Report from the AFSSA Expert Committee on Human Nutrition on food fortification by vitamin and mineral: meeting the nutritional and safety needs of the consumer

Case no. 2000-SA-0239
Author of the request : DGCCRF

With regard to the preliminary draft of the directive on the voluntary addition of vitamins and minerals to foods, specifically on measures which are likely to influence public health such as the definition of fortification, more precise conditions of use than those described in the project, and criteria for the maintenance of the highest possible levels of vitamins and minerals in foods. Questions are formulated regarding the rationale for fortification by minerals such as sodium, potassium and molybdenum. In this context, only a certain group of foods should be fortified.
Regarding the establishment of maximal levels, the Commission and certain Member States are in favour of a purely toxicological approach that takes into consideration tolerable upper intake level. Other countries such as France request that nutritional issues and arguments also be considered for setting the maximum level of minerals and vitamins.
It would be useful that the French delegation had at its disposal scientific arguments to justify its position.

1. General overview

A preface to the directive of the European Commission was presented in September 2000 to established harmonized regulations about the voluntary addition of vitamins and minerals to foods. The French delegation has certain reservations or questions concerning the establishment of maximum levels of vitamins and minerals as well as labelling of vitamin- or mineral-fortified foods.

Fortification experts have for several years questioned the rationale for fortification, leading to further questions i.e.:

- What is the micronutrient status of the population, and specifically:
    - Are there groups at risk for inadequate intake of nutrients? If so, which nutrients, to what degree, and what are the safety issues for the consumer?
    - Furthermore, how should these at-risk groups be reached without putting the rest of the population at risk of excess intake?

1.1 Objectives

As per the proposal of the AFSSA Expert Committee on Human Nutrition, a working group was created on 11 January 2001 and consisted of experts, representatives of administrations, the industry and professional organisations (Annex 1). Its mandate was to:

- " Propose a list of vitamins and minerals that could be added to commonly eaten foods,
- Propose minimum and maximum doses of these micronutrients[1];
- identify “vector” foods[2].”

1.2 Commonly eaten foods and populations concerned with these foods

The Comité d’Experts Spécialisé « Nutrition humaine » (CES) refers to commonly eaten food as all food that can be made available to the consumer, in all markets and for all members of the population, regardless of:

- age (including children of 4 years and above, adults and older people)
- physiological state (including for example pregnant women or highly physically active people)
- nutritional typology, including regional.

[1] It was considered most appropriate to propose a methodology to establish maximum fortification levels for these substances
[2] see chapter 6.2.1 : « vector foods » : appropriate or support foods

1.3 Basic principles

All statements on the fortification level must respond to the both public health and safety needs: fortification must therefore integrate the nutritional aspect as well as the consumer safety concern.

These two principles and the ensuing methodology, all fundamentally important, are further examined below.

The nutritional aspect is fundamental as it justifies food fortification. The first stage to determine which micronutrients can be fortificants is to carry out a situational analysis of the nutritional status of EU countries to establish for which nutrients is the population at risk of biological store depletion[3] or clinical deficiency[4] as defined in France by the Haut Comité de la Santé Publique (High Public Health Committee) (1).

The nutritional aspect of fortification also implies the development of a strategy to identify which foods should be fortified.

Finally, considering potential synergies and interaction of nutrients so as to end up with a properly balanced food.
These nutritional issues must be related to **consumer safety-indispensable aspect** of all public health policy- in terms of maximum content (toxicological concerns), quality of micronutrients (criteria for purity) and bioavailability.

This document presents a situation analysis on micronutrient intakes in France and puts forth tolerable upper intake limits. A proposed methodology aims to identify the proper micronutrients with which to fortify foods, and the content level of these micronutrients in foods. This methodology is herein applied to the situation in France.

1.4 Nutrition and public health in France : situation analysis

Many discussions and statements of opinion have taken place in the Conseil Supérieur d'Hygiène Publique de France (CSHPF) and the Commission interministérielle d'étude des produits destinés à une alimentation particulière (CEDAP), in terms of public health nutrition. These discussions are currently continuing at AFSSA. The following documents have served as background documents for this report:

* The Report (1998) on the assessment of the vitamin and mineral status of the French based on recent studies (2,3) allowed for certain nutrients to be classified for high, possible or no risk of biological store depletion in populations and others in terms of being consumed in excessive amounts relative to recommended intakes (Annex 3).

* The 2001 edition of " Apports nutritionnels conseillés pour la population française " (RNI) (4) (Recommended nutrient intake for the French population (RNI)) was the result of expert consensus and is a fundamental background document for the present exercise. It underlines the potential risks of fortification of foods and of increased consumption of supplements. Between the RNI and the tolerable upper intake levels is a controversial, uncertain zone. RNI must respond to 97,5% of population needs, as per latest knowledge.

* The High Public Health Committee (1), assesses the mineral and vitamin status of the French (both biological levels and intake) and puts forth recommendations for food complements, supplements and fortification. This has led to the establishment of the "Programme National Nutrition Santé", a national nutritional action plan for the next 5 years. It underlines that in so-called developed countries, the

[3] **Biological store depletion** : biological deficiency as manifested by depleted stores or functional effects due to a lack of the nutrient in question; although not clinically manifested, nutrient store depletion could affect disease states or otherwise alter the state of health of an individual.
[4] **Clinical deficiency** : Clinical manifestation of nutrient insufficiency .

