AGENCE FRANÇAISE
DE SÉCURITÉ SANITAIRE
DES ALIMENTS

Maisons-Alfort, 27 January 2009

OPINION

of the French Food Safety Agency (Afssa) on the assessment of the vitamin and mineral content of fortified foods and food supplements: summary

THE DIRECTOR GENERAL

On 11 September 2007, the French Food Safety Agency (Afssa) received a request from the Directorate General for Health (DGS), Directorate General for Food (DGA) and Directorate General for Competition, Consumer Affairs and Fraud Control (DGCCRF) to assess the vitamin and mineral levels of fortified foods and food supplements in the context of Regulation (EC) No 1925/2006[1] on the addition of vitamins and minerals and certain other substances to foods.

The contents of this opinion are as follows:

1 – REGULATORY AND SCIENTIFIC CONTEXT 2

1.1- REGULATORY CONTEXT 2
1.2- SCIENTIFIC CONTEXT 3

2 – APPROACH TO ASSESS THE VITAMIN AND MINERAL LEVELS OF FORTIFIED FOODS AND FOOD SUPPLEMENTS 4

3- ESTIMATION OF VITAMIN AND MINERAL INTAKE FROM BASE DIET AND FOOD SUPPLEMENTS IN FRANCE 6

3.1- VITAMIN AND MINERAL INTAKE FROM BASE DIET DEPENDING ON THE CONSUMPTION OF FOOD SUPPLEMENTS 6
3.2- VITAMIN AND MINERAL INTAKE FROM FOOD SUPPLEMENTS 7

4- CASES 1 AND 1B: ASSESSMENT OF THE MAXIMUM VITAMIN AND MINERAL FORTIFICATION LEVEL BY SIMULATION WHEN A EUROPEAN OR FRENCH TOLERABLE UPPER INTAKE LEVEL HAS BEEN SET 9

4.1- METHOD: CALCULATING NUTRITIONAL INTAKES BY SIMULATION (AFSSA, 2008D) 9
4.2- CASE 1A: ASSESSMENT OF THE MAXIMUM VITAMIN AND MINERAL FORTIFICATION LEVEL BASED ON THE TOLERABLE UPPER INTAKE LEVEL SET BY EFSA AND DIETARY INTAKE DATA 10
4.3- CASE 1B: ASSESSMENT OF THE MAXIMUM VITAMIN AND MINERAL FORTIFICATION LEVEL BASED ON DIETARY INTAKE DATA AND THE FRENCH TOLERABLE UPPER INTAKE LEVEL 13

5- CASES 2, 3, 4 AND 5: ASSESSMENT OF THE MAXIMUM VITAMIN AND MINERAL FORTIFICATION LEVEL BASED ON ALL THE OPINIONS CONCERNING THESE MICRONUTRIENTS, ISSUED BY AFSSA AND OTHER EUROPEAN BODIES 16

5.1- CASE 2: ASSESSMENT OF THE MAXIMUM VITAMIN AND MINERAL FORTIFICATION LEVEL FOR WHICH INTAKE DATA EXIST 16
5.2- CASE 3: MAXIMUM VITAMIN AND MINERAL FORTIFICATION LEVEL FOR WHICH A TOLERABLE UPPER INTAKE LEVEL HAS BEEN SET – INCA2 FINDINGS DO NOT PROVIDE ANY INTAKE DATA 17
5.3- CASE 4: ASSESSMENT OF THE MAXIMUM VITAMIN AND MINERAL FORTIFICATION LEVEL FOR WHICH NEITHER A TOLERABLE UPPER INTAKE LEVEL NOR INTAKE DATA EXIST 18
5.4- CASE 5: INFORMATION ON NUTRIENTS NOT IN ANNEX 1 OF DIRECTIVE 90/496 19

6- SUMMARY OF THE RECOMMENDED MAXIMUM FORTIFICATION LEVELS AND MAXIMUM DAILY DOSES IN FOOD SUPPLEMENTS 23

7- ANNEXES 25

8- BIBLIOGRAPHY 31

27-31, avenue
du Général Leclerc
94701
Maisons-Alfort cedex
Tel 01 49 77 13 50
Fax 01 49 77 26 13
www.afssa.fr

FRENCH
REPUBLIC

[1] Regulation (EC) No 1925/2006 of the European Parliament and of the Council of 20 December 2006 on the addition of vitamins, minerals and of certain other substances to foods. JO L 40 of 30.12.2006 :26.38.

1 – Regulatory and scientific context

1.1- Regulatory context

European Regulation (EC) No 1925/2006 on the addition of vitamins and minerals to foods came into force on 1 July 2007. It sought to set a harmonised Community basis for such practices to guarantee consumer safety and the free movement of goods. This Regulation defines the objectives, scope and conditions for adding vitamins and minerals and gives a list of substances that may be added to foods. The Commission is expected to recommend maximum fortification levels by 19 January 2009 at the latest. The Regulation also indicates that the minimum levels of vitamins and minerals in fortified foods must be the same as the significant levels required for such nutrients to be mentioned in nutrition labelling (Directive 90/496/EEC).

The maximum amounts must be based on:

- upper safe levels of vitamins and minerals established by scientific risk assessment based on generally acceptable scientific data, taking into account, as appropriate, the varying degrees of sensitivity of different groups of consumers ;
- intakes of vitamins and minerals from other dietary sources.

Moreover, one of the objectives of this Regulation (mentioned in article 3, 2b) is to improve the nutritional status of the population or specific population groups and/or correct possible deficiencies in dietary intakes of vitamins or minerals due to changes in dietary habits. This involves taking account of the population reference intakes.
Although the term “reference intakes” is not defined explicitly, it refers to the dietary reference values (DRVs) defined in the document put forward for public consultation by the European Food Safety Authority (EFSA). EFSA was unable to set ULs for each vitamin and mineral, since the data currently available only permitted this for 13 of the 34 nutrients considered here (vitamins A, D, E, B_3, B_6 and B_9, calcium, copper, iodine, zinc, selenium, molybdenum and fluoride). No findings are able to determine any nutritional benefit in exceeding the ANCs[2].

As a result, Afssa believes that it is neither appropriate in scientific terms nor consistent with the Regulation to take only the UL into account to the detriment of the ANCs.

It is important to remember that, until French Decree no. 2006-1264 and European Regulation No 1925/2006 came into force, the national regulations for fortification authorised the use of certain nutrients only in certain common foods in France, for instance:

- iodine and fluoride in table salt (Order of 28 May 1997, repealed by the Order of 24 April 2007 following Afssa’s opinion of 31 May 2006);
- goat’s milk fortified with folic acid (Order of 8 June 2000 based on the opinions of the French High Council for Public Hygiene (CSHPF) of 14 April 1998 and 11 May 1999);
- vitamin D in milk and chilled dairy products (Order of 11 October 2001 based on Afssa’s opinion of 1 June 2001);
- vitamin D_3 in vegetable oils (Order of 8 October 2004, based on Afssa’s opinions of 3 August 2001 and 15 June 2002);
- calcium in soybean-based products (Order of 8 October 2004, following several Afssa opinions, an the opinion of 22 March 2004 in particular).

[2] “Apports nutritionnels conseillés” are the French equivalent of the Population Reference Intakes (PRI)

1.2- Scientific context

In 2000, the DGCCRF asked Afssa to assess (request no. 2000-SA-0239) concerning a preliminary draft directive on the voluntary addition of vitamins and minerals to common foods. This request led to the publication of two complementary reports by Afssa:

- *the report on meeting the nutritional and safety needs of the consumer (2001):*

  This report recommended a method for obtaining optimum fortification levels which takes account not only of consumer safety but also of the nutritional benefit of fortification. The general approach comprises three main stages: (i) the study of the nutritional benefit (defined in relation to a potential deficiency), as well as of the risks incurred by fortification with a given vitamin or mineral , (ii) the list of micronutrients likely to be added in foods, based on a comparative analysis of the results of a simulation work carried out by the Observatory of Food Consumption of Afssa and a study by the International Life Science Institute (ILSI) and lastly (iii) the setting of the optimum fortification level (risk/benefit ratio study) and of the nutritional coherence between the nutrient incorporated and the food vector.

  Several optimum levels were put forward by this approach, based on the proportion of enriched foods consumed, the objective being that the highest consumers of the nutrient in question (> 95th percentile) not to exceed the tolerable upper intake levels and that the lowest micronutrient consumers (< 10th percentile) attain or approach the recommended daily allowances (RDAs) through fortification.

  The report highlighted the importance of balanced diet and a proper nutrient balance because of possible metabolic synergies between nutrients. It should also be noted that the food fortification vector must meet the nutritional requirements of the populations at risk of deficiency.

- *the report laying down the specification for the selection of a Nutrient-Vector Food pair (2004b):*

  This report defined a series of criteria to be met for nutrient-food couples, in a fortified product marketing context. These conditions concern both the incorporated nutrients and the food vectors.

  The report recommended a method for checking the two fortification requirements, namely the nutritional benefit of fortification and absence of risk for all fortified food consumers. There are three steps to checking the appropriateness of the nutrient-food vector couple: (i) identification of at-risk populations for each nutrient, (ii) assessment of the food vector choice and (iii) setting of the fortification level making it possible to take into account the safety and utility of fortification for a given nutrient-food vector couple.

  Based on the conditions laid down, only nutrients that are not consumed in high quantities in the base diet (nutrients for which the97.5th percentile of population intake does not already reach or exceed the ULs) can be added to foods. The approach taken therefore sought a nutritional benefit. Fortification must either help to correct a deficiency or inadequate intake or have a beneficial effect on health. Accordingly, it is also indicated that the manufacturer must identify the group(s) at risk of inadequate intake. These groups were identified by estimating the “prevalence of inadequate intake", based on the proportion of people with lower intakes than the estimated average requirements (EAR = 0.77ANC). “A group is defined as being at risk of inadequate intake if the 95% confidence interval of the prevalence of inadequate intake compared with requirements contains the value 70% rather than 50% for this group”.

  Concerning food vector selection, the manufacturer must study its nutritional characteristics in order to verify that excessive consumption would still be in line with the general nutritional recommendations. Moreover, the selected food vector must actually be consumed by the group(s) targeted for inadequate intake. It is also stated that priority must be given to foods that naturally contain the nutrient; otherwise additional information on the consumption of these foods by the targeted groups must be validated. Consumers must also be able to control what they eat, which requires clear and precise labelling.

The opinions issued on a case-by-case basis for applications for the vitamin and mineral fortification of foods up to the time the European Regulation came into force are based on the method described above. For each application assessed, the appropriateness of the nutrient-food vector couple and of fortification was verified. ***In conclusion, Afssa considers it essential that the nutritional benefit of fortification and nutrient intake level be justified for the general population or a sub-group of the population.***

2 – Approach to assess the vitamin and mineral levels of fortified foods and food supplements

In preamble to the response to request no. 2007-SA-0315, it should be noted that the fortification arrangements laid down by Regulation (EC) No 1925/2006 cover a new reality which could lead to the fortification of a very wide range of foods in addition to vitamin and mineral intake from base diet and to the consumption of food supplements.

This opinion intends to provide managers with non-exhaustive clarification and alert identification information:

- on questions about tolerable upper intake levels;
- on questions about food intake and the models put forward by various bodies and organisations to define maximum amounts in fortified foods and/or supplements;
- on the question of nutrients not listed in the Annex of Directive 90/496[3];
- on the special restrictions of use associated with possible interactions between vitamins and minerals.

A review of vitamin and mineral intake from base diet and supplements in France was carried out to begin with, and then the maximum levels of vitamins and minerals in fortified food and food supplements were estimated from the data available for each micronutrient: (i) a tolerable upper intake level (UL) could or could not be set by EFSA and (ii) the food intake could or could not be determined. The table below presents the different cases encountered in this assessment (*Table 1*):

Table 1: Presentation of the different cases possible based on the data available

Food intake data / **UL**	*YES*	*NO*
YES	***Case 1***	***Case 3***
NO	***Case 2***	***Case 4***

Case 1: food intake data and a European (case 1) or French (case 1b) tolerable upper intake level area available. EFSA has set an upper tolerable intake level for vitamins A, D, E, B_6 and B_9 and minerals and trace elements such as calcium, copper, iodine, selenium and zinc (Case 1). With no European UL for vitamin C or minerals and trace elements such as phosphorus, iron, manganese and magnesium, the UL put forward in the ANC book for the French population has been used (Case 1b). After setting the ANC for the nutrient in question, simulations were carried out to set the maximum limits for the fortification of these vitamins and minerals in foods and interpreted in comparison with the European or French UL.

Case 2: only food intake data are available (no tolerable upper intake level). Accordingly, the maximum levels for the fortification of vitamins B_1, B_2, B_5 and B_{12} and minerals and trace elements such as potassium, chloride, sodium and β-carotene in foods were estimated, after identifying the ANC for the nutrient in question, on the basis of all the opinions on these micronutrients issued to date by Afssa and other European and American bodies.

Case 3: only data on tolerable upper intake levels are available. Accordingly, the maximum levels for the fortification of vitamin B_3, fluoride and molybdenum in foods were estimated, after identifying the ANC for the nutrient in question, on the basis of all the opinions on these micronutrients issued to date by Afssa.

Case 4: no data on the tolerable upper intake levels or food intake are available. Accordingly, the maximum levels for the fortification of vitamins K and B_8 and chromium in foods were estimated, after identifying the ANC for the nutrient in question, on the basis of all the opinions on these micronutrients issued to date by Afssa and by other European bodies.

