. doi: 10.1210/jcem.78.2.8106628.

Kornprobst, J. M. 2005. "Substances naturelles d'origine marine : chimiodiversité, pharmacodiversité, biotechnologies." *Tec & Doc - Lavoisier Les milieux marins.* 2 vol.:246 p.

Kwak, K. W., K. S. Cho, O. J. Hahn, K. H. Lee, B. Y. Lee, J. J. Ko, et K. H. Chung. 2010. "Biological effects of fucoidan isolated from Fucus vesiculosus on thrombosis and vascular cells." *Korean J Hematol* 45 (1):51-7. doi: 10.5045/kjh.2010.45.1.51.

Laurberg, P., K. M. Pedersen, A. Hreidarsson, N. Sigfusson, E. Iversen, et P. R. Knudsen. 1998. "Iodine intake and the pattern of thyroid disorders: a comparative epidemiological study of thyroid abnormalities in the elderly in Iceland and in Jutland, Denmark." *J Clin Endocrinol Metab* 83 (3):765-9. doi: 10.1210/jcem.83.3.4624.

Le Bras, Q., M. Lesueur, S. Lucas, et S. Gouin. 2015. "Etude du marché français des algues alimentaires. Panorama de la distribution. Programme IDEALG Phase 2." *Les publications du Pôle halieutique AGROCAMPUS OUEST n°36, 42 p.*

Le Bras, Q., L. Ritter, D. Fasquel, M. Lesueur, S. Lucas, et S. Gouin. 2014. "Etude de la consommation des algues alimentaires en France. Programme IDEALG Phase 1. Etude nationale." *Les publications du Pôle halieutique AGROCAMPUS OUEST n°35, 72 p.*

Le Bras, Q., L. Ritter, D. Fasquel, M. Lesueur, S. Lucas, et S. Gouin. 2015. "Etude du marché français des algues alimentaires. Catalogue et analyse des produits existants. Programme IDEALG Phase 2." *Les publications du Pôle halieutique AGROCAMPUS OUEST n°37, 41 p.*

Lee, S. Y., D. L. Chang, X. He, E. N. Pearce, L. E. Braverman, et A. M. Leung. 2015. "Urinary iodine excretion and serum thyroid function in adults after iodinated contrast administration." *Thyroid* 25 (5):471-7. doi: 10.1089/thy.2015.0024.

Leung, A. M., et L. E. Braverman. 2012. "Iodine-induced thyroid dysfunction." *Curr Opin Endocrinol Diabetes Obes* 19 (5):414-9. doi: 10.1097/MED.0b013e3283565bb2.

Leung, A. M., et L. E. Braverman. 2014. "Consequences of excess iodine." *Nat Rev Endocrinol* 10 (3):136-42. doi: 10.1038/nrendo.2013.251.

Leung, A. M., L. E. Braverman, X. He, T. Heeren, et E. N. Pearce. 2012. "Breastmilk iodine concentrations following acute dietary iodine intake." *Thyroid* 22 (11):1176-80. doi: 10.1089/thy.2012.0294.

Mahapatra, D., et A. K. Chandra. 2017. "Biphasic action of iodine in excess at different doses on ovary in adult rats." *J Trace Elem Med Biol* 39:210-220. doi: 10.1016/j.jtemb.2016.10.006.

Martino, E., M. Safran, F. Aghini-Lombardi, R. Rajatanavin, M. Lenziardi, M. Fay, A. Pacchiarotti, N. Aronin, E. Macchia, C. Haffajee, et et al. 1984. "Environmental iodine intake and thyroid dysfunction during chronic amiodarone therapy." *Ann Intern Med* 101 (1):28-34.

Matos, J., C. Cardoso, N. M. Bandarra, et C. Afonso. 2017. "Microalgae as healthy ingredients for functional food: a review." *Food Funct* 8 (8):2672-2685. doi: 10.1039/c7fo00409e.

Medrano-Macias, J., P. Leija-Martinez, S. Gonzalez-Morales, A. Juarez-Maldonado, et A. Benavides-Mendoza. 2016. "Use of Iodine to Biofortify and Promote Growth and Stress Tolerance in Crops." *Front Plant Sci* 7:1146. doi: 10.3389/fpls.2016.01146.

Mendis, E., et S. K. Kim. 2011. "Present and future prospects of seaweeds in developing functional foods." *Adv Food Nutr Res* 64:1-15. doi: 10.1016/B978-0-12-387669-0.00001-6.

Moon, S., et J. Kim. 1999. "Iodine content of human milk and dietary iodine intake of Korean lactating mothers." *Int J Food Sci Nutr* 50 (3):165-71.

Müssig, K. 2009. "Iodine-Induced Toxic Effects due to Seaweed Consumption." *Comprehensive Handbook of iodine*:897-908.