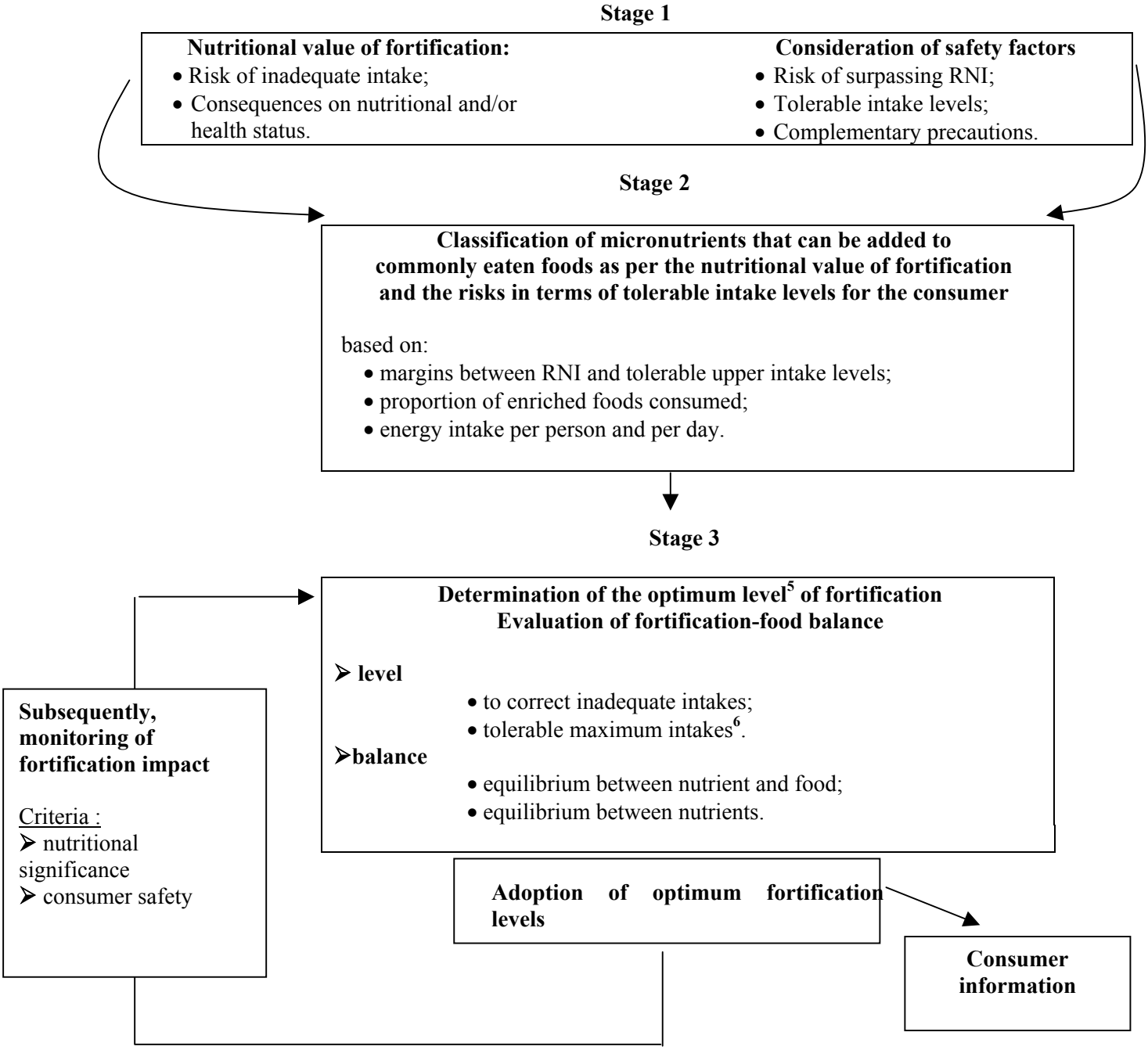
maladjustment of dietary intakes can generally not be considered the direct cause of common diseases, but diet (and the resulting nutritional status) is nonetheless an important determinant of disease.

Several simulations of micronutrient fortification of commonly eaten foods were carried out by the Observatoire des Consommations Alimentaires (OCA) in France (5) to determine, based on an actual and representative diet, beneficial and risk-free fortification for high consumers. However no quantifications for food fortification are put forth.

2. General procedure to define food fortification methods

The general procedure proposed here (Figure 1) is further developed in subsequent chapters. For each micronutrient, this procedure comprises :
1) An assessment of the nutritional value of fortification of a food by the nutrient in question, as well as safety considerations (stages 1a and 1b);
2) A proposed list of micronutrients that could be used as fortificants, as per their nutritional importance and safety considerations (stage 2);
3) The establishment of maximum fortification levels and an assessment of fortification equilibrium in foods via simulation studies (stage 3); and
4) Finally, the adoption of optimum levels and an evaluation of the relevance of fortification.

Figure 1. General procedure to define methods of fortification of commonly eaten foods



[5] **Optimum level**: The amount of a given micronutrient which can be added to a food without being a safety risk to the highest consumers (95th percentile) and which provides a potential nutritional value as it allows the lowest consumers (10th percentile) to reach or approximate the RNI.
6 **Maximum level**: The amount of a given micronutrient which can be added to a food without being a safety risk to the highest consumers (95th percentile).

3. Stage 1- a

Nutritional value of fortification with micronutrient: vitamins and mineral classification as per appropriate intakes in France

This first stage aims to outline the nutritional status of French population in terms of their micronutrient intakes. The analysis uses data from nutritional surveys carried out in France; these data were re-evaluated based on 2001 RNI (Annex 3). These RNI incorporate recent international data. Moreover, as it is impossible to determine with precision the proportion of individuals with inadequate micronutrient intakes, these issues are addressed in terms of **probability or risk**.

Risk of inadequate intake in the French population

Micronutrient deficiency is uncommon in France. However, risks of micronutrient store depletion exist in certain population groups, and dietary and nutritional surveys have established that certain population groups have insufficient intake relative to the RNI. The Working Group has therefore chosen to classify micronutrients in three categories (Table IA) .