Lastly, in addition to the four aforementioned cases, ***case 5 will concern nutrients that are not listed in the annex to Directive 90/496***, i.e. boron, nickel, tin, vanadium and silicon. There is neither an ANC nor a UL for these nutrients, except boron. The maximum levels for their fortification in foods were estimated on the basis of all the opinions on these micronutrients issued to date by Afssa and other European bodies.

[3] Directive 90/496/EEC on nutrition labelling of foodstuffs

The simulation work referred to above involves simultaneously testing, on the basis of recent French consumption data (national INCA2[4] study 2006-2007) for the general population, the maximum vitamin and mineral fortification levels in common foods and the maximum vitamin and mineral levels for food supplements, proposed by various European bodies.

Afssa would like to point out that the fortification levels obtained in this way are <u>maximum doses</u> that should not be exceeded and only take account of consumer safety, not the nutritional benefit of such a fortification, unlike the approach recommended by Afssa since 2001. Furthermore, no list of food vectors will be put forward, only possible interactions between vitamins and minerals will be mentioned. The experts of the "Human Nutrition" Scientific Panel, called on several times, reaffirm their support for the approach considering assessment of the nutritional benefit of fortification to be essential and point out the limits of this opinion, which only estimates the maximum fortification levels based on toxicity data.

[4] Second National Individual Study of Food Consumption.

3- Estimation of vitamin and mineral intake from base diet and food supplements in France

The INCA2 study gathers all of the participants' dietary intakes using food diaries filled in over 7 consecutive days by the participants (food and drinks consumed at each meal and between meals). The amounts consumed are estimated from a photo album (SU.VI.MAX, 1994). During the week in which they filled in the food diary, the participants also filled in a food supplement diary, if they consumed such products. Eventually, the study will also identify fortified foods (thanks to the names and brands of products collected and the drawing up of a nutritional composition table).

The foods consumed in INCA2 were matched with the food composition data from CIQUAL[5] tables, thanks to a list drawn up specifically for this study. By codifying the foods gathered in the diaries according to this list, each food could be linked to a nutritional composition vector containing 12 vitamins and 11 minerals.

The study was conducted from 2006 to 2007. In order to take account of dietary changes through the seasons, the survey was carried out three times over more than twelve months. It involved 4,079 participants aged between 3 and 79 years old (including 2,624 adults aged 18-79) living in mainland France. The participants were selected using a three-stage cluster sampling technique stratified on region and size of urban area. The random selection of households was made from the 1999 population census and the bases of new housing built between 1999 and 2004.
A weighting was allocated to each participant to ensure that the sample was representative at national level in line with socio-demographic criteria. Moreover, under-reporters (participants who said they consumed less than their requirements) were excluded from the analyses. The sample of non-under-reporting adults includes 1,918 people.

3.1- Vitamin and mineral intake from base diet depending on the consumption of food supplements

The data collected through INCA2 could be used to estimate nutritional intake from base diet for supplement users and non users (Table 2).
A variance analysis of the differences in average intake observed in supplement users and non users shows that:

- for 7 of the 12 vitamins, nutritional intake from base diet of supplements users and non users does not differ significantly. That said, for vitamins B_2, B_3, B_5 and B_{12}, nutritional intake from base diet in non supplement users exceeds intake in supplement users. Regarding vitamin C, supplement users have a higher intake from base diet than non users (Table 2).
- for 6 of the 11 minerals, nutritional intake from base diet in supplement users and non users does not differ significantly. That said, for sodium, zinc, phosphorus and potassium, nutritional intake from base diet in non supplement users exceeds intake in supplements users (Table 2).

[5] Food Quality Information Centre

Table 2: Nutritional intake from base diet in non-under-reporting adults (N=1,917), in non supplement users (N=1,456) and in supplement users (N=461).

	ANC[6]	General population	Non supplement users	supplement users	*p-value*
Retinol (µg)	800/600	701.1	717.8	642.7	ns
Beta-carotene equivalent (µg)		3329.6	3279.4	3506.1	ns
Vitamin D (µg)	5	2. 6	2.6	2.5	ns
Vitamin E (mg)	12	11.6	11.5	12	ns
Vitamin C (mg)	110	92.8	90.7	100.3	*
Vitamin B_1 (Thiamin) (mg)	1.3/1.1	1.2	1.2	1.2	ns
Vitamin B_2 (Riboflavin) (mg)	1.6/1.5	1.9	1.9	1.8	**
Vitamin B_3 (Niacin) (mg)	14/11	19.3	19.6	18.2	***
Vitamin B_5 (Pantothenic acid) (mg)	5	5.6	5.7	5.4	**
Vitamin B_6 (mg)	1.8/1.5	1.7	1.7	1.7	ns
Vitamin B_9 (Folates) (µg)	330/300	289.4	287.0	298.1	ns
Vitamin B_{12} (µg)	2.4	5.8	5.9	5.4	*
Sodium (mg)		2968.1	3032.5	2741.7	***
Magnesium (mg)	420/360	291.8	293.4	286.4	ns
Phosphorus (mg)	750	1265.4	1279.7	1215.2	**
Potassium (mg)		2980.0	3004.8	2892.9	*
Calcium (mg)	900	912.8	913.4	910.8	ns
Iron (mg)	9/16	13.1	13.2	12.8	ns
Manganese (mg)		2.9	2.9	3.2	***
Copper (mg)	2/1.5	1.5	1.4	1.5	ns
Zinc (mg)	12/10	10.7	10.9	10.1	***
Selenium (µg)	60/50	53.7	53.8	53.4	ns
Iodine (µg)	150	119.5	120.2	117.2	ns

*ns: not significant; * P<0.05; ** P<0.01; *** P<0.001*

3.2- Vitamin and mineral intake from food supplements

The definition of a food supplement[7] given to the INCA2 participants refers to the regulatory definition of food supplements, but may also include certain medicines containing micronutrients.

Concerning the prevalence of food supplement consumption in adults
Almost 20% of adults consumed at least one food supplement during the previous year and slightly over 11% during the seven days of the study. This practice is strongly associated with gender, since there are twice as many women as men consuming food supplements (p<0.001). The consumption of food supplements over the previous 12 months is strongly associated with the participant's education level, for both men (p=0.03) and women (p=0.001), with consumption prevalence increasing with education level.

Concerning the consumption patterns of food supplements over the year
Around two-thirds of food supplements consumed over the previous 12 months were taken as a form of treatment courses[8] by both adults and children. 23% of food supplements are consumed daily by adults. Moreover, 5% of adults consume them periodically (at least once a month).
On average, the duration of food supplement consumption is 133 days per year in adults.

[6] The ANCs are presented for men and then for women where there is a difference.
[7] "food supplements are vitamins, minerals, plant concentrates or extracts, amino acids, proteins, essential fatty acids (omega 3 for example), phyto-oestrogens, or any other type of food supplement in the form of pills, tablets, capsule, powder-filled pouches, syrups, etc."
[8] "Treatment course" in this context is defined as a consumption period of several days in a row (at least 3 days).
[8] "Treatment course" in this context is defined as a consumption period of several days in a row (at least 3 days).

Concerning the composition and type of food supplements consumed

Around a quarter of food supplements (26.7%) are composed exclusively of vitamins and/or minerals, while 36.4% are mixtures of vitamins/minerals with other substances. This means that around 63% of food supplements contain vitamins and minerals. Note that 22.6% of the various food supplements consumed over the 12 months prior to the study were medicines.

Vitamin D, E, C, B_1 and B_6 and iron intake from food supplements can account for 20 to 30% of the total intake of these nutrients in food supplement consumers. As a result, vitamin and mineral intake from food supplements is not insignificant and must be taken into account when assessing the maximum fortification levels.

4- Cases 1 and 1b: Assessment of the maximum vitamin and mineral fortification level by simulation when a European or French tolerable upper intake level has been set

In the aforementioned cases 1 and 2, the maximum vitamin and mineral fortification level is assessed on the basis of nutritional intakes estimated by simulation (Afssa, 2008d).

4.1- Method: calculating nutritional intakes by simulation (Afssa, 2008d)

The method firstly involves calculating the total nutritional intakes in the population from three possible sources: consumption of base diet, consumption of fortified foods and consumption of food supplements.
Nutritional intake from base diet is estimated by linking consumption data with CIQUAL's nutritional composition table.
With no specific data on fortified foods, nutritional intake from this source is estimated as follows: first of all, a list of foods consumed in the INCA 2 study that could be fortified is drawn up (non-processed foods such as eggs, meat and poultry, offal, fruit, vegetables, water and alcoholic drinks are fully excluded from this list, which contains 55% of the foods on the INCA 2 list). Then, for each individual, foods are picked at random from the list of foods that could be fortified and, based on a theoretically defined market share (10% and 25% appear to be rational, realistic choices given existing information on fortification[9] and 50% represents a high assumption for the share of fortified foods that it does not seem possible to exceed), they are allocated the maximum authorised level of fortification. According to this method, each participant in the INCA 2 survey would therefore consume, in theory, certain fortified foods throughout the week. For "fortified" foods, nutritional intake is calculated from the maximum fortification level.
The vitamin and mineral concentrations in food supplements are defined by the maximum daily level. Intakes from food supplements are added to intakes from base diet and fortified foods.

The maximum levels obtained by different mathematical models for fortified foods and food supplements are associated with these detailed and nationally representative findings of food and food supplement consumption.
The models below, as proposed by the European Commission, have been adopted for the simulations presented in this opinion:

- the model presented by the ILSI[10] aims to estimate the maximum vitamin and mineral fortification levels of foods (Flynn et al., 2003). It is based on the use of tolerable upper intake levels (ULs) as the total intake levels and on consideration of the consumption levels of nutrients and energy intakes observed at European level. Note that the consumption of food supplements is not taken into account. This model leads to a classification of nutrients depending on the possible fortification, expressed as a percentage of European RDAs;
- the model presented by Denmark (DFVR[11]) is based on the ILSI's model (Rasmussen et al., 2006). The general principle and parameters used are similar. The differences between this model and the ILSI's model lie in the consideration of food supplements, energy intakes, market shares estimated for fortified foods and of a specific estimation for children;
- the model presented by the European Responsible Nutrition Alliance (ERNA) and European Federation of Associations of Health Product Manufacturers (EHPM) for food supplements (ERNA/EHPM, 2004) intends to define maximum amounts for food supplements. The model has two stages to achieve this: (i) a categorisation of nutrients based on the risk of exceeding the UL (risk characterisation), and (ii) setting of a maximum amount from a model specific to each nutrient category.
- the BfR[12] model defines maximum vitamin and mineral amounts for both the fortified foods and food supplements (Domke, 2004b, Domke, 2004a). The BfR analyses each nutrient on a case-by-case basis and applies its model to it, using data from several expert groups (particularly SCF[13], EVM[14], IOM[15] and Afssa);

[9] The market shares of fortified foods are difficult to estimate. Some studies estimate intakes from these foods to be between 3 and 10% of a person's total energy intake. Note that these proportions can vary depending on the nutrient in question, and that the vitamin and/or mineral fortification of foods is limited for technological, economic and quality reasons amongst others.
[10] International Life Sciences Institute
[11] Danish Institute for Food and Veterinary Research.
[12] Federal Institute for Risk Assessment (Germany).
[13] Scientific Committee on Food (Europe)

- the French Order of 9 May 2006[16] sets maximum amounts in food supplements for vitamins and minerals.

So, for fortified foods, there are four series of maximum values obtained from the ILSI, DFVR and BfR models and a regulation based hypothesis (fortification assumption of up to 15% of the RDA for 100 kcal of food, which is a conventional assumption unconnected to the regulation on nutrition labelling of foodstuffs) respectively. For food supplements, there are two series of values obtained from the ERNA/EPHM and BfR models (maximum daily amount) as well as the French regulatory values from the Order of 9 May 2006. The maximum fortification values and maximum daily levels for food supplements put forward by the different models are presented in Annex 1.

Twelve combinations are possible between the four series of maximum values set for fortified foods and the three series of maximum daily amounts recommended for food supplements. To illustrate the results obtained by the method, five scenarios were selected to begin with (Table 3): the model presented by the BfR, setting maximum levels for both fortified foods and food supplements, is a scenario in itself (scenario 4); the combination of the ILSI's fortification levels and the ERNA/EPHM's levels in food supplements presents the highest levels in both cases (scenario 1); lastly, with no data on food supplements, it was agreed to combine the other three models setting fortification levels with the values set by the French regulations in 2006 for food supplements (scenarios 2, 3 and 5).

Table 3: Scenarios selected combining the maximum values for fortified foods and food supplements

Supplements / **Fortification**	ERNA-EHPM	BfR	French regulations – Order of 09/05/06
ILSI	***Scenario 1***		***Scenario 2***
Denmark (DFVR)			***Scenario 3***
BfR		***Scenario 4***	
15% of RDA			***Scenario 5***

Moreover, for each of the five scenarios, four assumptions of the market share of fortified foods among those that are likely to be so will be tested: 0%, 10%, 25% and 50%. This fairly wide range of market shares takes account of the fact that certain consumers can tend to favour fortified foods systematically.

The estimated total nutritional intakes are compared to the tolerable upper intake levels when they exist.
These simulations only concern the general population. Afssa assessed the maximum vitamin and mineral levels in foods and food supplements from different models developed by other institutes.
Two scenarios are the most protective in terms of public health. One comprises maximum fortification levels from the DFVR model and maximum levels in food supplements set by the French regulations; the other combines the maximum fortification levels and maximum levels of food supplements of the BfR model. However, the maximum fortification limits set by the BfR for vitamin B9 do not entirely do away with the risk of exceeding the tolerable upper intake level.
This approach was addressed in the opinion of 13 October 2008 (Afssa, 2008d).

