

**Risk Management in a Complex
World:
The Fourth Transatlantic Dialogue
on Precaution**

19 - 21 September 2004

Case Study: Health Supplements

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- founded November 2002
- assessment of risks in connection with food, chemicals, genetically modified animals, plants and microorganisms, plant protection products, animal feeds, biocides, novel foods
- advice to Federal ministries
- research
- recording of animal experiments + assessment of alternative methods
- reference laboratories
- communication of results of assessment

“Health” Supplement?

Two conditions:

- it is intended to promote/sustain health of the consumer, AND
- it has been shown to promote/sustain health of the consumer

While in doubt better:

- dietary or food supplement!

" Recourse to the precautionary principle presupposes that potentially dangerous effects deriving from a phenomenon, product or process have been identified, and that scientific evaluation does not allow the risk to be determined with sufficient certainty"

(Communication from the Commission on the precautionary principle dd 2 February 2000)

Food Supplements in the EC

(Directive 2002/46/EC of 10 June 2002)

Definition:

- a) “Food supplements” means *foodstuffs* the purpose of which is to supplement the normal diet and which are concentrated sources of nutrients or *other substances with a nutritional or physiological effect*, alone or in combination, marketed *in dose form* , designed to be taken in measured small unit quantities.
- b) “nutrients” means the following substances:
- i) vitamins
 - ii) minerals

Food Supplements in the EC

(Directive 2002/46/EC of 10 June 2002)

- Intention:** Harmonisation of differing national rules in the face of increasing number of products.
- Recognising:** Not everybody receives all nutrients in recommended amounts from his diet and some people wish to supplement their diets.
- Goal:** Protection of consumers by safety of and labelling on product.
- Scope:** Nutrients (vitamins, minerals, amino acids, essential fatty acids, fibre) and other ingredients (various plant and herbal extracts)
- 1rst stage: vitamins and minerals
 - 2nd stage: other nutrients or other substances with nutritional or physiological effect.

Food Supplements in the EC

The first stage rules

1. Positive list of vitamins and minerals
2. Positive list of vitamin and mineral compounds
(Revision possible if necessary)
3. Minimum and maximum levels for vitamins and minerals in supplements
4. Appropriate labelling
5. Facultative notification procedure in member states

Food Supplements in the EC

Positive list of vitamin and mineral compounds

1. Vitamins

2. Minerals

calcium

magnesium

iron

copper

iodine

zinc

manganese

phosphorus

sodium

potassium

selenium

chromium

molybdenum

fluoride

chloride

Food Supplements in the EC

Positive list of vitamin and mineral compounds

Compounds evaluated by the Scientific Committee on Food for safety and availability

However: differences in availability are not taken into account

Food Supplements in the EC

Minimum and Maximum levels have not yet been set.

Minimum levels shall be a *significant* amount per daily supplement.

Maximum levels set *shall* take into account

- a) upper safe levels
- b) intake from other dietary sources

"Due account *should* also be taken of reference intakes of vitamins and minerals for the population."