- **Category 1 :** Micronutrients which are known to be inadequately consumed, **with clinical (deficiency) or biological (store depletion) symptoms** in certain age groups, physiological states (e.g. pregnancy) and dietary typologies (including regional); the term **Micronutrients with risk of deficiency or store depletion** characterises this category of micronutrient.

- **Category 2 :** Micronutrients which might be inadequately consumed relative to the RNI, but which are **not clearly at risk of deficiency or store depletion**. For example the average intake of a population group can be inadequate relative to the RNI as described in Annex 3, but there is no biological deficiency marker, the latter is of questionable validity, the composition tables are unreliable, or epidemiological data are insufficient;

- **Category 3 :** Micronutrients for which **inadequate intake has not been demonstrated**.

Risk of excess intake as defined in Annex 3

On the other hand, certain micronutrients may be excessively consumed (high intakes as defined in Annex 3). This risk of excess intake can be manifested by clinical or biological anomalies in certain populations, age groups, or physiological states (Table I B). This category is thus important to consider when defining tolerable upper intake levels.

Table IA. Classification of micronutrients by degree of risk of inadequate intake in France (Annex 3)

Category	Criteria	Micronutrients
1	**Risk of clinical deficiency or biological store depletion** for certain age groups, certain physiological states, certain dietary typologies, and /or certain regions	vitamin D, pyridoxine (B6) (older people> 70 years) folic acid (B9)*, iodine, calcium, iron
2	Possible inadequate intake but **uncertainty on risk of clinical deficiency or biological store depletion** - absence or questionable validity of biological markers - unreliable composition tables - lack of epidemiological studies	thiamine (B1) pyridoxine (B6) (except older people), vitamin C, vitamin E, vitamin K magnesium, copper, zinc, selenium, chromium, fluoride

Category	Criteria	Micronutrients
3	**No evidence of inadequate intake**	Total vitamin A, riboflavin (B2), niacin (B3), pantothenic acid (B5), biotin (B8), cobalamine (B12) sodium, chlorine, potassium, phosphorus, molybdenum, manganese

* see ref 5 which shows that levels accessible by a normal diet appear to reduce the risk of cardiovascular diseases.

Table I B : Micronutrients for which there is a risk of excess intake in France (Annexe 3)

total vitamin A, cobalamine* (B12) calcium, zinc, iodine, phosphorus**, sodium**, fluoride**

* without potential deleterious excess
** see annex 4

Tables 1 A and 1 B illustrate the complex situation whereby for a single micronutrient, certain segments of the population have inadequate intakes whereas others may be at risk of excessive intake of that micronutrient, as per the RNI (vitamin B12, calcium, fluoride, iodine, zinc). Therefore in order to develop a sustainable and safe fortification strategy, these populations must be better defined and intake patterns better understood.

4. Stage 1-b
Safety considerations

The Scientific Committee on Food of the European Union is working on *"Tolerable upper intake levels"* for micronutrients in Europe (Table II). The upper levels of the SCF were used when available. When not, the CES proposed upper intake levels for several micronutrients in France (Table II), based on result from a CSHPF report in 1995 (6), where levels were reassessed based on recent data (Annexes 4 et 5). All tolerable upper intake levels for France incorporate dietary intake.

Table II. Comparison of tolerable upper intake level for dietary intake of micronutrients in France and in the EU (« *tolerable upper intake level* », SCF)

Tolerable upper intake levels / Micronutrients	France		European Union (SCF) (*"Tolerable upper intake level"*, 2000****)
	As a chronic daily intake	RNI (adult average) Multiplication Coefficient	
vitamin A (retinol)	1400 µg/d*	2	Expected
beta-carotene	8100 µg/d**	3,8	*****
vitamin D	25 µg/d***	5	Expected
vitamin E	52 mg/d*/°	4,3	Expected
vitamin K	-	-	-
thiamine (B1)	15 mg/d**	12,5	*****
riboflavin (B2)	17 mg/d**	11,3	*****
niacin (B3)	45 mg/d*	3,6	-
pantothenic acid (B5)	-	-	Expected
pyridoxine (B6)	7 mg/d***	4,1	Adults : 25 mg/d[1] Children 4-6 yrs 7 mg/d [1]
biotin (B8)	-	-	*****
folic acid (B9)	900 µg/d*/**	2,8	Adults: 1000 µg/d [2] Children 4-6 yrs : 300 µg/d [2]
	Retained value of tolerable upper intake level ◊ : 300 + 1 average adult RNI = 300 + 315 = 615 µg/d		
cobalamine (B12)	-	-	*****
vitamin C	1100 mg/d*	10	Expected
Calcium	2 g/d**/***	2,2	Expected
iron	28 mg/d**/***	2,25	Expected
iodine	500 µg/d***	3,3	Expected
magnesium	700 mg/d***	1,8	As of 4 yrs : 250 mg/d [2]
	Retained value of tolerable upper intake level ◊ : 250+ 1 average adult RNI = 250 + 390 = 640 mg/d		
zinc	15 mg/d***	1,4	Expected
copper	-	-	Expected
selenium	150 µg/d***	2,3	300 µg/d1
molybdenum	-	-	Adults : 600 µg/d [1 ?] Children 4-6 yrs : 200 µg/d[1 ?]
manganese	-	-	*****
fluoride	2,6 mg/d (0,04mg/kg)*	1	Expected

Sodium, potassium, chlorine and phosphorus are excluded from this list as they are minerals for which the nutritional benefits of using them as fortificants are not evident.

* according to tolerable upper intake levels, excluding dietary intake, of CSHPF 1995/96 (6), to which the average vitamin RNI (average of male and female RNI) was added

◊ Tolerable upper intake level considered for optimal levels for fortification (chapter 6). The SCF *"tolerable upper intake level"* for children of 4 years and above is maintained since commonly eaten foods include this age group (see Annex 2 definition).