4.2- Case 1a: Assessment of the maximum vitamin and mineral fortification level based on the tolerable upper intake level set by EFSA and dietary intake data

For the 10 nutrients for which EFSA has set a tolerable upper intake level (UL), the table below indicates the percentile thresholds for which the risk of exceeding the UL is reached depending on the

[14] Expert Group on Vitamins and Minerals (FSA expert group, UK)
[15] Institut of Medicine (USA)
[16] Order of 9 May 2006 on the nutrients that may be used to make food supplements. French Official Journal of 28 May 2006.

different scenarios and for a market share of fortified products of 25% (Table 4). These percentile thresholds are similar to those observed for a 50% market share (Table 5), except for vitamins E and B_9, in the case of scenario 3 (DFVR model combined with the French regulation).

Table 4: Summary of scenarios (market share of fortified products = 25%): percentile (Pn) beyond which the UL is exceeded

		UL	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5
Vitamins	**Vitamin A**	3000 µg	P95	P95	P95	P95	P90
	Vitamin D	50 µg	P70	P80	-	-	-
	Vitamin E	300 mg	P10	P10	-	-	-
	Vitamin B_6	25 mg	P60	P70	-	-	-
	Vitamin B_9	1000 µg	P70	P80	-	P60	-
Minerals	**Calcium**	2500 mg	P90	-	-	-	P95
	Copper	5 mg	P20	P20	-	-	P90
	Iodine	600 µg	P40	P40	-	-	-
	Selenium	300 µg	P70	P80	-	-	-
	Zinc	25 mg	P40	P40	P90	-	P70

Table 5: Summary of scenarios (market share of fortified products = 50%): percentile (Pn) beyond which the UL is exceeded

		UL	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5
Vitamins	**Vitamin A**	3000 µg	P95	P95	P95	P95	P90
	Vitamin D	50 µg	P20	P30	-	-	-
	Vitamin E	300 mg	P2,5	P2,5	P70	-	-
	Vitamin B_6	25 mg	P20	P20	-	-	-
	Vitamin B_9	1000 µg	P30	P30	P95	P10	-
Minerals	**Calcium**	2500 mg	P90	-	-	-	P80
	Copper	5 mg	P2,5	P2,5	-	-	P80
	Iodine	600 µg	P5	P5	-	-	-
	Selenium	300 µg	P20	P30	-	-	-
	Zinc	25 mg	P5	P5	P90	-	P40

The percentile shown indicates that the tolerable upper intake level is exceeded beyond it. A dash indicates that the UL is not exceeded. When several scenarios do not lead to the UL being exceeded for the nutrient in question, the highest levels are qualified as maximum levels.

From the simulation results, it appears that two scenarios are the most protective in terms of public health. One comprises maximum fortification levels from the DFVR model and maximum levels in food supplements set by the French regulations; the other combines the maximum fortification levels and maximum levels of food supplements of the BfR model. However, the maximum fortification limits set by the BfR for vitamin B_9 do not entirely do away with the risk of exceeding the UL.

With a 50% market share for fortified foods, scenario 4 is the one presenting the least risk of exceeding the UL for all nutrients simultaneously, except vitamin B_9 (for which the fortification value is very high).

Opting for a 50% market share instead of 25% leads to the same scenario results, depending on their protective nature, except for vitamin E.

In view of these simulation results and information obtained from:
- EFSA opinions, particularly on tolerable upper intake levels;
- Afssa opinion and reports on the nutrients mentioned;
- the general review of the European Commission, backed by several experts from the Human Nutrition and Additives, Flavourings and Processing Aids scientific panels;

Afssa recommends the following:

Vitamin A

The adult ANCs for vitamin A are 600 µg/d for women and 800 µg/d for men. French population intakes are estimated to be 704.5 µg/d on average and 2,389 µg/d for the 95th percentile.

The simulation studies show that fortification up to 15% of the RDAs (or 120 µg RE[17]/100 kcal) is likely to double the percentage of the general population which exceeds the tolerable upper intake level set by the SCF: vitamin A intake for around 6% of the general population would exceed 3,000 µg RE/d.

As a result, fortification does not seem desirable. Regarding food supplements, the maximum daily intake set by the Order of 9 May 2006 is maintained. However, labelling should be provided advising pregnant women or women hoping to fall pregnant against their consumption.

Additional information is presented in Annex 2.

Vitamin D

The ANC for vitamin D has been estimated to be 5 µg/d. French population intake is estimated to be 2.6 µg/d on average and 5.5 µg/d for the 95th percentile. This information does not take account of intake from medicines. Additional information is presented in Annex 2.

The simulation study indicates that the maximum level of fortification proposed by the DFVR, 3 µg/100 kcal, combined with the maximum daily intake of 5 µg in food supplements (Order of 9 May 2006) does not lead to the 50 µg/d UL being exceeded (scenario 3).

Vitamin E

The ANC for vitamin E is estimated to be 12 mg in adults. French population intake is estimated to be 11.6 mg/d on average and 22.1 mg/d for the 95th percentile.

The simulation study shows that the maximum level of fortification, 1.5 mg/100 kcal (or 15% of the RDA) combined with the maximum daily intake of 30 mg in food supplements (Order of 9 May 2006) does not lead to the European UL set at 300 mg/d being exceeded, even in the event that the market share of fortified food reaches 50% (scenario 5).

Vitamin B_6

The ANC for vitamin B_6 is estimated to be 1.5 mg in adults. French population intake is estimated to be 1.7 mg/d on average and 2.8 mg/d for the 95th percentile.

The simulation study indicates that the maximum level of fortification proposed by the BfR, 1.2 mg/100 kcal, combined with the maximum daily intake of 5.4 mg in food supplements does not lead to the 25 mg/d UL being exceeded (scenario 4).

Vitamin B_9

The adult ANCs for vitamin B_9 are 300 µg/d for women and 330 µg/d for men. French population intake is estimated to be 289.4 µg/d on average and 466.1 µg/d for the 95th percentile.

The simulation study indicates that the maximum level of folic acid fortification (synthetic form of vitamin B_9), i.e. 30 µg/100 kcal (or 15% of the RDA) combined with the maximum daily intake of 200 µg in food supplements (Order of 9 May 2006) does not lead to the UL set by the SCF at 1000 µg/d being exceeded for adults (scenario 5), even in the event that the market share of fortified foods reaches 50%.

Moreover, Afssa points out that special labelling should draw consumers' attention to the status of vitamin B_{12} (*Annex 2*) for vitamin B_9 fortification.

Afssa stresses that it is not possible to date to confirm the safety of folic acid supplements in the general population through fortification or food supplements (*Annex 2*).

Calcium

The ANC for calcium is estimated to be 900 mg in adults. French population intake is estimated to be 913.1 mg/d on average and 1,487.5 mg/d for the 95th percentile.

[17] RE: Retinol equivalent.

The simulation study indicates that the maximum level of fortification proposed by the DFVR, 43 mg/100 kcal, combined with the maximum daily intake of 800 mg in food supplements (Order of 9 May 2006) does not lead to the 2,500 mg/d UL being exceeded (scenario 3).

Copper

The ANC for copper is estimated to be 2 mg in adults. French population intake is estimated to be 1.5 mg/d on average and 2.8 mg/d for the 95th percentile.
The simulation study indicates that no fortification is possible, but that the maximum daily intake of 2 mg in food supplements (Order of 9 May 2006) does not lead to the European UL of 5 mg/d being exceeded (scenario 3).

Iodine

The ANC of iodine is approximately 150 µg in adults. French population intake is estimated to be 119.5 µg/d on average and 187.4 µg/d for the 95th percentile.
The simulation study indicates that the maximum level of fortification, 22.5 µg/100 kcal (or 15% of the RDA), does not lead to the 600 µg/d European UL being exceeded (scenario 5). Nevertheless, in line with the conclusions of its report (2005a), Afssa maintains its position on the risks of extending sources of iodine intake (Annex 2). Therefore, Afssa maintains a maximum fortification level of 20 µg /g of table salt and/or 20 µg/100g of bread products (bread, biscuits and pastries). In addition, a maximum daily dose of 150 µg in food supplements, i.e. the intake recommended in the Order of 9 May 2006 is maintained.

Selenium

The adult ANCs for selenium are 50 µg/d for women and 60 µg/d for men. French population intake is estimated to be 53.7 µg/d on average and 87.3 µg/d for the 95th percentile.
The simulation study indicates that the maximum level of fortification, 9 µg/100 kcal (or 15% of the RDA), combined with the maximum daily intake of 50 µg in food supplements (Order of 9 May 2006) does not lead to the 300 µg/d European UL being exceeded (scenario 5).

Zinc

The ANC for zinc is estimated to be 12 mg in adults. French population intake is estimated to be 10.7 mg/d on average and 17.3 mg/d for the 95th percentile.
The simulation study indicates that no fortification is possible, but that the maximum daily intake of 2.25 mg in food supplements does not lead to the European UL of 25 mg/d being exceeded (scenario 4).

4.3- Case 1b: Assessment of the maximum vitamin and mineral fortification level based on dietary intake data and the French tolerable upper intake level

For these nutrients, only food intake data and a French UL are available. After identifying the ANC of the nutrient in question and commenting on the absence of a UL set by EFSA, simulation work to set maximum fortification levels of foods with these vitamins and minerals was conducted and interpreted with regard to a UL put forward in the ANC book for the French population (Martin et al., 2001).
For the 5 nutrients for which a French UL has been set, the table below indicates the percentile thresholds for which the risk of exceeding the UL is reached depending on the different scenarios and for a market share of fortified products of 25% (Table 6). These percentile thresholds are similar to those observed for a 50% market share (Table 7).

Table 6: Summary of scenarios (market share of fortified products = 25%): percentile (Pn) beyond which the French UL is exceeded

	UL	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5
Vitamin C	500 mg	P10	P80	P70	P70	-
Phosphorus	2500 mg	P60	P70	P70	-	P95
Iron	28 mg	P50	P50	P95	-	P80
Manganese	10 mg	-	-	-	-	-
Magnesium	700 mg	P90	P90	-	-	P90

Table 7: Summary of scenarios (market share of fortified products = 50%): percentile (Pn) beyond which the French UL is exceeded

	UL	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5
Vitamin C	500 mg	P2.5	P2.5	P30	P30	-
Phosphorus	2500 mg	P20	P30	P30	-	P80
Iron	28 mg	P10	P10	P95	-	P50
Manganese	10 mg	-	-	-	-	P97.5
Magnesium	700 mg	P60	P60	-	P97.5	P70

Vitamin C

The ANC for vitamin C is estimated to be 110 mg/d in adults. French population intake is estimated to be 92.8 mg/d on average and 194.6 mg/d for the 95th percentile.

EFSA (2004a) notes that, from 3 g/d over the food intake, the most commonly reported problems concern the gastro-intestinal tract (flatulence, diarrhoea and so on). The few studies having specifically searched for the harmful effects of vitamin C suggest a low toxicity. Nevertheless, EFSA mentions the risk of kidney stones and concludes with the need for more in-depth studies to set a tolerable upper intake level.

In view of the new findings described in *Annex 2* on the potentially pro-oxidant effects of vitamin C, it seems that total daily intake of vitamin C should not exceed 500 mg.

The simulation study indicates that the maximum fortification level, 9 mg/100 kcal (or 15% of the RDA), combined with the maximum daily intake of 180 mg in food supplements (Order of 9 May 2006) does not lead to a total daily intake exceeding 500 mg (scenario 5).

Phosphorus

The ANC for phosphorus is estimated to be 750 mg/d in adults. French population intake is estimated to be 1,265.3 mg/d on average and 1,915.3 mg/d for the 95th percentile.

EFSA believes that the gastro-intestinal effects occasionally reported for intakes exceeding 750 mg/d does not enable a tolerable upper intake level to be set.

However, France has set a UL of 2,500 mg/d in the book on ANCs for the French population (Guégen, 2001).

The simulation study indicates that no fortification is acceptable in common food, but that the maximum daily intake of 250 mg in food supplements does not lead to the French UL of 2,500 mg/d being exceeded (scenario 4).

Afssa also recalls that excess phosphorus consumption can disrupt the calcium/phosphorus balance which, in the long term, can cause hypocalcaemia with secondary hyperparathyroidism and therefore recommends that food supplements containing phosphorus also provide calcium.

Iron

The ANC for iron has been estimated to be 9 mg/d for men and 16 mg/d for pre-menopausal women. French population intake is estimated to be 13.1 mg/d on average and 21.2 mg/d for the 95th percentile.
EFSA notes the existence of epidemiological studies reporting a link between high iron intake and an increase in such chronic diseases as cardiovascular diseases, type 2 diabetes and digestive cancers, even if there are confounding factors. EFSA believes that the data are inadequate for a tolerable upper intake level to be set. With regard to intake levels observed in European countries, it notes that the risk of harmful effects from high dietary intakes of iron (including fortified foods but excluding food supplements) is low, except for haemochromatosis homozygotes.
France has set a UL of 28 mg/d (Coudray and Hercberg, 2001).
The value proposed by the EVM, 17 mg/day of iron in food supplements only, is relatively similar to the one set in the French Order of 9 May 2006 for food supplements only (14 mg/d).
The 17 mg intake recommended by the EVM from food supplements has not been tested, but it seems, after analysing the five scenarios, that firstly, no fortification is acceptable and secondly 14 mg/d supplements also lead to the 28 mg/d limit being exceeded for percentiles over P90 (scenario 3). To date, no data cast doubt over the maximum daily intake in food supplements, 14 mg/d, set by the French regulations.
Moreover, Afssa states that iron supplements should not be taken at the same time as vitamin C supplements because of problems of absorption competition with calcium.