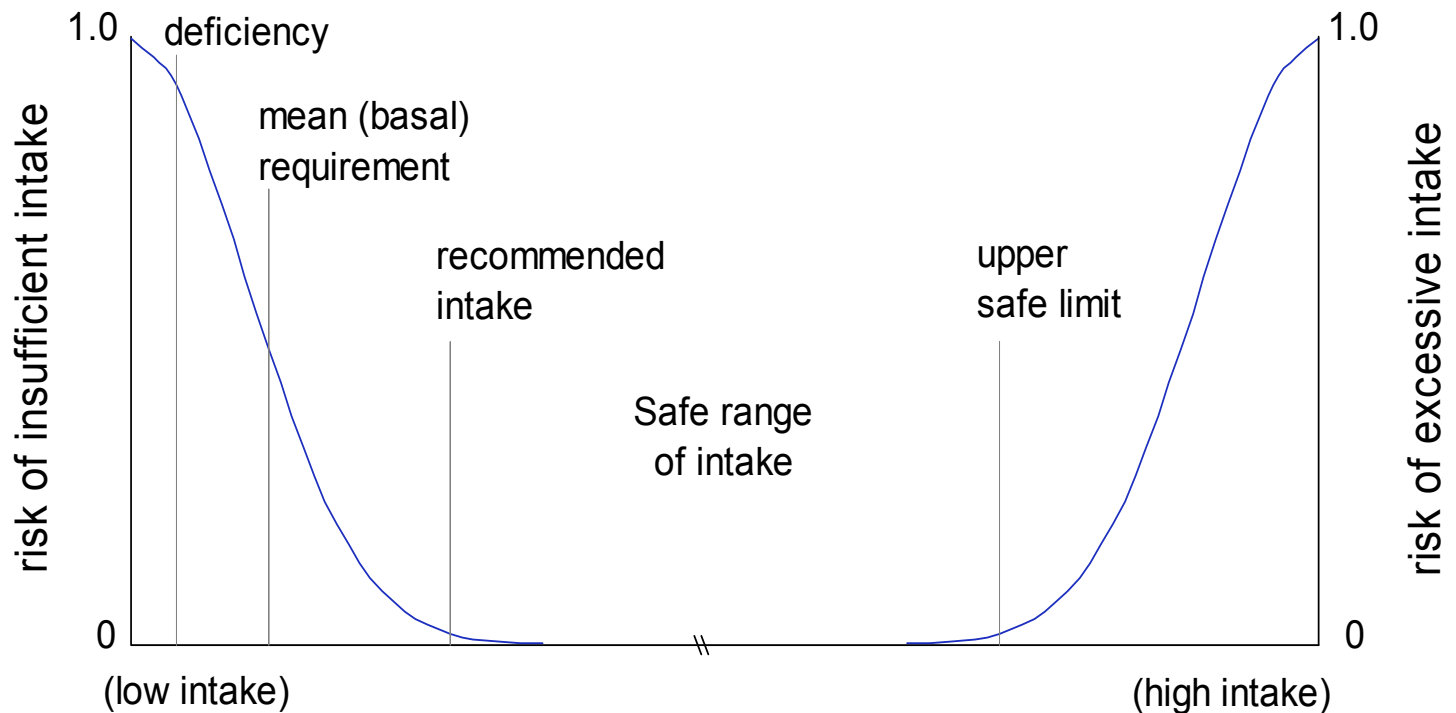
Food Supplements in the EC

Are maximum levels for minerals and vitamins set according to directive 2002/46/EC in food supplements a precautionary measure?

- “potentially dangerous effects”: YES
- “risk not determined with certainty”: NO
(in most cases)