° Ref (7) recently confirmed the risks of the chronic ingestion of a dose equivalent to the French tolerable upper intake level.

** according to (8) and (9)

*** Ref (4) and Annexes 4 and 5, and/or to take into consideration excessive intake risks in young children.

****SCF *"tolerable upper intake level"* : "*the maximum level of total chronic daily intake of a nutrient (from all sources) judged to be unlikely to pose a risk of adverse health effects to humans*".

***** insufficient data

1 : Dietary intake is considered when the SCF *" tolerable upper intake level"* was determined.

2 : Dietary intake is not considered when the SCF *" tolerable upper intake level"* was determined.

Table II illustrates the discrepancies between the tolerable upper intake levels and RNI and therefore underlines the need to address each nutrient separately. Although certain tolerable intake levels differ from RNI by a factor of 10 or more (i.e. vitamins B1, B2 and C), others approximate them (less than 3 times difference) which suggest a potential risk of excess intake when these vitamins or minerals are used for fortification (i.e. vitamin A, folic acid, calcium, iron, magnesium, iodine, zinc, selenium, fluoride). This first analysis does not take into consideration high consumers; thus, the next steps in our methodology.

The following must be taken into consideration:

- consumers of food supplements. The directive project expects that the intakes by food supplements will be taken into consideration when fortification levels are set. This category of consumers is all the more important to consider since in France they appear to have satisfactory dietary habits (Annex 6). They therefore have lesser needs than others in terms of fortified foods. Their consumption of fortified foods could only increase the intake imbalance in the population;

- non adults populations and physiological states (pregnancy) which can modify needs and sensitivity to excessive intake (4) ;

- the existence of genetic or pathological anomalies, particularly digestive, often hidden in the population (hemochromatosis and untreated chronic intestinal conditions, for example), which also affect fortification levels (10) ;

- nutrient interactions, such as iron and vitamin C, B12 and folic acid, or competition between minerals (Annexes 4 and 5).

5. Stage 2
Classification of micronutrients likely to be added to commonly eaten foods in terms of nutritional value of fortification and safety risks for the consumer

To decide which micronutrients are most likely to be added to commonly eaten foods in terms of fortification and the determination of maximum levels, a method based on joint OCA and ILSI-Europe methodologies is proposed (9, 11).

5.1 OCA study: Modelling of vitamin and mineral food fortification in France : method and analysis

This study (9) aimed to determined, based on an actual and representative dietary intake, a level of fortification which would benefit the population with intakes below the RNI for a given nutrient, all the while limiting the potential long-term risks of high consumers. The details of this study are presented in Annex 7.

The simulation resulted in a categorization of micronutrients as follows:

1) micronutrients which, when consumed, *even at maximum levels* (100% RDA/100 kcal and 50 or 100% proportion of enriched foods consumed) *remain well within the tolerable intake levels:* vitamins B2, C, probably vitamin B1;

2) micronutrients for which average intakes are far from tolerable intake levels but *for which proposed fortification levels are close or exceed tolerable intake levels. This warrants further debate and more in-depth research on these nutrients*: beta-carotene, vitamins D, E, B6, B9, and calcium, iron and magnesium ;

3) micronutrients for which *average dietary intakes are too close to tolerable intake levels* to consider general fortification without risking excessive consumption: vitamin A, as retinol. This does not exclude a study of fortification on a particular population group.

5.2. ILSI- Europe Study

The methodology proposed by ILSI Europe in 2001 to determine the tolerable upper content level of added micronutrients in foods (11) was included in the discussion on food fortification methodologies. Further details can be found in Annex 8.

The preliminary ILSI-Europe document makes the following fundamental points:

1) "The draft EC proposal is for a harmonised regulatory framework on the voluntary addition of vitamins and minerals to foods. In many European countries, specific foods are required by regulation to be restored to "natural" levels, because they replace similar foods of major importance in the diet (e.g. margarine replacing butter), or to restore processing losses. These are distinguished here from foods to which nutrients are added voluntarily and fortification is taken to mean voluntary addition in the context of this reference base model."
[These restored foods are not dealt with in the present document] ;

2) The European Commission has recently published the preliminary draft of a directive which aims to establish a regulatory framework on the voluntary addition of vitamins and minerals to foods. This project is based on the need to ensure consumer safety and to build a solid scientific base for all future regulations which define food fortification;

3) Consumers of food complements must benefit from protective measures by established upper limits for nutrients as well as proper labelling.

Several of the underlying principles of the ILSI-Europe approach are considered in the elaboration of the present methodology:

- Population energy intakes are divided by 100 kcal sections, to which a nutrient is added for fortification. There is concern in France about this approach in that it takes energy as a point of reference as opposed to weight or portion size. However certain micronutrients such as calcium and vitamin D may need particular treatment (by 100 g or 100 ml) as they are added to foods with variable energy contents (whole-and skimmed milk products, water, etc) ;

- The document looks at the highest percentiles (95^{th} percentile) of energy intakes (3600 kcal/j) to establish the number of sections (thus n=36) which becomes the protective measure for the consumer;

- The document does not address the issue of the proportion of enriched foods consumed[7] ;

- Finally, the ILSI Europe approach allowed for a certain flexibility in its application as it can be adapted to national dietary needs.

ILSI-Europe's classification of likely vitamins and minerals fortificants has maintained upper intake levels recently adopted by the Comité scientifique de l'Alimentation Humaine (SCF) (Table II), and pending the finalisation of the latter, has included available evaluations from different countries (12).

According to ILSI Europe, the analysis demonstrates that the present reference base model shows that, even with fortification of 25% of all potentially fortifiable foods for each individual nutrient,

[7] Proportion of enriched foods consumed: For a given individual, the amount of fortified foods consumed, as a proportion of all potentially fortifiable foods consumed by that person.

nutritionally significant amounts (10% RDA per 100 kcal portion) of all micronutrients examined, except retinol, could be added safely to foods. This include zinc, calcium, phosphorus, and magnesium for which the margin between the intakes of high consumers and the upper limit is comparatively low."