Nishiyama, S., T. Mikeda, T. Okada, K. Nakamura, T. Kotani, et A. Hishinuma. 2004. "Transient hypothyroidism or persistent hyperthyrotropinemia in neonates born to mothers with excessive iodine intake." *Thyroid* 14 (12):1077-83. doi: 10.1089/thy.2004.14.1077.

Nisizawa, K., H. Noda, R. Kikuchi, et T. Watanabe. 1987. "The main seaweed foods in Japan." *Hydrobiologia* 151 (1):pp 5-29.
OMS. 1988. "World Health Organization. Toxicological evaluation of certain food additives and contaminants."
OMS. 2004. "Iodine status worldwide. WHO Global Database on Iodine Deficiency. Organisation Mondiale de la Santé (World Health Organization)." *WHO Library Cataloguing-in-Publication Data*.
Philpott, J, et M. Bradford. 2006. "Seaweed: Nature's Secret for a Long and Healthy Life?" *The Nutrition Practitioner*.
Sawka, A. M., I. Ibrahim-Zada, P. Galacgac, R. W. Tsang, J. D. Brierley, S. Ezzat, et D. P. Goldstein. 2010. "Dietary iodine restriction in preparation for radioactive iodine treatment or scanning in well-differentiated thyroid cancer: a systematic review." *Thyroid* 20 (10):1129-38. doi: 10.1089/thy.2010.0055.
Shi, X., C. Han, C. Li, J. Mao, W. Wang, X. Xie, C. Li, B. Xu, T. Meng, J. Du, S. Zhang, Z. Gao, X. Zhang, C. Fan, Z. Shan, et W. Teng. 2015. "Optimal and safe upper limits of iodine intake for early pregnancy in iodine-sufficient regions: a cross-sectional study of 7190 pregnant women in China." *J Clin Endocrinol Metab* 100 (4):1630-8. doi: 10.1210/jc.2014-3704.
Suzuki, H., T. Higuchi, K. Sawa, S. Ohtaki, et Y. Horiuchi. 1965. ""Endemic coast goitre" in Hokkaido, Japan." *Acta Endocrinol (Copenh)* 50 (2):161-76.
Synadiet. 2016. "Chiffres clés 2016 du marché des compléments alimentaires en France.".
Teas, J., S. Pino, A. Critchley, et L. E. Braverman. 2004. "Variability of iodine content in common commercially available edible seaweeds." *Thyroid* 14 (10):836-41. doi: 10.1089/thy.2004.14.836.
UE. 1997. "Règlement (CE) n° 258/97 du Parlement européen et du Conseil du 27 janvier 1997 relatif aux nouveaux aliments et aux nouveaux ingrédients alimentaires."
Zava, T. T., et D. T. Zava. 2011. "Assessment of Japanese iodine intake based on seaweed consumption in Japan: A literature-based analysis." *Thyroid Res* 4:14. doi: 10.1186/1756-6614-4-14.
Zimmermann, M. B. 2013. "Iodine deficiency and excess in children: worldwide status in 2013." *Endocr Pract* 19 (5):839-46. doi: 10.4158/EP13180.RA.
Zimmermann, M., et F. Delange. 2004. "Iodine supplementation of pregnant women in Europe: a review and recommendations." *Eur J Clin Nutr* 58 (7):979-84. doi: 10.1038/sj.ejcn.1601933.

ANNEX 1

Presentation of the participants

PREAMBLE: The expert members of the Expert Committees and Working Groups or designated rapporteurs are all appointed in a personal capacity, *intuitu personae*, and do not represent their parent organisation.

WORKING GROUP ON "PLANTS"

Chairman

Mr Bernard WENIGER – Retired, University Lecturer (Strasbourg University) – Speciality: pharmacognosy

Members

Ms Sabrina BOUTEFNOUCHET – University Lecturer (Paris-Descartes University) – Speciality: pharmacognosy

Mr Pierre CHAMPY – University Professor (Paris-Sud University) – Speciality: pharmacognosy

Ms Hanh DUFAT – University Lecturer (Paris-Descartes University) – Speciality: pharmacognosy

Mr Mohamed HADDAD – Research Manager (IRD, Toulouse - Institute of Research for Development) – Speciality: pharmacognosy

Mr Thierry HENNEBELLE – University Professor (Lille II University) – Speciality: pharmacognosy

Mr Serge MICHALET – University Lecturer (Claude Bernard University, Lyon I) – Speciality: pharmacognosy

Mr Claude MOULIS – Retired, Professor Emeritis – Speciality: pharmacognosy

Ms Céline RIVIERE – University Lecturer (Lille II University) – Speciality: pharmacognosy

Ms Catherine VONTHRON-SENECHEAU – University Lecturer (Strasbourg University) – Speciality: pharmacognosy

RAPPORTEURS

Ms Sabrina BOUTEFNOUCHET – University Lecturer (Paris-Descartes University) – Speciality: pharmacognosy

Ms Hanh DUFAT – University Lecturer (Paris-Descartes University) – Speciality: pharmacognosy

Ms Catherine VONTHRON-SENECHEAU – University Lecturer (Strasbourg University) – Speciality: pharmacognosy

Mr Bernard WENIGER – Retired, University Lecturer (Strasbourg University) – Speciality: pharmacognosy.