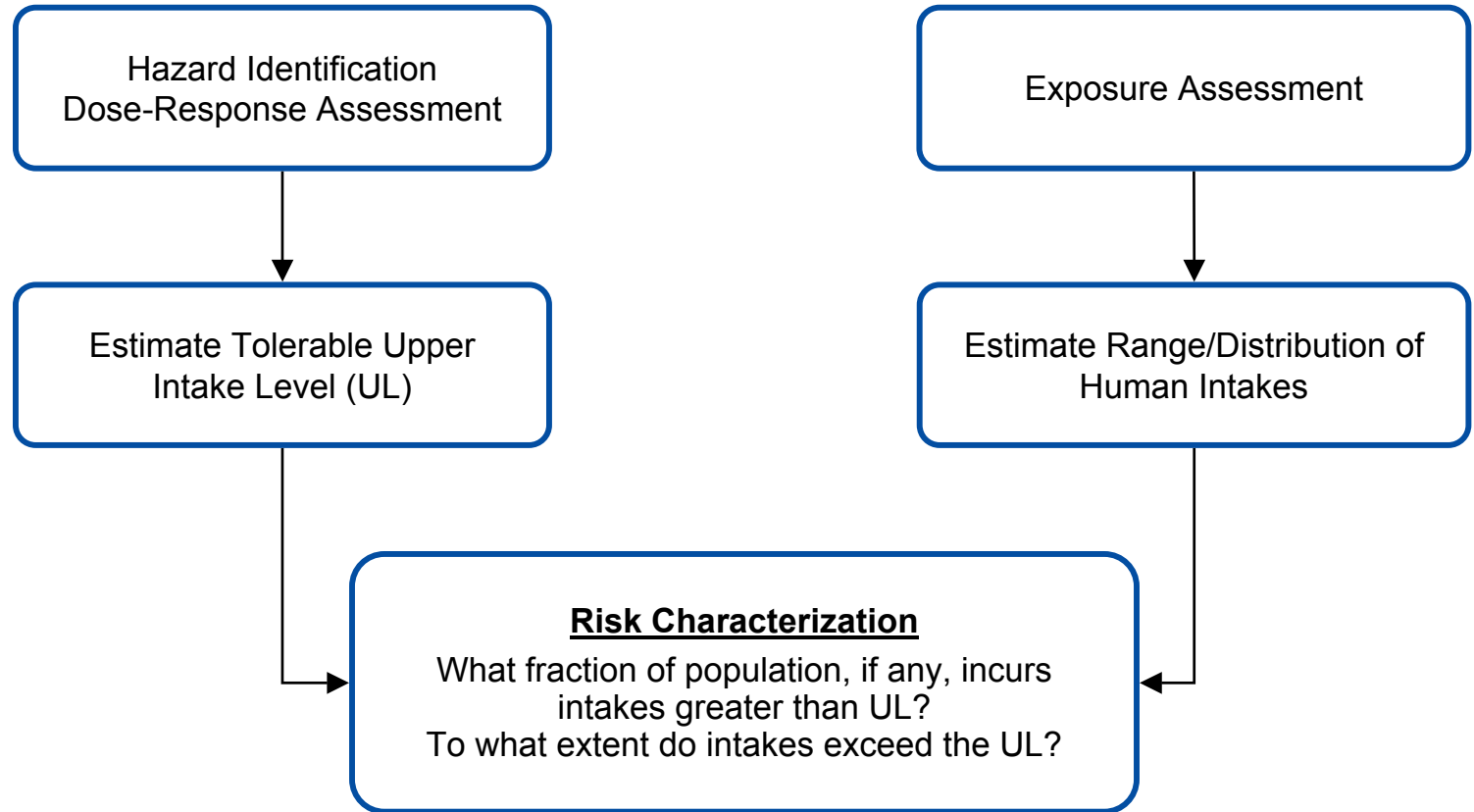
The concept of a safe intake range

(adapted from Health and Welfare, Canada, 1983)



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Risk Assessment Model for Nutrient Toxicity



IOM, Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride (1997)

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Definitions

Tolerable upper intake level (UL) – 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.

“Tolerable intake” in this context connotes what is physiologically tolerable and is a scientific judgement as determined by assessment of risk, i.e. the probability of an adverse effect occurring at some specified level of exposure. ULs may be derived for various lifestage groups in the population.

The UL is not a recommended level of intake.

Scientific Committee on Food 2000 - April 2003

22 Opinions on Tolerable Upper Intake Levels

Vitamins	UL (adults)	Minerals	UL (adults)
β-carotene	–	manganese	–
vitamin B ₆	25 mg	selenium****	0.3 mg
vitamin B ₁₂	–	molybdenum	0.6 mg
folic acid	1 mg	magnesium*	250 mg
vitamin B2	–	iodine	0.6 mg
vitamin B1	–	zinc	25 mg
biotin	–	copper	5 mg
pantothenic acid	–	calcium	2500 mg
	10 mg	chromium(III)***	–
niacin {	nicotinic acid	900 mg	
vitamin A**	nicotinamide	3 mg RE	
vitamin D		0.05 mg	
vitamin E		300 mg	
vitamin K		–	

- * valid for readily dissociable Mg salts in supplements, water and added to food only
- ** preformed only
- *** does not apply to chromium picolinate
- **** does apply to selenate, selenite and selenium from food

Derivation of ULs for vitamins by the SCF

	UL (adults)	LOAEL	NOAEL	UF	adverse effect	decisive data	age group
vitamin B ₆	25 mg	100 mg/d		2x2	neurotoxicity (human)	Dalton and Dalton, 1987	extrapolation for body weight
folic acid	1 mg	5 mg/d		5	masking of haematological signs in B ₁₂ -deficiency (human)	several	extrapolation for body weight
nicotinic acid	10 mg	30 mg/d		3	flushing (human)	Sebrell & Butler, 1938	extrapolation for body weight
nicotinamide	900 mg		25 mg/kg/d	2	– (human)	supplementation trials in diabetes mellitus	extrapolation for body weight
vitamin A	3 mg	3 mg/d		1.0	teratogenicity (human)	Rothman et al, 1995	extrapolation for body weight ^{0.75} Not applicable to postmenopausal women
vitamin D	0.05 mg (adults) 0.025 mg (0-24 mon)		0.1 mg/d 0.025 mg/d	2.0 1.0	hypercalcaemia and elevated serum 25(OH)D hypercalcaemia	Tjellesen et al, 1986 Vieth et al, 2001 Ala-Houhala, 1985 Vervel et al, 1997	applicable to children >10 years also applicable to children 3-10 years
vitamin E	300 mg		540 mg/d	2.0	blood clotting	Meydani et al, 1998	extrapolation for body weight ^{0.75}