ILSI Europe comes to the conclusion that nutrients can be categorised in four bands :

1) Nutrients which could be added safely to foods at levels greater than 1 EC RDA per 100 kcal portion, regardless of assumptions of likely proportions foods fortified in the diet. These include vitamins B12, C, E, riboflavin, pantothenic acid, niacin (as nicotinamide), and thiamine.

2) Nutrient that could be added safely to foods at levels above 50% of the EC RDA per 100 kcal portion, making the assumption that fortification of a quarter of all potentially fortifiable foods in the diet is unlikely to be exceeded for any individual nutrient. These include vitamin B6, D, acid folic, biotin, iodine, copper, iron and selenium.

3) Nutrients that could be added safely to foods at levels between 10 and 18% of the EC RDA per 100 kcal portion, assuming that fortification of a quarter of all potentially fortifiable foods is unlikely to be exceeded for each individual nutrient. These include zinc, calcium, phosphorus and magnesium.

4) Retinol, for which intake at the current 95th centile from food sources approaches the UL for some population groups in EU."

5.3. Comparison of results from the OCA and ILSI Europe studies in terms of consumer safety

OCA (9) and ILSI-Europe (11) data were compared in terms of safety to the consumer to classify micronutrients by two methods (Table III). Generally speaking, this comparison illustrates three levels of risks associated to fortification by micronutrient:

1) Micronutrients for which fortification presents **no risk** (category 1 in both OCA and ILSI-Europe studies).

2) Micronutrients for which fortification presents **a moderate risk** (category 2, OCA and categories 2 and 3, ILSI Europe).

3) Micronutrients for which fortification presents **a major risk** (category 3, OCA and category 4, ILSI Europe).

Table III. Comparison of results from the OCA and ILSI Europe studies in terms of consumer safety

Micronutrient \ Risk in terms of consumer safety		No risk		Moderate risk		High risk	
		OCA	ILSI Europe*	OCA	ILSI Europe**	OCA	ILSI Europe
vitamins	**A (retinol)**					+	+
	beta-carotene				+		
	D				+	+	
	E		+	+°			+
	thiamine (B1)	(+)	+			(+)	+
	riboflavin (B2)	+	+			+	+
	niacin (B3)						
	nicotinamide		+				+
	pantothenic acid (B5)		+				+
							+
	cobalamine (B12)	+	+			+	+
	C	+	+				
	pyridoxine (B6)			+	+		
	biotin (B8)				+		
	folic acid (B9)			+	+		
minerals	**calcium**			+	+		
	iron			+	+		
	iodine				+		
	magnesium			+	+		
	zinc				+		
	copper				+		
	selenium				+		
	phosphorus				+		

According to ILSI Europe, micronutrients in this column can enrich foods:
*more than 100% RDA /100 kcal.
** 10 - 100% RDA /100 kcal
() : according to ref (9)
° ref (7) has recently confirmed the risks of chronic intake of a dose equivalent to the French tolerable intake level.

It appears that the global classification, without quantitative measures, lies within ILSI Europe and OCA findings. Vitamin E is the only one for which there is a different classification: without risk (ILSI) and moderate risk (OCA).

5.4. Proposal for the selection of vitamins and minerals likely to fortify commonly eaten foods

Conclusions from studies on the risk of inadequate intake (Table I) and on the risk of surpassing tolerable upper intake limits (Tables II and III) have been crosschecked. A classification of vitamins and minerals likely to fortify commonly eaten foods has been drawn up according to two sets of criteria:

- Nutritional value (risk of deficiency or store depletion in the French population, or eventually risk of inadequate intake for low consumers and/or certain age groups or physiological states)

- Safety risk to the consumer (general population of high consumers) when commonly eaten foods are fortified (Table IV).

Vitamin K, molybdenum, manganese and chromium have been included in the following table without concluding on risk of excessive intake or of surpassing tolerable intake levels.

Table IV. Classification of micronutrients likely to be added to commonly eaten foods in terms of nutritional value of fortification and safety risks for the consumer (based on Tables I, et II et III)

Nutritional value of fortification		**YES (risk of deficiency or depleted stores)**		**UNCERTAIN (uncertainty on risk of inadequate intake and no evidence of deficiency or depleted store)**		**NO (inadequate intake not demonstrated)**	
Risk of surpassing tolerable upper intake limits		no	yes*	no	yes*	no	yes*
vitamins	**A (retinol)**						++
	beta-carotene						+
	D		+				
	E				+		
	K			**?**	**?**		
	thiamine (B1)			+			
	riboflavin (B2)					+	
	niacin (B3)						
	nicotinamide**						+
	nicotinic acid						+
	pantothenic acid (B5)					+	
	pyridoxine (B6)		+				
	biotin (B8)					+***	
	folic acid (B9)		+				
	cobalamine (B12)					+	
	C			+			
Minerals	**calcium**		+				
	iron		+				
	iodine		+				
	magnesium				+		
	zinc				+		
	copper				+		
	selenium				+		
	molybdenum					**?**	**?**
	manganese					**?**	**?**
	chrome			**?**	**?**		
	fluoride				+		
	sodium						+
	chloride, phosphorus, potassium					**?**	**?**

*The risk of surpassing tolerable intake levels for the general population or high consumers have been identified as (++) if it is significant or (+) if it warrants further studies to determine acceptable fortification levels.
** see study in ref (13) on increase of homocystenaemia with chronic intake of nicotinamide.
*** see Annex 5 : although ILSI Europe has classified this micronutrient as potentially risky, there is no evidence to our knowledge which supports this.