Manganese

A specific ANC cannot be set for manganese. French population intake is estimated to be 2.9 mg/d on average and 5.1 mg/d for the 95th percentile.
According to an SCF opinion, EFSA believes that the margin between intakes causing harmful effects in animals and humans and estimated intakes in food is very slight. Given the risks of neurotoxicity, particularly in some population sub-groups, the SCF considers that exceeding the base diet intake of manganese (between 1 and 9 mg/d depending on the type of food) poses a risk without associated potential benefit. Despite this, it believes that findings of human studies are limited, and that the NOAEL[18] set on the basis of animal studies is not valid. It concludes that data are inadequate to set a tolerable upper intake level (SCF, 2000c). However, France has set a UL of 10 mg/d in the publication on ANCs for the French population (Arnaud, 2001).
The simulation study indicates that no fortification is acceptable, but that the maximum daily intake of 3.5 mg in food supplements (Order of 9 May 2006) does not lead to the French UL of 10 mg/d being exceeded (scenario 3).

Magnesium

The ANC for magnesium has been estimated to be 420 mg/d for men and 360 mg/d for women. French population intake is estimated to be 291.7 mg/d on average and 457.8 mg/d for the 95th percentile.
A NOAEL has been defined for this nutrient on the basis of pharmaceutical studies, without taking account of food intake. The SCF therefore believes that a tolerable upper intake level cannot be set.
Afssa retains the arguments identifying a UL of 700 mg/d set by Rayssiguier, Boirie and Durlach (2001)
It seems, after analysing the five scenarios, that no fortification is acceptable. 300 mg/d supplements do not lead to the French UL being exceeded (scenario 3).

[18] No Observed Adverse Effect Level: value based on toxicological studies carried out on humans or animals over a variable short-term period.

5- Cases 2, 3, 4 and 5: Assessment of the maximum vitamin and mineral fortification level based on all the opinions concerning these micronutrients, issued by Afssa and other European bodies

5.1- Case 2: Assessment of the maximum vitamin and mineral fortification level for which intake data exist

Food intake data are available for these nutrients. After identifying the ANC of the nutrient in question and commenting on the absence of a tolerable upper intake level set by EFSA, the maximum fortification levels of foods with these micronutrients were estimated from all of the opinions concerning these micronutrients, issued to date by Afssa and other European and American bodies.

Vitamins B_1 (thiamin), B_2 (riboflavin), B_5 (pantothenic acid) and B_{12} (cobalamin)

The adult ANCs for vitamin B_1 are 1.1 mg/d for women and 1.3 mg/d for men. French population intake is estimated to be 1.2 mg/d on average and 2.0 mg/d for the 95th percentile.
According to an SCF opinion, EFSA concludes that existing data do not make it possible to set a UL, but that it seems, in view of the studies available, that commonly observed intakes (between 1 and 2 mg/d on average depending on European country, food and supplement intakes combined) do not pose a risk for the general population (SCF, 2001b).

The adult ANCs for vitamin B_2 are 1.5 mg/d for women and 1.6 mg/d for men. French population intake is estimated to be 1.9 mg/d on average and 2.9 mg/d for the 95th percentile.
According to an SCF opinion, EFSA reports a few studies in animals but does not believe that a UL can be set. It points out that there are no studies in humans reporting adverse effects, although this does not mean that adverse effects could not occur during high intake (SCF, 2000e). However, it considers that the commonly observed intakes, excluding food supplements (around 1.5 mg/d on average depending on European country) do not pose a risk for the general population.

The ANC for vitamin B_5 is estimated to be 5 mg in adults. French population intake is estimated to be 5.6 mg/d on average and 8.5 mg/d for the 95th percentile.
According to an SCF opinion, EFSA reports a few gastrointestinal effects during very high intake of pantothenic acid (10-20 g/d) and indicates that it does not have sufficient data to set a UL (SCF, 2002b). It notes that few consumption data are available and reports an estimated average intake (base diet and supplements combined) of 6.5 mg/d depending on European country. The SCF does not believe that intakes beyond base diet intake pose a risk for the general population.

The ANC for vitamin B_{12} is estimated to be 2.4 µg/d in adults. French population intake is estimated to be 5.8 µg/d on average and 14.5 µg/d for the 95th percentile.
According to an SCF opinion, EFSA indicates that there are no reported adverse effects to be able to set a UL. The SCF does, however, note cases of adverse effects when intake exceeds 1,000 µg/d for prolonged periods in patients suffering from vitamin B_{12} intestinal absorption problems (SCF, 2000f). It does not believe that the commonly observed intakes (between 1 and 32 µg/d on average depending on European country, food and supplement intakes combined) pose a risk for the general population.

Afssa's report (2001) on "the fortification of common foods with vitamins and minerals" and opinion (2004d) also consider that vitamins B_1, B_2, B_5 and B_{12} belong to the group of micronutrients for which no toxicity, even at high intake, has been observed to date. In the latter opinion, it was considered that maximum levels in food supplements, of up to 4.2 mg for vitamin B_1, 4.8 mg for vitamin B_2, 18 mg for vitamin B_5 and 3 µg for vitamin B_{12}, do not pose health risks.
The values proposed by the EVM, combining food, supplement and fortification intake, of 100 mg/d for vitamin B_1, 40 mg/d for vitamin B_2, 200 mg/d for vitamin B_5 and 2 mg/d for vitamin B_{12}, do not call for any particular comments to date.

β-carotene

β-carotene is a form of vitamin A intake. Only ANC for vitamin A, in retinol equivalent, has been set. French population intake is estimated to be 3.3 mg/d on average and 7.3 mg/d for the 95th percentile.
According to an SCF opinion (SCF, 2000a), EFSA particularly highlights (i) the multitude of β-carotene intakes (natural food, food additives, supplements) and (ii) the low margin between the intakes for

which benefits of β-carotene have been reported and those for which adverse effects have been described in smokers. In this context, the SCF states that β-carotene should be used with great care in food supplements.
Afssa also points out the many intakes of this micronutrient and recommends caution given the risk for people exposed to an environmental carcinogen (tobacco, asbestos), particularly as a food supplement (2006).
The European Commission reports values and recommendations issued by various bodies: (i) EVM, 7 mg/d for food supplements only (with warning for smokers), (ii) BfR, 2 mg/d for food supplements only, no fortification authorised and (iii) Danish expert group, 5 mg/d.
Afssa notes that these values are similar to those for which adverse effects are associated. As knowledge currently stands (Annex 2), Afssa believes it prudent not to recommend the fortification of common food with β-carotene. The simulation results show that a 7 mg intake from food supplements leads to a total β-carotene intake of around 13 mg/d. Given the possible conversion of β-carotene into vitamin A, this intake would add to vitamin A intakes which already exceed the tolerable upper intake level at the 97.5th percentile. Therefore, food supplement intake, if it were to continue for β-carotene, should in any case be kept at the lowest values, with a warning for people exposed to an environmental carcinogen (tobacco, asbestos).

Potassium
It has not been possible to set a specific ANC for potassium. In France, dietary intake of potassium is 2980 mg on average and 4416.5 mg for the 95th percentile. This amply covers the minimum EAR of 585 mg (Martin et al., 2001).
EFSA believes the risk of adverse effects to be low when dietary intake is in the range of those observed in European countries (5-6 g/d in adults). However, gastrointestinal effects have been observed in healthy adults when taking potassium supplements at doses of between 1 and 5 g/d and effects on cardiac function have been reported for an intake of 5-7 g/d in apparently healthy adults. EFSA nevertheless believes that the data are inadequate for a UL to be set.
Afssa's opinion (2008a) considers that a modification of the maximum level in food supplements, set in the Order of 9 May 2006 at 80 mg/d to 800 mg/d (element), in the form of citrate and bicarbonate salts, is admissible. As a result, the additional intake, combining supplement and fortification intake, of 1,000 mg/d for adults, proposed by the BfR and reported by the European Commission, does not call for any particular comments.

Chloride and Sodium
The ANC for chloride is closely associated with the one for sodium, in the form of sodium chloride. These are still being debated at present. In France, dietary intake of sodium is 2967.4 mg on average and 4872.1 mg for the 95th percentile.
EFSA (2005a; 2005d) concluded that data are insufficient to set a UL for sodium and chloride.
The EVM does not think that a UL can be set for these substances and recommends that sodium and chloride not be used in food supplements.
Afssa also pointed out that chloride and sodium are unintentionally incorporated in the form of ions in processed foods, to guarantee the neutrality of the salts incorporated. The opinion stipulates that these substances could be incorporated according to the *quantum satis* principle, so as to meet the possible technological requirements of formulation (2003a). The disadvantages of adding sodium for nutritional purposes are also discussed in the report entitled "Salt: assessment and recommendations" (2002).
Afssa therefore believes that no addition of chloride or sodium is possible in food supplements or in common foods outside of their technological and organoleptic uses.

5.2- Case 3: Maximum vitamin and mineral fortification level for which a tolerable upper intake level has been set – INCA2 findings do not provide any intake data

Only data on tolerable upper intake levels are available for these nutrients. After identifying the ANC for the nutrients in question, vitamin B_3, fluoride and molybdenum, the maximum fortification levels of foods with this vitamin and these trace elements were estimated from all of the opinions concerning these micronutrients, issued to date by Afssa and by other European bodies.

Vitamin B_3

The ANC for vitamin B_3, in the form of nicotinic acid and nicotinamide, is estimated to be 14 mg/d NE[19] for men and 11 mg/d NE for women.

According to an SCF opinion, EFSA has set a UL for each of the 2 forms of niacin: the UL for nicotinamide is estimated to be 900 mg/d and for nicotinic acid, 10 mg/d (SCF, 2002a).

The levels of different forms of niacin in food cannot be distinguished from the food composition table composed by Afssa. It is possible, from the INCA 2 study, to estimate dietary intake of niacin to be 19.3 mg on average and 31.0 mg for the 95th percentile. The tolerable upper intake level of the 2 forms of intake cannot be identified with regard to niacin intake. The results of OCA-EN simulations cannot be interpreted as a result.

In the EVM's review (2002) on niacin, it is stated that the most widespread form in food supplements is nicotinamide, at doses of between 100 and 250 mg, and that nicotinic acid is the form used to restore niacin levels in flour up to 1.6 mg/100 g of flour, which makes up for loss from technological processes. The dose currently authorised in France by the Order of 9 May 2006 is 54 mg for nicotinamide and 8 mg NE for nicotinic acid in food supplements.

Afssa recommends that the nicotinamide form of niacin be preferred if fortification is considered.

Fluoride

The ANC for fluoride is estimated to be 2.5 mg/d for men and 2 mg/d for women.

EFSA (2005b) believes that data are sufficient to set a tolerable upper intake level, and estimates this to be 7 mg/d for adults.

According to the bibliographical data presented in Annex 2, Afssa maintains its cautionary view as to the risks associated with fluoride and states that an extension of fluoride sources, via fortification and food supplements, would in any case lead to uncontrolled exposure and risks of dental fluorosis, particularly because of the highly varied fluoride levels in tap water and mineral water. Afssa does not recommend that fortification be extended to other food vectors than those already used (salt or even chewing gum) and confirms that fluoride should not be incorporated in food supplements.

Molybdenum

It has not been possible to set a specific ANC for molybdenum, because it can only be pinpointed between 30 and 50 µg/d from the available bibliographical data.

According to an SCF opinion (2000d), Afssa believes data to be sufficient to set a UL and estimates this to be 600 µg/d. It also notes that interactions with the metabolism and use of other nutrients, particularly copper and iron, have been observed.

With no intake data or new bibliographical data, there are no arguments to justify a reconsideration of the maximum daily dose in food supplements: 150 µg/d, set by the French regulations. Given the insufficient bibliographical data, fortification is not scientifically justified.

5.3- Case 4: Assessment of the maximum vitamin and mineral fortification level for which neither a tolerable upper intake level nor intake data exist

After identifying the ANC of the nutrient in question and commenting on the absence of a tolerable upper intake level, the maximum fortification levels of foods with these two vitamins and this trace element were estimated from all of the opinions concerning these micronutrients, issued to date by Afssa and other European bodies.

Vitamin K_1 (phylloquinone)

The ANC for vitamin K is estimated to be 45 µg/d in adults.

According to an SCF opinion (2003), EFSA does not believe there to be any relevant data for setting a tolerable upper intake level. Moreover, it points out that, through a limited number of studies in humans, there does not appear to be an adverse effect associated with additional phylloquinone intake over 10 mg/d for limited periods of time, and that these findings tally with the results of studies conducted in animals. That said, the SCF highlights the risks incurred by patients taking oral anticoagulants and vitamin K supplements at the same time.

In its literature review, the European Commission reports the value of 1 mg/d (additional intake), set by the EVM.

[19] Niacin Equivalent (NE): sum of niacin obtained through our food and of niacin supplied by endogenous synthesis from tryptophan (60 mg of tryptophan = 1 mg of nicotinamide = 1 mg of nicotinic acid).

Although a UL cannot be defined for the general population, Afssa believes that the high prevalence of people taking oral anticoagulants justifies extreme caution over the fortification of common foods with vitamin K (2008c).
As a result, Afssa is opposed to the possibility of fortifying common foods with vitamin K as it poses a risk that is very difficult to control in people taking oral anticoagulants.
Afssa also maintains the maximum dose of 25 µg/d for food supplements, which does not appear to pose a risk for patients taking oral anticoagulants, and upholds its rejection of using higher doses, even when these are labelled, supposedly dissuading people on oral anticoagulants from consuming these food supplements.