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Derivation of ULs for minerals by the SCF

	UL (adults)	LOAEL	NOAEL	UF	adverse effect	decisive data	age group
selenium	0.3 mg		0.85 mg/d	3	selenosis (human)	Yang et al, 1989 Yang & Zhou, 1994	extrapolation for body weight
molybdenum	0.6 mg		0.9 mg/kg/d	100	reproductive toxicity (rats)	Fungwe et al, 1990	extrapolation for body weight
magnesium	250 mg	360 mg/d	250 mg/d	1	diarrhea (human)	many	applicable to children from 4 years on. No UL for age 1-3 years
iodine	0.6 mg		1.8 mg/d	3	elevation of serum TSH	Paul et al, 1988; Gardner et al, 1988	extrapolation for body weight ^{0.75}
zinc	25 mg		50 mg/d	2.0	copper status	Davis et al, 2000; Milne et al, 2001; Bonham et al, 2002	extrapolation for body weight ^{0.75}
copper	5 mg		10 mg/d	2.0	liver function (human)	Pratt et al, 1985	extrapolation for body weight ^{0.75}
calcium	2500 mg		2500 mg/d	1.0	intervention studies in adults	many	not applicable to children and adolescents

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European Food Safety Authority, Panel on Nutrition, Dietetic Products and Allergies, June 2003 – today

	UL	<i>to be done</i>
vanadium	–	iron
vitamin C	–	fluoride
silicon	–	phosphorus
boron	10mg	nickel
		tin
		sodium
		potassium
		chloride

Comparison of ULs derived by SCF/EFSA with ULs derived by FNB of IOM

	SCF/EFSA	FNB
number of ULs defined	15 ^{*,***}	23 ^{**}
number based on human LOAEL	4 (29%)	10 (43%)
UF applied	1–5	1–5
number based on animal LOAEL	1	2 (9%)
UF applied	60	36–300
number based on human NOAEL	9 (64%)	8 (35%)
UF applied	1–3	1–2,5
number based on animal NOAEL	1 (7%)	3 (13%)
UF applied	100	30–300

* nicotinic acid (LOAEL) and nicotinamide (NOAEL) separately

** fluoride (LOAEL for children; NOAEL for adults) and vitamin A (LOAEL for young women; NOAEL for all others) counted double

*** nickel, fluoride, phosphorus still under evaluation; no UL defined for vitamin C, iron, manganese, vanadium

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Differences between ULs derived by SCF/EFSA with ULs derived by FNB of IOM

- Only three of the ULs are the same.
- As a rule European ULs are lower

This has several causes:

- ◆ different data basis: → vitamin B₆, zinc;
- ◆ same data basis, but separate evaluation for two different vitamin forms: → nicotinic acid, nicotinamide;
- ◆ same data basis but different selection as LOAEL or NOAEL: → calcium, magnesium, iodine;
- ◆ same data basis but application of different uncertainty factor: → selenium, copper, molybdenum, boron;
- ◆ human versus animal data: → vitamin E

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No UL can be derived – what does it mean?

- ◆ No adverse effect can be identified:
→ biotin, thiamin, riboflavin
- ◆ Adverse effects identified but insufficient dose-response data:
→ manganese, β -carotene, vitamin C, silicon (animals)
- ◆ Insufficient data, but adverse effects possible:
→ vanadium, pantothenic acid (g doses)
- ◆ Insufficient data, adverse effects not seen at identified dosis:
→ chromium (1 mg), vitamin K (10 mg), vitamin B₁₂ (1-5 mg)

Conclusions

- ◆ ULs are derived from a risk assessment based on, in most cases, insufficient and not systematically gathered data.
- ◆ They are based on the best possible judgement at a given time.
- ◆ They should not be considered and used as isolated figures but as part of the complete risk characterisation.