Other micronutrients could have been included but at the time of drafting of this report, they were lacking certain criteria such as nutritional value, consumer safety, specification, bioavailability.

This table highlights three categories of micronutrients:

1) **Those for which fortification of commonly eaten foods could have added nutritional value** due to existing risk of deficiency or store depletion in certain population groups in France (vitamin D, vitamin B6, folic acid, calcium, iron, and iodine). However, further simulation studies are needed to establish optimal fortification levels in order to minimise the risk of surpassing tolerable intake levels;

2) **Those for which the nutritional value of fortification is uncertain**, where intakes lower than RNI in certain segments of the population are not accompanied by symptoms of deficiency or store depletion. Where fortification is considered however, it must be preceded by simulation studies (as above in category 1). This is indispensable for micronutrients for which there is a risk of surpassing tolerable intake levels (i.e. vitamin E, magnesium, zinc, copper, selenium, fluoride) ;

3) **Those for which there are no arguments in favour of added nutritional value with fortification**. Here, fortification is not justified by micronutrients for which there are risks of surpassing tolerable intake levels (i.e. vitamin A). This is still being discussed for riboflavin (B2), pantothenic acid (B5), biotin (B8), cobalamine (B12), chloride, phosphorus, potassium and sodium in terms of vitamin and/or mineral synergies.

5.5. Proposal for the establishment of fortification commonly eaten foods by vitamins and minerals

OCA and ILSI-Europe methodologies gave comparable qualitative results but quantitative results were incomparable. This is in part due to :

- ILSI-Europe's selection of foods to be fortified (50%), variable according to circumstances or country;
- The maximum level of 95% of proportion of enriched foods consumed: not only would the highest from the 95th percentile (and not the average) have to be taken, but as for tolerable upper intake levels defined by the SCF, adjustable levels as per new European surveys and studies;

  For these two aspects, a policy of surveillance via a regularly updated database could be proposed as a platform for collaboration in Europe;

- The upper levels chosen by ILSI Europe which are often higher than those of the CSHPF.

These differences led us to propose modifications in the risk assessment (next stage).

6. Stage 3
Determination of optimal levels for fortification and evaluation of fortification balance

6-1 Fortification levels

6.1.1 Tolerable maximum levels (= fortification level in terms of percentile of consumers who reach the tolerable intake level)

The method used for this evaluation is described in Annex 9. Using a Monte-Carlo[8] - type method of simulation (14), it is possible to test the impact of fortification for all values between 1 and 100% RDA/100 kcal to **estimate the link between the fortification level and the consumer percentile that reach the tolerable intake level**. A similar approach considers fortification levels in terms of % RDA / 100 g or 100 ml for fortification of non nutrient-dense foods (e.g. water in drinks) or energy-poor (low lipid or glucose content) (e.g. "light", "skimmed" foods). Such an approach has been used in France to proposed milk and milk product fortification by vitamin D (15).

The value of this approach is to estimate what percentile of consumers under the tolerable upper intake level corresponds to a fortification level calculated with one method or another (ILSI Europe, OCA, or others).

6.1.2 Proposals of optimal fortification levels for 9 micronutrients achieved through the OCA simulation method (9)

Simulation studies by the OCA (9) have allowed the development of predictive intake values by percentile of population. These predictive values were obtained by testing several hypotheses of proportion of enriched foods consumed (3, 5, 10, 50 and 100%) and fortification levels (10, 20, 40 and 100% RDA/100 kcal).

The objectives were:

- To permit low micronutrient consumers (< 10^{th} percentile) to attain or approximate RDA (for the indicate percent consumption)[9] ;
- That the fortification level be acceptable in terms of safety, that is that high consumers (>95^{th} percentile) do not surpass the tolerable intake level proposed in this report, based on *tolerable upper intake level* determined by the SCF or, when these were not available, maximum intake levels determined in France (Table II).

The combined hypotheses responding to these objectives have been identified by assessing predictive intake values by population percentile in the OCA simulation (9).

As an example, Table V presents results of the analysis on fortification levels of vitamin B9, a category 1 vitamin (risk of deficiency or store depletion for certain segments of the French population).

[8] The Monte Carlo method is the general method of probability simulation. We chose the foods to be enriched according to a binomial law by taking into consideration Proportion of enriched foods consumed.
[9] Note: this does not imply that lowest consumers will have equal access to fortified foods in relation to their actual diet.

Table V : Zone of fortification benefit by vitamin B9, concluded from results from the OCA simulation method (9) and tolerable upper intake levels

	Proportion of enriched foods consumed	Significance for low consumers				Absence of risk for high consumers			
		RDA/ 100 kcal				RDA : 100 kcal			
		10%	20%	40%	100%	10%	20%	40%	100%
Vitamin B9	3%	No	No	No	yes	yes	yes	yes	yes
	5%	No	No	No	yes	yes	yes	yes	No
	10%	no	yes	yes	yes	yes	yes	yes	No
	50%	yes	yes	yes	yes	yes	No	No	No
	100%	yes	yes	yes	yes	yes	no	no	No

Zone which represents a value for low consumers or zone where the fortification level is inadequate for high consumers.

Zone which has value for low consumers, but where the fortification level is inadequate for high consumers

Zone wherein the fortification level is adequate for high consumers but has no value for low consumers.

Zone of value = Zone which represents a value for low consumers, and where the fortification level is adequate for high consumers.

Other micronutrients, for which there exists (or not) a risk of deficiency and/or inadequate intake, have been analysed using the same methodology than for vitamin B9 (Tables VI.1, VI.2, et VI.3 and Annex 9).