EXPERT COMMITTEE

The work that is the subject of this Opinion was monitored and adopted by the following CES:

CES on "Human Nutrition" – 2015-2018

Chairman

Mr François MARIOTTI – Professor (AgroParisTech) – Specialities: metabolism of proteins, amino acids, nutritional requirements and recommendations, postprandial metabolism, cardiometabolic risk

Members

Ms Catherine ATLAN – Doctor (Luxembourg Hospital Centre) – Specialities: endocrinology, metabolic diseases

Ms Catherine BENNETAU-PELISSERO – Professor (Bordeaux Sciences Agro) – Specialities: phyto-oestrogens, isoflavones, endocrine disruptors, bone health

Ms Marie-Christine BOUTRON-RUAULT – Research Director (CESP Inserm) – Specialities: nutritional epidemiology and cancer, digestive system

Mr Jean-Louis BRESSON – University Professor – Hospital Practitioner (AP-HP Necker Hospital – Sick Children, Centre for Clinical Investigation 0901) – Specialities: epidemiology, immunology, infant nutrition, pregnant women and proteins

Mr Olivier BRUYERE – University Professor (University of Liège) – Specialities: epidemiology, public health, osteoporosis

Ms Blandine de LAUZON-GUILLAIN – Research Manager (Inserm, CRESS, Villejuif) – Specialities: epidemiology, infant nutrition, nutrition of pregnant and breastfeeding women, public health

Ms Anne GALINIER – University Lecturer – Hospital Practitioner (Paul Sabatier University – Toulouse University Hospital) – Specialities: metabolism of adipose tissue/obesity, pathophysiology

Mr Jean-François HUNEAU – Professor (AgroParisTech) – Speciality: human nutrition

Ms Emmanuelle KESSE-GUYOT – Research Director (INRA, UMR Inserm U1153 / INRA U1125 / CNAM / University of Paris 13) – Specialities: epidemiology, nutrition and pathologies, nutrition and public health

Ms Corinne MALPUECH-BRUGERE – University Lecturer (University of Auvergne) – Specialities: nutrition of pathologies, metabolism of macro- and micronutrients

Ms Catherine MICHEL – Research Manager (INRA, UMR INRA/University, Nantes) – Specialities: infant nutrition, intestinal microbiota, colic fermentation, prebiotics

Ms Beatrice MORIO-LIONDORE – Research Director (INRA Lyon) – Specialities: human nutrition, energy metabolism

Ms Jara PEREZ-JIMENEZ – Contract Researcher (ICTAN – CSIC, Madrid) – Specialities: micro-constituents, nutrition and pathologies, bioavailability

Mr Sergio POLAKOFF – Research Manager (INRA Clermont-Ferrand/Theix) – Specialities: nutrition and pathologies, nutrition and public health, energy metabolism

Mr Jean-Marie RENAUDIN – Hospital Practitioner (Emilie Durkheim Hospital Centre) – Speciality: allergology

Ms Anne-Sophie ROUSSEAU – University Lecturer (University of Nice Sophia Antipolis) – Specialities: nutrition and physical activity, bioavailability, oxidative stress

Mr Luc TAPPY – University Professor – Hospital Practitioner (University of Lausanne) – Specialities: endocrinology, metabolism of carbohydrates

Mr Stéphane WALRAND – Research Director (INRA Clermont-Ferrand/Theix) – Specialities: pathophysiology, protein metabolism and amino acids

ANSES PARTICIPATION

Scientific coordination

Mr Youssef EL OUADRHIRI – Scientific Coordinator – Risk Assessment Department

Scientific contribution

Ms Irène MARGARITIS – Head of the Nutritional Risk Assessment Unit – Seconded University Professor (University of Nice Sophia Antipolis) – Risk Assessment Department

Mr Aymeric DOPTER – Deputy Head of Unit – Risk Assessment Department

Administrative secretariat

Ms Virginie SADE – Risk Assessment Department

HEARINGS WITH EXTERNAL EXPERTS

Ms Frédérique SAVAGNER – University Professor – Hospital Practitioner (UMR Inserm 1048 Federated Biology Institute - Toulouse University Hospital - Purpan Hospital) - Specialities: hormonology, molecular endocrinology