Vitamin B_8 (biotin)

The ANC for vitamin B_8 is estimated to be 50 µg/d in adults.
According to an SCF opinion (2001a), EFSA does not believe that a tolerable upper intake level can be set because of a lack of dose-response studies, or that there are enough data to assess the safety of very high biotin intake. It does not believe that the commonly observed intakes (between 28 and 53 µg/d on average depending on European country, food and supplement intakes combined) pose a risk for the general population.
Afssa's report (2001) on "the fortification of common foods with vitamins and minerals" and opinion of 12 October 2004 also consider that vitamin B_8 belongs to the group of micronutrients for which no toxicity, even at high intake, has been observed to date (2004d). In the latter opinion, a maximum level in food supplements of up to 450 µg was not considered to pose a health risk. In its general review, the European Commission reports the value put forward by the EVM (0.9 mg/d, food supplement and fortification combined). This value does not call for any particular comments to date.

Chromium

The ANC for chromium is estimated to be 65 µg/d in men and 55 µg/d in women.
This note only considers trivalent chromium, an oxidised form found naturally in food. Trivalent chromium is found in various forms on the market, including chromium picolinate, chromium chloride and chromium sulphate.
EFSA (2004c) reports a limited number of studies on oral supplements of chromium trivalent and sets a supplement guideline value of 1 mg/d, in addition to chromium intakes from base diet which can reach 170 µg/d. This supplement guideline value does not concern chromium picolinate as EFSA does not consider bioavailability data in humans to be sufficient enough to make a decision. Moreover, according to the bibliographical data (Annex 2), Afssa believes that:

- the possible benefits claimed only seem to be demonstrated on advanced forms of obesity and insulin resistance and would therefore fall within the medical field;
- there is no argument to suggest a possible reduction in the risk of obesity and insulin resistance associated with chromium consumption in the general population;
- metabolic effects depend to a very large extent on the form of intake, evoking pharmacological effects associated with chromium picolinate more than nutritional effects associated with the trace element itself;
- the potential toxicity of long-term supplements, in its form of intake, cannot be excluded.

As a result, Afssa does not recommend the fortification of foods with chromium for the general population, irrespective of the form of intake.

5.4- Case 5: Information on nutrients not in Annex 1 of Directive 90/496

There are no ANCs or ULs for these nutrients, except boron, for which a UL has been set by EFSA.
After explaining the absence of a tolerable upper intake level, the maximum fortification levels of foods with these nutrients (nickel, tin, vanadium and silicon) were estimated from all the opinions concerning these micronutrients, issued to date by Afssa and by other European bodies.

Boron

EFSA (2004b) recalls that no biochemical function involving boron has been identified to date in humans and subsequently, boron is not considered to be an essential nutrient for human. Interactions with the metabolism and use of other nutrients, particularly calcium, have been observed. Boron absorption causes adverse effects in animals and cases of poisoning have been reported in humans. EFSA has set a UL of 10 mg/d in adults (0.16 mg/kg of body weight/d), as well as ULs in children, which vary depending on age. Afssa recalls that water, particularly mineral water, can be a high source

of boron: for example, in Germany, the average boron levels in drinking water have been estimated to be 2 mg/L, with bottled water possibly containing more than 4.35 mg/L of boron (mean: 0.75 mg/L). EFSA points out that, based on the limited data available, boron intakes from food and water in the European Union are below the UL set, but that the consumption of supplements containing boron may lead to intakes exceeding the UL.
Afssa (2005c) also highlights the complexity of managing boron intake through water, as it can be found in high amounts in some types of water. Afssa also reports the European work under way to limit boron concentration in drinking water, so as to maintain an acceptable level for human health (drinking water and natural mineral water). Water treatment techniques intending to reduce boron levels are still complex to apply. As a result, like EFSA, Afssa concludes that the possibility of incorporating boron in food supplements would pose a risk of consumers exceeding the tolerable upper intake level.

Afssa repeats its opposition to the addition of boron in food supplements and states that it would not be possible to control the effects of fortifying foods due to the risk of accumulation. Moreover, this fortification would go entirely against the efforts to reduce boron levels in mineral water and tap water.

Nickel
EFSA (2005c) recalls that nickel is not an essential nutrient for humans. Moreover, in rats, the ingestion of nickel salts at a dose of 1.3 mg/kg of body weight/day can trigger adverse effects on various organs (kidneys, spleen, lungs and myeloid system) and increases the rate of perinatal mortality. Afssa also recalls that nickel triggers allergic reactions. In people who are sensitised to nickel through skin contact or suffering from contact allergic dermatitis (disease estimated to affect 15% of women, but often goes undiagnosed), oral or skin exposure to nickel salts has been known to cause eczema on hands. Cases of eczema getting worse on hands in people sensitised to nickel have been reported from oral doses of nickel of around 500 µg/d (around 8 µg/kg of body weight/day).
EFSA reports the following estimates of nickel consumption: average intakes vary from 82 µg/d to 150 µg/d and can reach 900 µg/d (around 15µg/kg of body weight/day) when high amounts of food containing nickel (cocoa, dried fruit, pulses) are consumed. Moreover, a deterioration in kitchen utensils which can contaminate food can also increase the amount of nickel ingested. Finally, EFSA estimates that (i) dietary intake is 90 to 500 times below the lowest dose having caused adverse effects in rats, (ii) average dietary intakes account for around a third of the lowest intakes having triggered an aggravation of eczema in people sensitised to nickel, and (iii) data are insufficient to set a tolerable upper intake level.

In the FSA's document, the EVM notes the arguments developed by EFSA and indicates that the IOM (2000) has set a UL of 1 mg/d in adults, which takes account of the risk of nickel sensitisation. The EVM adopts the 1.3 mg/kg of body weight/day dose as the LOAEL, obtained from a study in rats of nickel chloride supplements through drinking water for 11 weeks, and applies a safety factor of 300. A value of 260 µg/d, including dietary intake, is set and considered to be acceptable for sensitive people. This value includes a contribution of 5 µg/d of nickel via food supplements (FSA).

In 2007, in the report entitled "Assessment of the health risks associated with situations where the quality references and limits of water for human consumption are exceeded", Afssa drew up a datasheet on nickel after consulting the "Water[20]" and "RCCP[21]" Scientific Panels. In this datasheet (Afssa, 2005b), Afssa particularly recalls that "measures should be taken to meet the quality limit (20 µg/L) set for water by the French public health code as soon as possible". This conclusion is based on the analysis of nickel toxicity (listed as a possible carcinogen for humans by the IARC[22]), its renal toxicity in animals and humans and the risk of exacerbating allergic reactions.
Moreover, an Afssa opinion (2008b) has been issued on the human risks of accidental contamination by nickel of fodder for animal feed and fruit and vegetables for human consumption. Notable differences in metabolism and toxicity between the different physicochemical forms (speciation) of nickel in humans and animals have been reported (Ishimatsu et al., 1995).
In conclusion, Afssa highlights the discrepancy of adopting a supplementation approach (food supplements and fortification of common foods combined) by a non-essential nutrient, when (i) measures have been taken to limit nickel intake from drinking water to the public health validated limits

[20] Assessment of water-related risks.
[21] Assessment of risks related to Chemical and Physical Contaminants and Residues.
[22] International Agency for Research on Cancer.

(tolerable daily intake: 22 μg/kg of body weight/day, set by WHO in 2005) and (ii) risks have been observed in people sensitised to nickel.

Tin

EFSA (2005e) recalls that tin is not considered to be an essential nutrient, but is found in foods in the form of tin salts or tin chloride and is authorised as a food additive (E512). In France, average tin intake is estimated to be about 2.7 mg/d, the main sources being tinned fruit and vegetables. Given the low absorption of inorganic compounds, tin presents low toxicity compared with organotin. Furthermore, short-term studies conducted in humans have shown a reduction in zinc absorption for tin intakes of between 30 and 50 mg/d. EFSA does not believe there to be enough data to set a tolerable upper intake level.

In 2003, the EVM reported a 90-day study in rats that made it possible to set a NOAEL of 22-33 mg/ of tin/kg of body weight/day. The EVM (2003) applied a safety factor of 100 and did not consider the 13 mg/d dose to pose any risk of adverse effects.
However, one study reveals that, *in vivo* in rabbits, a 20 mg/kg dose of tin chloride over 12 weeks affects the quantity and quality of spermatozoids and fertility parameters, resulting in an overall reduction of 41% in the functional fraction of sperm (Yousef, 2005). Afssa subsequently believes that the supplementation value set by the EVM (13 mg/d) cannot be adopted and agrees with EFSA on the impossibility of setting a UL for tin.

Tin can contaminate food. Maximum regulatory levels of tin have been set (Regulation (EC) No 1881/2006) for tinned food (200 mg/kg of food), cans of drink (100 mg/kg of drink) and infant preparations (50 mg/kg of food).

Afssa highlights the discrepancy of adopting a supplementation approach (food supplements and fortification of common foods combined) by a non-essential nutrient with regard to the maximum levels adopted in foods for this substance as a contaminant.

Vanadium

EFSA (2004e) recalls that vanadium is not considered to be an essential nutrient for humans. It also points out that ingestion of vanadium-containing products harms the kidneys, spleen, lungs and adversely affects blood pressure in rats. Vanadium also affects reproduction and development in mice and rats. In humans, it can cause digestive problems. However, current data do not enable a tolerable upper intake level to be defined. Normal food provides around 10 to 20 µg a day, which is below the doses triggering adverse effects (by a factor of 3). However, intake from supplements used by athletes and body-builders (up to 0.3 mg/kg of body weight/day) can reach similar levels to those causing toxic effects in rats and humans (0.2 mg/kg of body weight/day).
EFSA (2008) insists that prolonged consumption of such supplements poses a risk. It, and particularly the AFC[23] Scientific Panel, has recently issued an unfavourable opinion on compounds containing vanadium which can be used in some types of foodstuff, including food supplements[24].
The bioavailability of these vanadium-containing compounds, except vanadium pentoxide (around 2.5% absorption of the vanadium ingested), is higher (between 12 and 60 %) than that of vanadium absorbed as part of a normal diet (less than 5 %). Consequently, consumers may be exposed to higher doses of vanadium through products containing these five compounds (vanadium citrate, bismaltolato oxo vanadium, bisglyinato oxo vanadium, vanadyl sulphate and ammonium monovanadate) than in a normal diet. In view of the information it had on the bioavailability of vanadium and the conclusions of the opinion adopted in 2004, the AFC Scientific Panel concluded that the safety of six vanadium sources, added to foods intended for the general population (including food supplements) and to foods for particular nutritional uses, could not be determined.

The IOM (2001) recommends a 1.8 mg/d dose, all intakes combined, based on the intakes observed in western diets and in account of the fact that adverse effects are not observed for these levels.

Like EFSA (2008b), Afssa is against the addition of vanadium, a non-essential nutrient, to common food and food supplements, on the basis of the assessments and risks mentioned.

[23] Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food.
[24] Vanadium citrate, bismaltolato oxo vanadium and bisglycinato oxo vanadium added for nutritional purposes to foods for particular nutritional uses and foods (including food supplements) intended for the general population and vanadyl sulphate, vanadium pentoxide and ammonium monovanadate added for nutritional purposes to food supplements.

Silicon

EFSA (2004d) recalls that silicon is not considered to be an essential nutrient for humans. It is found in foods in the form of silicon dioxide (silica) and silicates and can also be added as an anti-caking or defoaming agent in the form of silica, silicates and dimethyl polysiloxane.

In human and animal tissue, silicon can be found in 3 forms: water-soluble inorganic compounds (orthosilic acid and orthosilicates), silicone and silicone complexes and lastly insoluble polymers (polysilicic acids, silicon dioxide, silicates, amorphous silicon and quartz). Dietary intake of silicon (20 to 50 mg of silicon/day) is estimated to be 0.3 to 0.8 mg/kg of body weight/day in someone weighing 60 kg. These values do not seem to be associated with adverse effects. In dogs and guinea-pigs, the short-term oral ingestion of sodium or magnesium silicate (1.8 g/kg of body weight/day) adversely affects the kidneys, but not silicon dioxide or aluminium silicate at similar doses. The long-term oral administration of silicon dioxide at high doses (between 1170 mg and 3500 mg/kg of body weight/day, for 12 or 24 months) curbs growth in rats and mice (Takizawa et al., 1988). Instead of being considered toxic, this effect has been attributed to a nutritional imbalance due to the high dose of silica added to the diet. In humans, except for kidney stones reported in some studies (Farrer and Rajfer, 1984; Lee et al., 1993), mainly associated with the long-term use of antacid substances containing silicate, there are few adverse effects caused by the oral ingestion of silicon. EFSA believes that a maximum tolerable intake cannot be defined based on the data available.

The EVM (2003) thinks that, on the basis of the aforementioned study by Takizawa et al. (1988), a NOAEL of 2500 mg of silicon dioxide/kg of body weight/day or 1250 mg of silicon/kg of body weight/day can be set. The EVM (2003) applied a safety factor of 100 and did not consider the 700 mg/d dose of additional silicon intake to pose any risk of adverse effects.

Afssa (2004a) recalls that synthetic silica (silicon dioxide: E551) is authorised and used *quantum satis* in food supplements as an anti-caking agent. The other authorised forms of silica as additives are as follows: calcium silicate (E552), magnesium silicate and magnesium trisilicate (E553a i) and ii), sodium aluminosilicate (E555), potassium aluminium silicate (E556), calcium aluminosilicate (E559) and aluminium silicate (E559).

Afssa stresses the fact that silicon absorption in the intestine depends on the form and structure of the silicon ingested. As a result, Afssa believes that the dose put forward by the EVM, 700 mg/d in the form of silicon dioxide, for which we have sufficient experience of use as an anti-caking agent, does not pose a risk. Moreover, Afssa does not see any interest in adding silicon, a non-essential nutrient, to common food or food supplements.