Table VI.1. Examples of optimum fortification levels for micronutrients for which there is a risk of deficiency or store depletion

Micronutrient	10% proportion of enriched foods consumed		50% proportion of enriched foods consumed		100 % proportion of enriched foods consumed	
	% RDA/100 kcal	amount/d /100 kcal	% RDA /100 kcal	amount/d /100 kcal	% RDA /100 kcal	amount/d /100 kcal
vitamin D	impossible	impossible	10-20%	0,5-1 µg	10%	0,5 µg
vitamin B6	100%	2 mg	10-20%	200-400 µg	10%	200 µg
B9 (folic acid)*	20-40%	40 à 80 µg	10 %	20 µg	10 %	20 µg
calcium	impossible	impossible	20%	160 mg	10%	80 mg
iron	impossible	impossible	impossible	impossible	impossible	impossible

Impossible : it is impossible to define an optimal fortification level according to stated objectives.
*by taking into consideration the tolerable upper intake level established by the SCF for children and dietary intake measured by the average RNI (average of male and female values).

Table VI.2. Examples of optimum fortification levels for micronutrients for which there is a risk of inadequate intake without signs of deficiency or store depletion

Micronutrient	10% proportion of enriched foods consumed		50% proportion of enriched foods consumed		100 % proportion of enriched foods consumed	
	% RDA/100 kcal	amount/d /100 kcal	% RDA /100 kcal	amount/d /100 kcal	% RDA /100 kcal	amount/d /100 kcal
vitamin E	100%	10 mg	20%	1 mg	10 - 20%	1 - 2 mg
vitamin C	100%	60 mg	20 - 100%	12 - 60 mg	10 - 40%	6 -24 mg
magnesium*	impossible	impossible	impossible	impossible	impossible	Impossible

Impossible : it is impossible to define an optimal fortification level according to stated objectives.
*by taking into consideration the tolerable upper intake level established by the SCF for children and dietary intake measured by the average RNI (average of male and female values).

Table VI.3. Examples of optimum fortification levels for micronutrients for which there is no risk of inadequate intake

Micronutrient	10% proportion of enriched foods consumed		50% proportion of enriched foods consumed		100 % proportion of enriched foods consumed	
	% RDA/100 kcal	amount/d /100 kcal	% RDA /100 kcal	amount/d /100 kcal	% RDA /100 kcal	amount/d /100 kcal
vitamin A	impossible	impossible	impossible	impossible	impossible	impossible
vitamin B2	100%	1.6 mg	10 - 40%	160 – 640 µg	10 - 40%	160 - 640 µg

Impossible : it is impossible to define an optimal fortification level according to stated objectives.

From the above analysis emerge three categories of micronutrients:

1) **Micronutrients for which it is possible to determine fortification levels which meet nutritional and toxicological criteria defined above** (vitamins B2, B6, B9, C and E).

For these micronutrients, **the proportion of enriched foods consumed** must be identified**,** either by approximating the most realistic level from a technical-economic point of view, either by trying to reduce the risk of surpassing population recommendations by proposing a hypothesis that certain high consumers consume only fortified products among those that are fortifiable (100 % proportion of enriched foods consumed).

2) **Micronutrients for which it has been impossible to determine an optimum fortification level** regardless of the enriched proportion (vitamin A). This supports the argument against fortifying commonly eaten foods with this vitamin.

3) **Micronutrients in an intermediary position** (vitamin D, calcium, iron, magnesium), where an optimal fortification level has not been found in all studied proportion of enriched foods consumed and in particular in proportion of enriched foods consumed closest to the achievable level (10%).

With regards to these micronutrients the **question is raised about fortification through specific foods likely to be consumed by populations at risk of deficiency or store depletion**, instead of the general fortification of commonly eaten foods.

6.2 Other issues about fortification

6.2.1 Nutrient and food balance

One of the objectives stated in chapter 1.1 addresses "vector" foods. However as this term rather applies to general public health measures of food fortification (such as iodine in salt), it seems appropriate to rename the term as "appropriate foods" or "support foods".

Fortified foods should all in principle meet certain conditions such as represent products or categories of foods mainly consumed by the proportion of the general population which lies below the minimum nutritional goal, all the while offering *minimum risk*. Fortification must under no circumstance worsen poor population intakes.

It is essential that the effects of fortification on the presentation, role or taste of a food be taken into consideration, and that fortified foods are not prohibitively expensive, particularly affecting populations already at risk of inadequate intake.

Finally, it is worth reiterating that a fortified food must clearly have added nutritional value.

A list of foods *likely to be fortified among commonly eaten foods* was drawn up jointly with representatives of the food industry in France during the OCA study. It can be found in an annex of reference 9 and could serve as the basis for future discussions on "support foods". The following have been excluded from this list:

- Fresh non-processed foods,
- Products that are neither packaged nor labelled,
- Products with a particular image or regional specialities
- Products with no energy content as the methodology calls for calculations per 100 kcal.

Moreover, the identification of at-risk groups depends on the situation and dietary behaviour of each population. The principle of "support foods" hinges on cultural habits of each region and country.

The relative bioavailability of a micronutrient used for fortification will need to be established by human or animal studies.

Finally, criteria for purity of micronutrients used for fortification must also be established according to regulations.

6.2.2 Nutrient balance

A balanced and diversified diet is essential in order to maintain nutrient balance (4). This principle also applies to the nature and quantity of nutrients used to fortify a food. This implies respecting natural physiological balance, delicate homeostatic regulation, and the *composition of the intestinal environment,* by ensuring a balanced intake of nutrients (even of those which are considered low risk at high doses).
It has been suggested that excessive intakes of iron (especially accompanied by excessive vitamin C intakes) might explain free radicals (hydroxyls) induced by a Fenton reaction, found in sufficient quantities to initiate colon cancer (16).

A list of vitamins and minerals that complement each other should be drawn up and taken into consideration during food fortification since vitamins and minerals function in metabolic synergy (e.g. folic acid and vitamin B12, or calcium and vitamin D). To not consider these interactions might have detrimental effects on health and would go against the very point of fortification, that is to restore intakes and nutrient levels.