How to convert an Upper safe level (for the daily intake) into a maximum level of a food supplement

- 1) UL = maximum level
- 2) NOAEL = maximum level
- 3) $\frac{UL}{\text{factor}}$ = maximum level
- 4) UL - intake from other sources = maximum level
- 5) $\frac{UL - \text{intake from other sources}}{\text{factor}}$ = maximum level

Example Calcium

NOAEL = 2500mg UL = 2500mg RDA adults = 1000 mg

Intake: men 18-24y 90th percentile: >2500 mg/d
men/women 65-79y 10th percentile: 600 mg
median intake all ≥ 1000 mg

- 1) UL = maximum level \rightarrow 2500 mg/daily portion
- 2) NOAEL = maximum level \rightarrow 2500 mg/daily portion
- 3) $\frac{UL}{\text{factor e.g.3}}$ = maximum level \rightarrow 800 mg/daily portion
- 4) UL - intake from other sources = maximum level
90th percentile young men \rightarrow 0 mg/daily portion
10th percentile old men/women \rightarrow 1900 mg/daily portion
50th percentile all \rightarrow 1500 mg/daily portion
- 5) $\frac{UL - \text{intake from other sources}}{\text{factor e.g.2}}$ = maximum level
90th percentile young men \rightarrow 0 mg/daily portion
10th percentile old men/women \rightarrow 850 mg/daily portion
50th percentile all \rightarrow 750 mg/daily portion

Uncertainties inherent in the setting of maximum levels for vitamins and minerals

- Upper safe levels:
- database insufficient
 - different results from different assessors
 - no upper safe level identifiable for different reasons

Intake from other dietary sources: database insufficient

Reference intakes: European data from 1994

Conclusion

Risk assessment in the setting of maximum levels for vitamins and minerals for supplements is useful and necessary.

Routine application of a single formula can lead to strange results.

If ULs have not been defined for various reasons, a formula is impossible.

If intake data are insufficient or lie within a wide range, considered choices have to be made.

Food Supplements in the EC

Other nutrients than vitamins and minerals and “other substances” with a nutritional or physiological effect will at the earliest be dealt with on 12 July 2007.

Until then

- their names and nature have to be given on the label
- their amounts in numerical form shall be declared

Unsolved problems with food supplements — "other substances" with a nutritional or physiological "effect"

- 1) Risk assessment not possible because
 - substances not clearly identified (extracts)
 - intake and dose-response data not available
 - adverse effects post-hoc
- 2) Reliance on empiricism
- 3) Drugs camouflaged as food

Personal questions:

- 1) Why should anybody want to supplement his/her diet with (much) more than the recommended amount?
- 2) Who will understand recommended amounts when supplements with multiples of recommended amounts are authorised?

Thank you for your attention

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Definitions

2. ***To whom does a UL apply?*** – all groups of the general population (excluding those receiving the nutrient under medical supervision), including sensitive individuals, throughout the life stage – except in some cases discrete, identifiable sub-populations (e.g. those with genetic predisposition or certain disease states) that may be especially vulnerable to one more adverse effects. The exclusion of such sub-populations will be considered on a nutrient by nutrient basis.

The 4 steps of risk assessment

- ◆ ***hazard identification:***
summary of the evidence that a nutrient causes one or more types of adverse effects
- ◆ ***hazard characterisation:***
qualitative and quantitative, including a dose response (frequency and severity) assessment. From these data a UL is derived taking into account uncertainties of the data.
- ◆ ***exposure assessment:***
distribution of total daily nutrient intake in the population
- ◆ ***risk characterisation:***
based on the conclusions from steps 1 to 3 the risk of the population or groups of the population is described to exceed the UL and to incur adverse effects.

Data selection criteria

◆ **hazard identification:**

- preferable human data
- experimental data
- quality and completeness of the data base
- causality (temporal relationship, consistency, strength of association, dose-response relationships, specificity, biological plausibility, coherence)
- highly sensitive sub-populations
- “adversity” of effect
- mechanisms of adverse effects

◆ **hazard characterisation:**

- preferable human data
- bioavailability
- dose-response
- UL > RDA!
- NOAEL or LOAEL and critical endpoint
- route of exposure
- duration of intake
- uncertainty assessment in setting UL