It also points out the existence of silicon dioxide nanoparticles (potential impact on bioavailability), without it being possible to identify the applications clearly.

6- Summary of the recommended maximum fortification levels and maximum daily doses in food supplements

The table below presents the dietary intakes (from INCA2) and dietary reference values (ANC and UL) used to estimate the maximum levels in fortified foods and/or food supplements, which are also summarised below:

Table 8: Summary of the maximum fortification levels and maximum daily doses recommended with account taken of intake data (INCA2) and tolerable upper intake levels (UL).

	Total daily dietary intake (INCA2)		Dietary reference values		Estimated maximum level	
	Average intake	95th percentile	ANC*	UL (SCF)	Food supplements (daily dose)	Fortification of common foods (/100 kcal)
Retinol (µg)	704.5	2389	800/600	3000	800	0
Vitamin D (µg)	2.56	5.46	5	50	5	3
Vitamin E (mg)	11.63	22.06	12	300	30	1.5
Vitamin K (µg)			45		25	0
Vitamin B_1 (mg)	1.23	1.96	1.3/1.1		100	
Vitamin B_2 (mg)	1.87	2.94	1.6/1.5		40	
Vitamin B_3 (mg)	19.29	30.96	14/11	(a) 900, (b) 10	-	-
Vitamin B_5 (mg)	5.63	8.53	5		200	
Vitamin B_6 (mg)	1.74	2.76	1.8/1.5	25	1.2	5.4
Vitamin B_8 (µg)			50		0.9	
Vitamin B_9 (µg)	289.4	466.1	330/300	1000	200	30
Vitamin B_{12} (µg)	5.81	14.54	2.4		2	
Vitamin C (mg)	92.8	194.6	110		180	9
Beta-carotene (mg)	3332.9	7307.2			7	0
Calcium (mg)	913.1	1487.5	900	2500	800	43
Magnesium (mg)	291.7	457.8	420/360		300	0
Iron (mg)	13.12	21.22	9/16		14	0
Copper (mg)	1.46	2.78	2/1.5	5	2	0
Iodine (µg)	119.5	187.4	150	600	150	20 (c)
Zinc (mg)	10.69	17.28	12/10	25	2.25	0
Manganese (mg)	2.92	5.11			3.5	0
Sodium (mg)	2967.4	4872.1			not justified	
Potassium (mg)	2979.7	4416.5			1000	
Selenium (µg)	53.7	87.3	60/50	300	50	9
Chromium (µg)			65/55		25 (d)	0
Molybdenum (µg)				600	150	0
Fluoride (mg)			2.5/2	7	0	not justified (e)
Chloride (mg)					not justified	
Phosphorus (mg)	1265.3	1915.3	750		250	0
Nickel					not justified	
Boron					not justified	
Vanadium					not justified	
Tin					not justified	
Silicon					700 (f)	0

(a) Nicotinamide, (b) nicotinic acid, (c) level expressed in 20 µg /g of table salt and/or 20 µg/100g of bread products, (d) in the form of chromium chloride and chromium sulphate, (e) excluding already fortified foods: table salt and chewing gum, (f) in the form of silicon dioxide, (-) impossible to make a decision.

* The ANCs are presented for men and then for women when there is a distinction

Afssa would like to point out that the fortification levels mentioned in Table 8 are maximum levels that should not be exceeded and which only take account of consumer safety, not the nutritional benefits of such a fortification.

In conclusion, Afssa recalls that:

- this opinion seeks to provide administrators with non-exhaustive **clarification** on a case-by-case basis and alert identification information on the fortification methods provided for by Regulation (EC) No 1925/2006;
- the notion of the nutritional benefit of fortification is key: the estimated average requirement should be considered to determine the **optimum fortification levels** and the tolerable upper intake level only enables **maximum fortification levels** to be set;
- it is essential to eat **a balanced, varied diet** to obtain the correct balance of nutrients. Disruption, via excess intake of certain nutrients, of the natural physiological balances, often complex mechanisms of homeostasis maintenance and regulation of the intestinal environment composition should be avoided;
- **consumer information** should be provided in the event of vitamin and mineral fortification;
- the **public health impact** of consuming fortified foods and food supplements must be **assessed on a regular basis**.

7- Annexes

Annex 1: Maximum fortification values and maximum daily doses for food supplements put forward by different models.

Table 1.1: Maximum amounts (in mg or µg/100 kcal), calculated according to the different models for vitamins for fortified foods

Models / Vitamins	ILSI	Denmark (DFVR)	BfR	15% RDA[25]
Total vitamin A (µg)	0	0	0	120
Beta-carotene (µg)	-	0	0	
Vitamin B_1-thiamin (mg)	10	5	1.3	0.2
Vitamin B_2-riboflavin (mg)	44	3	1.5	0.24
Vitamin B_3-niacin (mg)	191	48	17	2.7
Vitamin B_5-pantothenic acid (mg)	109	17	6	0.9
Vitamin B_6-pyridoxin (mg)	5	1	1.2	0.3
Vitamin B_9-folic acid (µg)	122	45	200	30
Vitamin B_{12} (µg)	662	190	3	0.15
Vitamin C (mg)	403	84	100	9
Vitamin D (µg)	9	3	0	0.75
Vitamin E (mg)	218	32	0	1.5

Table 1.2: Maximum amounts (in mg or µg/100 kcal), calculated according to the different models for minerals for fortified foods

Models / Minerals	ILSI	Denmark (DFVR)	BfR	15% RDA
Calcium (mg)	30	43		120
Copper (mg)	2	0	0	0.3
Iron (mg)	5	0	0	2.1
Iodine (µg)	165	0	0	22.5
Magnesium (mg)	54	0	15	45
Manganese (mg)	-	-	0	0.3
Phosphorus (mg)	312	294	0	120
Potassium (mg)	-	-	0	300
Selenium (µg)	47	2	0	9
Sodium (mg)	-	-	0	90
Zinc (mg)	5	0	0	1,8

[25] This hypothesis is conventional and unrelated to the regulation.

Table 1.3: Maximum amounts (in daily dose) to consider for vitamins via food supplements

Models / Vitamins	ERNA-EPHM	BfR	French regulations: Order of 9 May 2006
Total vitamin A (µg)	1000*	400	800
Beta-carotene (µg)	7*	2	-
Vitamin B_1-thiamin (mg)	-	4	4.2
Vitamin B_2-riboflavin (mg)	-	4,5	4.8
Vitamin B_3-niacin (mg)	820	17	54
Vitamin B_5-pantothenic acid (mg)	-	18	18
Vitamin B_6-pyridoxin (mg)	93*	5.4	2
Vitamin B_9-folic acid (µg)	600	400	200
Vitamin B_{12} (µg)	-	9*	3
Vitamin C (mg)	1750	225	180
Vitamin D (µg)	35	5	5
Vitamin E (mg)	970*	15	30

* when several values were put forward, the highest was selected

Table 1.4: Maximum amounts (in daily dose) to consider for minerals via food supplements

Models / Minerals	ERNA-EPHM	BfR	French regulations: Order of 9 May 2006
Calcium (mg)	1500*	500	800
Copper (mg)	2-	0	2
Iron (mg)	20*	0	14
Iodine (µg)	200*	100	150
Magnesium (mg)	250	250	300
Manganese (mg)	2	0	3.5
Phosphorus (mg)	1250	250	450
Potassium (mg)	-	500	80
Selenium (µg)	200	30	50
Sodium (mg)	-	0	
Zinc (mg)	15	2.25	15

Annex 2: Additional information on vitamin A, β-carotene, folic acid, vitamin C, vitamin D, iodine, fluoride and chromium.

Regarding vitamin A

The vitamin formulations supplying vitamin A include retinol, retinol acetate, retinol palmitate and beta-carotene.

In 2004, Afssa's report on the assessment of nutritional requirements for animals of vitamins A, D and E and of the risks for animal and consumer health of high intakes in food-producing animals (2004c) notes that: (i) the nutritional requirements of vitamin A for the French population are covered by a balanced and varied diet; (ii) there are no groups at risk of inadequate vitamin A intake, based on INCA 1 findings and (iii) vitamin A belongs to the micronutrients for which there is a risk of exceeding the French safety guidelines, particularly in infants and young children whose average vitamin A intakes exceed the ANCs.

The SCF (2002c) states that post-menopausal women should restrict their total intake to 1500 µg/d due to the increase in fracture risk associated with high intakes.

Publications confirm that the prevalence of inadequate total vitamin A intake is very low in French adults, and much lower than for other vitamins or minerals (Touvier et al., 2005, de Lauzon et al., 2004). No groups at risk of total vitamin A deficiency can be identified in the French population.

To date, Afssa considers that these findings do not cast doubt over the tolerable upper intake levels and confirms the restriction regarding vitamin A intake in post-menopausal women. Afssa also reports that, according to the consumption data from the INCA2 study, 3% of the adult population exceed the UL and 13.5% of post-menopausal women exceed the 1500 µg/d limit.

Regarding β-carotene

The adverse effects associated with high intakes of β-carotene partly depend on its form of intake and exposure of consumers to environmental carcinogens (tobacco, asbestos). This is because, during the consumption of common foods (excluding fortified foods), the only side effects reported when ingesting high doses of β-carotene concern an orange discolouration of the skin (carotenodermia) (Bendich, 1988).

However, the ATBC[26] and CARET[27] studies report that β-carotene supplements at a daily dose of 20 to 30 mg are associated with an increase in the risk of lung cancer . Moreover, Touvier et al. demonstrated that female smokers with a high intake of β-carotene had a higher risk of lung cancer (Touvier et al., 2005). In the SU.VI.MAX study, daily 6 mg supplements of β-carotene increased skin cancer risks (melanoma) in adult women (in this study, the supplements contained a cocktail of nutrients: 120 mg of vitamin C, 30 mg of vitamin E, 6 mg of β-carotène, 100 mg of selenium and 20 mg of zinc) (Hercberg et al., 2007).

It should be noted that the mechanisms leading to the cancer increase in these population groups have not been described.

Regarding folic acid

The SCF (2000b) has set a tolerable upper intake level for **folic acid**, a synthetic form of vitamin B_9, of 1000 µg/d for adults, and states that this UL also applies to pregnant and breastfeeding women. This UL is based on the observation of neurological symptoms (numbness and pins and needles in the extremities, poor coordination, cognitive problems) due to **folic acid** supplements (5 mg/d) in patients suffering from pernicious anaemia, a rare form of anaemia due to vitamin B_{12} deficiency. This is because the correction of anaemia in B_{12} deficient people with vitamin B_9 supplements increases the likelihood of neurological disorders. No UL could be set for the natural form of vitamin B_9 (**folates**). Additional folic acid intake is currently obtained via fortified foods (breakfast cereals).

Without presupposing EFSA's forthcoming conclusions on the risks and benefits of folic acid fortification for the general population, Afssa would already like to mention the conflicting results of recent publications, indicating either a reduction or an increase in the cancer risk from high vitamin B_9 intakes (folic acid and/or folates).

One study showed that people presenting methylenetetrahydrofolate reductase (MTHFR) polymorphism, inducing lower folate plasma levels, had a reduced risk of colon cancer (Van Guelpen et al., 2006). In a prospective study on 25400 women, the ingestion of natural dietary **folates** (up to

[26] Alpha-Tocopherol Beta-Carotene cancer prevention study.
[27] Beta-Carotene and Retinol Efficacy Trial.

337 µg/d) or of fortified foods providing up to 412 µg/d of folates, would not be significantly linked to breast cancer risk, while **folic acid** supplements at doses over 400 µg/d would increase the relative risk of breast cancer (Stolzenberg-Solomon et al., 2006). In the same way, in an intervention study recommending **folic acid** supplementation for colorectal adenoma prevention, supplementation (1 mg/d over 3 to 8 years) is associated with an increased risk in the spread of colorectal adenoma towards the large adenoma stage and with the incidence of other cancers, particularly prostate cancer (Cole et al., 2007). This risk may be associated either with stimulation of DNA synthesis or DNA hypermethylation by methyltetrahydrofolate (product of the reduction of methylenetetrahydrofolate by MTHFR).
Furthermore, it is acknowledged that folic acid supplementation in women at the very beginning of pregnancy has a beneficial effect on the prevention of neural tube defects.

Regarding vitamin C
Even if the pro-oxidant effects of vitamin C described to date need confirming by other studies, the findings in the literature agree on the pro-oxidant effects of intakes from 500 mg/d or plasma levels exceeding 100 µM. This plasma level exceeds the one observed after dietary intake of vitamin C (up to 200 mg), namely 60-80 µmol/l. These pro-oxidant effects are therefore specific to vitamin C intakes in addition to food, insofar as only supplements can reach 500 mg/d doses and plasma levels of 100 µM.

Afssa (*currently being written*) also states that:
- the pro-oxidant effect of vitamin C, like its antioxidant effect, is tissue-specific;
- vitamin C can have pro-oxidant effects in the presence or not of iron, independently of its antioxidant properties;
- the pro-oxidant and antioxidant effects of vitamin C can lead to a modification in the adaptive response during high intake, the consequences of which can be interpreted in stress situations on certain exposed tissues;
- vitamin C may release iron from complexation sites, making it possible to regulate its pro-oxidant activity;
- interaction between iron and vitamin C would seem to favour the Fenton reaction and the production of the highly reactive radical hydroxyl.