7. Nutritional information for the consumer

Consumers must be properly informed about food fortification by vitamins and minerals, particularly in terms of identifying nutrients to restore deficiencies, emphasising that a fortified food

does is not in itself "protective" and that one should aim to get all nutrient requirements through a diverse and balanced diet.

8. Monitoring of the impact of fortification

The impact of fortification on inadequate intakes and the appearance of deleterious effects should be monitored by food safety institutes both at the national and European level.

Conclusion

In the framework of future European debates on food fortification by vitamins and minerals, AFSSA has been requested to:

- Examine the list of vitamins and minerals put forth by the European Commission;
- Suggest a method to establish minimum and maximum vitamin and mineral levels;
- Choose foods or food groups appropriate for fortification.

As a response to these objectives, the **Comité d'Experts Spécialisé « Nutrition humaine » put forth a three-step methodology, based on a procedure which integrates the nutritional aspect and consumer safety criteria,** considered fundamental, in order to help improve the nutritional status of low consumers while protecting high consumers.

The nutritional procedure (stage 1 a) consists in determining the risks of inadequate intake and the consequences in terms of clinical deficiency or biological store depletion for each mineral and vitamin, but also the risks of surpassing the RNI (2001). The results of this evaluation have emphasised the specific nature of each micronutrient; it follows that each should be considered individually.

The safety procedure (stage 1 b) aims to protect the consumer from the risk of toxicity, based on the tolerable upper intake level defined by the SCF. When these are unavailable, limits proposed by the CSHPF and CEDAP (8 et 9) are used, pending further information from the SCF.

By combining the results of stages 1a and 1b (stage 2), and using simulation studies based on actual dietary intake, a micronutrient classification emerges in terms of nutritional value and safety risks.

Finally, a method to determine optimum fortification levels of micronutrients in commonly eaten foods is put forth (stage 3). These optimum levels should allow the lowest consumers ($< 10^{th}$ percentile) to reach or approximate the RDA, while ensuring that the highest consumers ($>95^{th}$ percentile) do not surpass the tolerable upper intake limit. The analysis of 10 micronutrients using this method demonstrates that it is possible to identify optimum levels for vitamins such as vitamins B2, B6, B9, C and E, for example.

The debate on "support foods" or food most appropriate for fortification, continues, backed up by population studies and surveys. Also the interaction between micronutrients continues to be discussed based on existing or future scientific data.

Finally, the need to regularly evaluate the public health impact of consuming fortified foods has been emphasised.

Bibliographic references

(1) Rapport du Haut Comité de la Santé Publique, " Pour une politique nutritionnelle de santé publique en France – Enjeux et propositions ", juin 2000 (éditions ENSP)
(2) Report on « l'Estimation de la situation nutritionnelle en vitamines et éléments minéraux de populations françaises d'après des enquêtes récentes » (Avis de la CEDAP n° 24 du 28 janvier 1998)
(3) Potier de Courcy G. et les membres du groupe de travail de la CEDAP sur les substances nutritives. Estimation du statut en vitamines et minéraux de la population française, d'après des enquêtes récentes. Cah Nutr Diét*,* 1999, 34, 77-87
(4) ANC 2001. *Apports nutritionnels conseillés pour la population française*, A. Martin coordinateur. 605 p. Editions Tec et doc. Lavoisier (English version in progress)
(5) Voutilainen S., Rissanen TH, Virtanen J, Lakka TA, Salonen JT, Low dietary folate intake is associated with an excess incidence of acute coronary events. Circulation, 2001, 103, 2674-2680.
(6) Les limites de sécurité dans les consommations alimentaires des vitamines et des minéraux Conseil supérieur d'hygiène publique de France. Avis du 12 septembre 1995. Tec et Doc Lavoisier. Paris. 1996, 172 pp.
(7) Leppälä JM, Virtamo J, Fogelholm R, Albanes D, Taylor PR, Heinonen OP. Vitamin E and beta carotene supplementation in high risk for stroke. A subgroup analysis of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. Arch Neurol, 2000,57,1503-1509
(8) Avis n°27 du 21 octobre 1998 de la CEDAP, relatif à une méthodologie de simulation des modalités d'enrichissement des aliments en vitamins et minéraux.
(9) *Modelling of vitamin and mineral food fortification in France:method and analysis*, 2000 (joint document).
(10) Brissot P, Deugnier Y, Haemochromatosis, in : N McIntyre, JP Benhamou, J Bircher, M Rizzetto, J Rodes (eds), Oxford Textbook of Clinical Hepatology, Oxford University Press, Oxford 1999, 1379-91
(11) ILSI-Europe draft entitled " *Vitamins and minerals ; a model for safe addition to foods "*, and presented to the working group the 27th of march, 2001 by Mrs Valérie Rolland, Professor Albert Flynn and Dr. Detlef Müller
(12) Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. A Report of the Panel on Micronutrients, Subcommittees on Upper Reference Levels of Nutrients and Interpretation and Use of Dietary Committee on the Scientific Evaluation of Dietary Reference Intakes. Food and Nutrition Board, Institute of medecine. National Academy Press. Washington, D.C. 2001
(13) Garg R, Malinow M R, Pettinger M, Upson B, Hunninghake D. Niacin treatment increases plasma homocysteine levels. Am Heart J, 1999, Vol 138 (6) part 1, 1082-1087
(14) Tassi P. (1985) Méthodes statistiques. Editions Economica.
(15) Verger P, Garabédian M, Potier de Courcy G, *et al.* A methodology for risk assessment of micronutrients in fortified foods. Food. Chem. Toxicol. (sous presse).
(**16**) Babbs CF. Free radicals and the etiology of colon cancer. Free Rad Biol Med, 1990, 8, 191-200.