Regarding vitamin D
Afssa recalls that exogenous vitamin D intake comes not only from our diet but also from medicines for a not insignificant proportion of the general population (prevention of vitamin D deficiency in infants up to 2-5 years old, in pregnant women and in the elderly). However, the adverse effects of chronic intakes over 20-40 µg/d, on renal function and the risk of nephrolithiasis for example, have not been studied in much detail. As a result, it would be prudent to limit the fortification vectors to a few types of food (milk and dairy products, oils and spreadable fats, milk substitutes), as is currently the case in most European countries.

Regarding chromium
Chromium toxicity, reported in the scientific literature, mainly concerns chromium picolinate (2-pyridinecarboxylic acid salt, which is better absorbed than other forms). *In vitro* studies reveal a clastogenic effect of chromium picolinate and some authors consider it to be a mutagen (Stearns et al., 2002, Whittaker et al., 2005, Coryell & Stearns, 2006). That said, another study measuring the DNA oxidative damage of keratinocytes (Hininger et al., 2007) did not reveal any genotoxicity.
The *in vivo* studies available to date do not provide any arguments demonstrating a risk associated with exposure to chromium picolinate in rodents. Concerning the genotoxicity risk , a recent study on chromosomal aberration in rats receiving chromium picolinate (at doses of 33, 250 or 2000 mg/kg of body weight) proved negative (Komorowski et al., 2008). Another recent study in mice shows that a daily dietary intake of chromium picolinate of up to 200 mg/kg of food during gestation and breastfeeding did not result in any adverse effects on the neurological development of the litter(Bailey et al., 2008).
As for toxicity studies in humans, none have revealed a toxic effect of chromium picolinate at doses ranging from 500 µg/d to 1 mg/d for periods running from 4 to 10 months (Anderson et al., 1997, Cheng et al., 1999, Cefalu et al., 1999).
The new studies available to date seem to dismiss the risk of toxicity on the genome and neurological development, under physiological intake conditions. However, given the data mentioned previously and the study by Preuss et al., (2008) which shows that chromium has different effects depending on supplement form, Afssa believes that: (i) there are not enough data to set a tolerable upper intake

level, (ii) the safety of prolonged chromium picolinate supplementation has not been determined and (iii) the use of chromium is more for therapeutic than nutritional purposes.

The results' analysis of trivalent chromium supplement trials clearly distinguishes two types of population: (i) the general population, in which no response to supplementation has been observed (Althuis et al., 2002) and (ii) specific populations (the elderly, obese people, metabolic syndrome sufferers and type 2 diabetics), with chromium deficiency and who may respond depending on the form, dose and duration of the supplementation.
Over the last ten years, studies have revealed the role of chromium in improving glycaemic control and associated biological parameters, in glucose-intolerant people (Ravina et al., 2005), type 1 and 2 diabetics and people suffering from gestational diabetes or diabetes induced by corticosteroids (Anderson, 2000). Intervention studies have shown a decrease in insulin resistance (Martin et al., 2006, Albarracin et al., 2008) for chromium picolinate intakes of 1,000 µg and 600 µg respectively. These effects seem to be dose-dependent and associated with supplement form. Another study, for which 400 µg/d of chromium was administered in yeast form rather than as chromium picolinate, does not confirm these results (Kleefstra et al., 2007).
Accordingly, Afssa believes that chromium's
effectiveness on insulin resistance has only been proven for chromium picolinate and for advanced forms of obesity and severe insulin resistance (Wang et al., 2007).
In the general population however, studies have demonstrated that using chromium in the form of picolinate to lose weight (Lukaski et al., 2007) or to increase muscular mass is not appropriate (Lukaski, 2000; Pittler et al., 2003).

Regarding fluoride
The main and most common risk associated with excess fluoride intake via ingestion is dental fluorosis. This is caused by excess fluoride intake, over several months or years, during the period of tooth mineralisation. Excess fluoride intake while the enamel is maturing but before the teeth push through, between birth and the age of 8, when enamel formation is complete, can lead to a reduction in the enamel mineral content and to dental fluorosis, not only of milk teeth but above all of permanent teeth. The incidence and severity of the dental fluorosis depends on the level ingested. Fluorosis is irreversible and characterised by the stained appearance of dental enamel. In France, the prevalence of dental fluorosis is estimated to be around 3% according to epidemiological surveys.

In adults, fluoride accretion in the bones increases bone density, but excess intake (above 8 mg/d) over a long period of time can cause skeletal fluorosis, characterised by affected bones, joints (arthritis) and ligament and tendon supporting tissues. Studies have shown that oral administration for therapeutic purposes of fluorides over several years (from 0.6 mg per kg of body weight and per day) in post-menopausal women significantly increased the risk of non-vertebral bone fractures (EFSA, 2005).

In 2008, EFSA's opinion on sodium monofluorophosphate points out that the tolerable upper intake levels for fluoride, based on age (EFSA, 2005), can be exceeded when supplementation is recommended, particularly for children drinking water containing 1 mg/L of fluoride. EFSA (2008c), like Afssaps (2008) considers there to be a risk of moderate dental fluorosis from an intake of 0.1 mg per kg of body weight and per day.
Afssaps states in its progress report published in 2008 that, at this dose, metabolic alterations of ameloblasts and odontoblasts can be observed. The accumulation of and unfamiliarity with diverse sources of fluoride intake (drinking water, foods, fluoride supplements given particularly to young children) are what cause most cases of dental fluorosis. As a result, Afssaps recommends that a personalised assessment of daily fluoride intake be carried out prior to any recommendation for fluoride medication (drops/tablets). Accordingly, in keeping with Afssa's view of the conditions for using drinking water (2003b), Afssaps believes that the recommended dose for fluoride is 0.05 mg per kg of body weight per day, without exceeding 1 mg per day, all fluoride intakes combined, when the water consumed contains fluoride levels of less than or equal to 0.3 mg/L. In regions where tap water contains more than 0.3 mg/L of fluoride, no supplementation is needed.
These findings confirm the difficulty of a policy for using fluoride in preventing tooth decay, in a context where intake sources are numerous.

Regarding iodine

In industrialised countries, dairy products are the main source of iodine intake. The estimated average requirement is 120 µg/d.

Afssa's opinion of 31 July 2002 reports a fortification level of 10-15 µg/g to 15-20 µg/g of iodised salt for households, canteens and restaurants.

For the record, Afssa's report entitled "Assessment of the nutritional impact of introducing iodised compounds in processed food products" indicates various points that should be taken into account to correct iodine deficiency in the French population, while protecting young children from the risk of exceeding the tolerable upper intake level, without the use of systematic fortification:

- any proposal of a new food vector for iodine with a view to improving iodine intake in the general population must be associated with a 15-20% reduction in iodine concentrations in dairy products, since current levels expose high consumers, and particularly young children, to risks of exceeding the ULs. The proposals enabling the achievement of this prerequisite to any fortification are discussed in the forthcoming report entitled "Impact of animal nutrition practices on the composition of animal products for human consumption. The case of iodine" (*currently being written*);
- A 20 µg fortification of iodine per 100 g of bread, crispbreads and croissant-type pastries that may be fortified with iodine would have a particularly marked impact on the breakdown of dietary iodine intake in the population. This fortification accounts for an average reduction of around 50% in the risk of inadequate iodine intake in adults, and reduces the prevalence of dietary iodine intakes falling below the basic requirement to less than 5%;
- table salt could be an iodine fortification vector in bread products (bread, crispbreads, croissant-type pastries);
- the concentration of iodine in salt intended for the iodine fortification of bread, crispbreads and croissant-type pastries is independent of the iodine level of table and cooking salt and its variation is linked to evolving trends in consumption of such products.

8- Bibliography

Afssa (2001) Conditions pour un enrichissement satisfaisant pour la nutrition et la sécurité des consommateurs, http://www.afssa.fr/Documents/NUT-Ra-vitaminesmineraux.pdf.

Afssa (2002), Report on Salt:Evaluation and recommendations, http://www.afssa.fr/Documents/NUT-Ra-Sel.pdf.

Afssa (2003a) Avis du 28 avril 2003 relatif à l'évaluation du projet d'arrêté concernant les nutriments et les substances pouvant être employés dans la fabrication des compléments alimentaires. Plus précisément, l'évaluation concerne la détermination de doses maximales pour la vitamine K, le fluor, le chlore, le sodium et le phosphore,http://www.afssa.fr/Documents/NUT2003sa0032.pdf.

Afssa (2003b) Rapport du Comité d'experts spécialisé "Eaux" concernant la proposition de fixation d'une valeur limite pour le fluor dans les eaux minérales naturelles. http://www.afssa.fr/Documents/EAUX-Ra-Fluor.pdf.

Afssa (2004a) Avis du 16 décembre 2004 relatif à l'évaluation de l'emploi dans les compléments alimentaires d'un ingrédient alimentaire composé de deux substances : acide silicique et hydrolysat de collagène de poisson et des justificatifs concernant l'allégation « Protection de la peau et des cheveux contre les effets du vieillissement par un apport de silicium biodisponible » http://www.afssa.fr/Documents/NUT2004sa0211.pdf.

Afssa (2004b) Specification for the selection of a Nutrient-Vector Food pair, http://www.afssa.fr/Documents/NUT-Ra-AlimentsvecteursEN.pdf

Afssa (2004c) Evaluation des besoins nutritionnels des animaux en vitamines A, D et E ainsi que des risques pour la santé animale et la santé du consommateur, liés à des apports élevés chez les animaux producteurs d'aliments. http://www.afssa.fr/Documents/ALAN-Ra-vitaminesADE.pdf.

Afssa (2004d) Avis du 12 octobre 2004 relatif à l'évaluation de deux projets de textes concernant les compléments alimentaires : justification des teneurs maximales nulles pour le fluor et la vitamine K, proposition d'une mention obligatoire prévenant les patients sous anti-coagulants de ne pas consommer de compléments alimentaires contenant de la vitamine K, et évaluation toxicologique de nouvelles teneurs maximales pour les vitamines E, B1, B2, PP, B5, B6, B12, B8, C., http://www.afssa.fr/Documents/NUT2004sa0210.pdf.

Afssa (2005a) Évaluation de l'impact nutritionnel de l'introduction de composés iodés dans les produits agroalimentaires, http://www.afssa.fr/Documents/NUT-RA-impactiode.pdf.

Afssa (2005b) Evaluation des risques sanitaires liés au dépassement de la limite de qualité du nickel dans les eaux destinées à la consommation humaine, Evaluation des risques sanitaires liés aux situations de dépassement des limites de références de qualité des eaux destinées à la consommation humaine, Fiche 12, http://www.afssa.fr/Documents/EAUX-Ra-LimitesRef.pdf.

Afssa (2005c) Avis du 1 décembre 2005 relatif à une demande d'évaluation relative à un projet de directive visant à compléter la liste des vitamines et minéraux pouvant être utilisés dans les compléments alimentaires : ajout du bore dans l'annexe 1 et de l'acide borique, duborate de sodium et du 5-MéthylTétraHydroFolate (5-MTHF) dans l'annexe 2 de la directive 2002/46/CE relative aux compléments alimentaires, http://www.afssa.fr/Documents/NUT2005sa0340.pdf.

Afssa (2006) Avis du 16 janvier 2006 relatif à l'évaluation de la sécurité et des allégations (concernant le bronzage) d'un complément alimentaire, à base d'un extrait de fougère (Polypodium leucotomos), de thé vert, de béta-carotène et de magnésium, http://www.afssa.fr/Documents/NUT2004sa0314.pdf.

Afssa (2008a) Avis du 28 janvier 2008 relatif à l'évaluation des justificatifs concernant le dépassement des doses maximales admises par l'arrêté du 9 mai 2006 relatif aux nutriments pouvant être employés dans des compléments alimentaires pour le potassium à la dose de 800 mg (élément), sous forme de bicarbonate ou citrate au lieu de la dose de 80 mg autorisée, http://www.afssa.fr/Documents/NUT2006sa0358.pdf.

Afssa (2008b) Avis du 1 juillet 2008 relatif à la demande d'informations générales sur la toxicité du Nickel dans la chaîne alimentaire, http://www.afssa.fr/Documents/RCCP2007sa0245.pdf.

Afssa (2008c) Avis du 13 juillet 2008 relatif à l'évaluation des teneurs en vitamines et minéraux des denrées enrichies et des compléments alimentaires: vitamine K, http://www.afssa.fr/Documents/NUT2007sa0315.pdf.

Afssa (2008d) Opinion of 13 October 2008 on the estimation of vitamin and mineral levels for fortified foods and supplements: synopsis of a risk assessment tool based on vitamins and minerals intakes from the INCA 2 data, according to different scenarios

Afssaps (2008) Using fluoride to prevent tooth decay in children under 18 years of age, www. afssaps.sante.fr.

Albarracin, C. A., Fuqua, B. C., Evans, J. L. and Goldfine, I. D. (2008) Chromium picolinate and biotin combination improves glucose metabolism in treated, uncontrolled overweight to obese patients with type 2 diabetes, Diabetes Metab Res Rev, 24, 41-51.

Anderson, R. A. (2000) Chromium in the prevention and control of diabetes, Diabetes Metab, 26, 22-7.

Anderson, R. A. (1997a) Chromium as an essential nutrient for humans, Regul Toxicol Pharmacol, 26, S35-41.

Arnaud,J. (2001) Apports nutritionnels conseillés pour la population française, Paris

Bagchi, D., Stohs, S. J., Downs, B. W., Bagchi, M. and Preuss, H. G. (2002) Cytotoxicity and oxidative mechanisms of different forms of chromium, Toxicology, 180, 5-22.

Bailey, M. M., Boohaker, J. G., Jernigan, P. L., Townsend, M. B., Sturdivant, J., Rasco, J. F., Vincent, J. B. and Hood, R. D. (2008) Effects of Pre- and Postnatal Exposure to Chromium Picolinate or Picolinic Acid on Neurological Development in CD-1 Mice, Biol Trace Elem Res, 124, 70-82.

Bendich, A. (1988) The safety of beta-carotene, Nutr Cancer, 11, 207-14.

Cefalu, W. T., Bell-Farrow, A. D., Stegner, J., Wang, Z. Q., King, T., Morgan, T. and Terry, J. G. (1999) Effect of chromium picolinate on insulin sensitivity in vivo, J. Trace Elem. Exp. Med., 12, 71-83

Cheng, N., Zhu, X., Shi, H., Wu, W., Chi, J., Cheng, J. and Anderson, R. A. (1999) Follow-up survey of people in China with type 2 diabetes mellitus consuming supplemental chromium, J. Trace Elem. Exp. Med., 12, 55-60.

Cole, B. F., Baron, J. A., Sandler, R. S., Haile, R. W., Ahnen, D. J., Bresalier, R. S., McKeown-Eyssen, G., Summers, R. W., Rothstein, R. I., Burke, C. A., Snover, D. C., Church, T. R., Allen, J. I., Robertson, D. J., Beck, G. J., Bond, J. H., Byers, T., Mandel, J. S., Mott, L. A., Pearson, L. H., Barry, E. L., Rees, J. R., Marcon, N., Saibil, F., Ueland, P. M. and Greenberg, E. R. (2007) Folic acid for the prevention of colorectal adenomas: a randomized clinical trial, Jama, 297, 2351-9.

Coryell, V. H. and Stearns, D. M. (2006) Molecular analysis of hprt mutations induced by chromium picolinate in CHO AA8 cells, Mutat Res, 610, 114-23.

Coudray, C and Hercberg,S in Martin, A., Azaïs-Braesco, V., Bresson, J. L., Couet, C., Cynober, L., Guéguen, L., Lairon, D., Laville, M., Legrand, P., Patureau Mirand, P., Pérès, G., Potier de Courcy, G. and Vidailhet, M. (2001) Apports nutritionnels conseillés pour la population française, Paris.

De Lauzon, B., Volatier, J. L. and Martin, A. (2004) A Monte Carlo simulation to validate the EAR cut-point method for assessing the prevalence of nutrient inadequacy at the population level, Public Health Nutr, 7, 893-900.

Domke, A. (2004a) Use of Minerals in Foods - Toxicological and nutritional-physiological aspects, Federal Institute for Risk Assessment (BfR).

Domke, A. (2004b) Use of Vitamins in Foods - Toxicological and nutritional-physiological aspects., Federal Institute for Risk Assessment (BfR).

EFSA (2004a) Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies (NDA) a request from the Commission related to the Tolerable Upper Intake Level of Vitamin C (L-Ascorbic acid, its calcium, potassium and sodium salts and L-ascorbyl-6-palmitate), The Efsa journal, 59, http://www.efsa.europa.eu/cs/BlobServer/Scientific_Opinion/opinion_nda_06_ej59_vitc_en1,2.pdf.

EFSA (2004b) Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to the Tolerable Upper Intake Level of Boron (Sodium Borate and Boric Acid), The Efsa journal, 80, http://www.efsa.europa.eu/cs/BlobServer/Scientific_Opinion/opinion_nda08_ej80_boron_v2_en1.pdf.

EFSA (2004c) Opinion of the scientific panel on dietetic products, nutrition and allergies on a request from the commission related to the tolerable upper intake level of Chromium.

EFSA (2004d) Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to the Tolerable Upper Intake Level of Silicon., The Efsa journal, 60, 1-11.

EFSA (2004e) Opinion of the scientific panel on dietetic products, nutrition and allergies on a request from the commission related to the tolerable upper intake level of Vanadium, The Efsa journal, 33, 1-22.

EFSA (2005a) Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to the Tolerable Upper Intake Level of Chloride, The Efsa journal, 210, http://www.efsa.europa.eu/cs/BlobServer/Scientific_Opinion/nda_opinion_ej210_chloride_v2_en1,1.pdf.

EFSA (2005b) Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to the Tolerable Upper Intake Level of Fluoride, The Efsa journal, 192, 1-65.

EFSA (2005c) Opinion of the scientific panel on dietetic products, nutrition and allergies on a request from the commission related to the tolerable upper intake level of Nickel, The Efsa journal, 146, 1-21.

EFSA (2005d) Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to the Tolerable Upper Intake Level of Sodium, The Efsa journal, 209, http://www.efsa.europa.eu/cs/BlobServer/Scientific_Opinion/nda_opinion_ej209_sodium_v2_en1.pdf.

EFSA (2005e) Opinion of the scientific panel on dietetic products, nutrition and allergies on a request from the commission related to the tolerable upper intake level of Tin, The Efsa journal, 254, 1-25.

EFSA (2008a) Calcium fluoride as a source of fluoride added fornutritional purposes to food supplements 1 Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food, The EFSA Journal 882, 1-15.

EFSA (2008 b) Vanadium citrate, bismaltolato oxo vanadium and bisglycinato oxo vanadium added for nutritional purposes to foods for particular nutritional uses and foods (including food supplements) intended for the general population and vanadyl sulphate, vanadium pentoxide and ammonium monovanadate added for nutritional purposes to food supplements, The Efsa journal, 634, 1-15.

EFSA (2008c) Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food related to Sodium monofluorophosphate as a source of fluoride added for nutritional purposes to food supplements, The Efsa journal, 886

ERNA/EHPM (2004) Vitamin and Mineral Supplements : a risk management model.

EVM (2002) Review of niacin.

EVM (2003) Safe upper levels for vitamins and minerals, Food Standard Agency, http://www.foodstandards.gov.uk.

Farrer, J. H. and Rajfer, J. (1984) Silicate urolithiasis, J Urol, 132, 739-740.

Flynn, A., Moreiras, O., Stehle, P., Fletcher, R. J., Muller, D. J. and Rolland, V. (2003) Vitamins and minerals: a model for safe addition to foods, Eur J Nutr, 42, 118-30.

FSA Comparison of upper levels set for individual nutrients by EVM and IOM where EFSA/SCF did not set tolerable upper intake levels (with focus on supplemental intake, EVM.

Guégen,L. (2001) Apports nutritionnels conseillés pour la population française, Paris

Hercberg, S., Ezzedine, K., Guinot, C., Preziosi, P., Galan, P., Bertrais, S., Estaquio, C., Briancon, S., Favier, A., Latreille, J. and Malvy, D. (2007) Antioxidant supplementation increases the risk of skin cancers in women but not in men, journal of Nutrition, 137, 2098-2105.

Hininger, I., Benaraba, R., Osman, M., Faure, H., Marie Roussel, A. and Anderson, R. A. (2007) Safety of trivalent chromium complexes: no evidence for DNA damage in human HaCaT keratinocytes, Free Radic Biol Med, 42, 1759-65.

IOM (2000) Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc Food and Nutrition Board and Institute of Medicine.

Ishimatsu, S., Kawamoto, T., Matsuno, K. and Kodama, Y. (1995) Distribution of various nickel compounds in rat organs after oral administration, Biol Trace Elem Res, 49, 43-52.

Lukaski, H. C. (2000) Magnesium, zinc, and chromium nutriture and physical activity, Am J Clin Nutr, 72, 585S-93S.

Lukaski, H. C., Siders, W. A. and Penland, J. G. (2007) Chromium picolinate supplementation in women: effects on body weight, composition, and iron status, Nutrition, 23, 187-95.

Kleefstra, N., Houweling, S. T., Bakker, S. J., Verhoeven, S., Gans, R. O., Meyboom-de Jong, B. and Bilo, H. J. (2007) Chromium treatment has no effect in patients with type 2 diabetes in a Western population: a randomized, double-blind, placebo-controlled trial, Diabetes Care, 30, 1092-6.

Komorowski, J. R., Greenberg, D. and Juturu, V. (2008) Chromium picolinate does not produce chromosome damage, Toxicol In Vitro, 22, 819-26.

Lee, M. H., Lee, Y. H., Hsu, T. H., Chen, M. T. and Chang, L. S. (1993) Silica stone--development due to long time oral trisilicate intake, Scand J Urol Nephrol, 27, 267-9.

Martin, A., Azaïs-Braesco, V., Bresson, J. L., Couet, C., Cynober, L., Guéguen, L., Lairon, D., Laville, M., Legrand, P., Patureau Mirand, P., Pérès, G., Potier de Courcy, G. and Vidailhet, M. (2001) Apports nutritionnels conseillés pour la population française, Paris.

Martin, J., Wang, Z. Q., Zhang, X. H., Wachtel, D., Volaufova, J., Matthews, D. E. and Cefalu, W. T. (2006) Chromium picolinate supplementation attenuates body weight gain and increases insulin sensitivity in subjects with type 2 diabetes, Diabetes Care, 29, 1826-32.

Pittler, M. H., Stevinson, C. and Ernst, E. (2003) Chromium picolinate for reducing body weight: meta-analysis of randomized trials, Int J Obes Relat Metab Disord, 27, 522-9.

Preuss, H. G., Echard, B., Perricone, N. V., Bagchi, D., Yasmin, T. and Stohs, S. J. (2008) Comparing metabolic effects of six different commercial trivalent chromium compounds, J Inorg Biochem, 102, 1986-90.

Rasmussen, S. E., Andersen, N. L., Dragsted, L. O. and Larsen, J. C. (2006) A safe strategy for addition of vitamins and minerals to foods, Eur J Nutr, 45, 123-35.

Ravina, A., Slezak, L., Rubal, A. and Mirsky, N. (1995) Clinical use of the trace element chromium (III) in the treatment of diabetes mellitus, J Trace Elem Exper Med, 8, 183–190.

Rayssiguier, Y., Boirie, Y., Durlach, J. in Martin, A., Azaïs-Braesco, V., Bresson, J. L., Couet, C., Cynober, L., Guéguen, L., Lairon, D., Laville, M., Legrand, P., Patureau Mirand, P., Pérès, G., Potier de Courcy, G. and Vidailhet, M. (2001) Apports nutritionnels conseillés pour la population française, Paris.

SCF (2000a) Opinion of the scientific committee on food on the tolerable upper intake level of beta carotene.

SCF (2000b) Opinion of the scientific committee on food on the tolerable upper intake level of folate.

SCF (2000c) Opinion of the scientific committee on food on the tolerable upper intake level of manganese.

SCF (2000d) Opinion of the scientific committee on food on the tolerable upper intake level of molybdenum.

SCF (2000e) Opinion of the scientific committee on food on the tolerable upper intake level of vitamin B2.

SCF (2000f) Opinion of the scientific committee on food on the tolerable upper intake level of vitamin B12.

SCF (2001a) Opinion of the scientific committee on food on the tolerable upper intake level of biotin.

SCF (2001b) Opinion of the scientific committee on food on the tolerable upper intake level of vitamin B1.

SCF (2002a) Opinion of the scientific committee on food on the tolerable upper intake level of nicotinic acid and nicotinamide (niacin).

SCF (2002b) Opinion of the scientific committee on food on the tolerable upper intake level of pantothenic acid.

SCF (2002c) Opinion of the scientific committee on food on the tolerable upper intake level of preformed Vitamin A (retinol and retinyl esters).

SCF (2003) Opinion of the scientific committee on food on the tolerable upper intake level of vitamin K.

Stolzenberg-Solomon, R. Z., Chang, S. C., Leitzmann, M. F., Johnson, K. A., Johnson, C., Buys, S. S., Hoover, R. N. and Ziegler, R. G. (2006) Folate intake, alcohol use, and postmenopausal breast cancer risk in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, Am J Clin Nutr, 83, 895-904.

Stearns, D. M., Silveira, S. M., Wolf, K. K. and Luke, A. M. (2002) Chromium(III) tris(picolinate) is mutagenic at the hypoxanthine (guanine) phosphoribosyltransferase locus in Chinese hamster ovary cells, Mutat Res, 513, 135-42.

SU.VI.MAX (1994) Portions alimentaires : manuel photos pour l'estimation des quantités.

Takizawa, Y., Hirasawa, F., Noritomi, E., Aida, M., Tsunoda, H. and Uesugi, S. (1988) Oral ingestion of SYLOID to mice and rats and its chronic toxicity and carcinogenicity., Acta Med Biol, 36, 27-56.

Touvier, M., Boutron-Ruault, M. C., Volatier, J. L. and Martin, A. (2005) Efficacy and safety of regular vitamin and mineral supplement use in France: results from the ECCA study, Int J Vitam Nutr Res, 75, 201-9.

Van Guelpen, B., Hultdin, J., Johansson, I., Hallmans, G., Stenling, R., Riboli, E., Winkvist, A. and Palmqvist, R. (2006) Low folate levels may protect against colorectal cancer, Gut, 55, 1461-6.

Wang, Z. Q., Qin, J., Martin, J., Zhang, X. H., Sereda, O., Anderson, R. A., Pinsonat, P. and Cefalu, W. T. (2007) Phenotype of subjects with type 2 diabetes mellitus may determine clinical response to chromium supplementation, Metabolism, 56, 1652-5.

Whittaker, P., San, R. H., Clarke, J. J., Seifried, H. E. and Dunkel, V. C. (2005) Mutagenicity of chromium picolinate and its components in Salmonella typhimurium and L5178Y mouse lymphoma cells, Food Chem Toxicol, 43, 1619-25.

Yousef, M. I. (2005) Protective role of ascorbic acid to enhance reproductive performance of male rabbits treated with stannous chloride, Toxicology, 207, 81-9.

The Director General
Pascale Briand