

Context Paper

prepared by WHO staff, in cooperation with FAO staff

CHARGES AND QUESTIONS

**FAO/WHO Nutrient Risk Assessment Workshop:
A Model for Establishing Upper Levels of Intake for Nutrients and Related
Substances**

2–6 May 2005 WHO Headquarters, Geneva

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I. INTRODUCTION TO CONTEXT PAPER

2 Nutrient risk assessment is a science-based process. As it relates to this workshop,
nutrient risk assessment (a) identifies the upper levels of intake for nutrients and related
4 substances which if exceeded may cause adverse effects, and (b) characterizes the risk
involved. The process provides information for making decisions regarding food
6 fortification, formulated 'functional foods,' infant formula, dietary/food supplements, and
dietetic foods (foods for special dietary uses). Such decisions relate to protecting public
8 health and to the practice of setting science-based standards for food. With the increased
world-wide availability of these products, there is a need for an international approach for
10 nutrient risk assessment—that is, for a set of nutrient risk assessment methods that can be
used in the international setting. Just as international nutrient reference values are needed
12 to specify the adequate levels of nutrient intake, upper levels of intake are needed to
address the potential for adverse effects. In addition, methods are needed to assess a
14 population's exposure to the nutrient and to characterize the risk that would be posed by
exceeding an upper level of intake.

16

The Food and Agriculture Organization (FAO) and the World Health Organization
18 (WHO) are convening a workshop for the purpose of identifying a model that can be used
to establish international upper levels of intake for nutrients and related substances and to
20 identify principles for nutrient exposure assessment and for characterizing the risk
associated with intakes above the upper level. In short, the workshop is to focus on the
22 steps, decision points, and key considerations associated with nutrient risk assessment.

24 This context paper, which was prepared by WHO staff in collaboration with FAO staff,
contains important information to help participants prepare for the workshop:

- 26 - charges for the workshop,
- general questions about nutrient risk assessment to be addressed during the workshop,
28 - background information about risk assessment in general,
- available information about nutrient risk assessment in particular, including three
30 national/regional models in current use. These are: (i) EU-SCF/EFSA: European
Union, Scientific Committee on Food and the European Food Safety Authority (1);

32 (ii) UK-EVM: Expert Group on Vitamins and Minerals, United Kingdom, Food
Standards Agency (2); and (iii) US-IOM: Institute of Medicine, United States of
34 America, National Academies of Science (also encompasses Canada) (3).

36 Some of this information has been taken from the Background Paper developed by
FAO/WHO (4) and posted on the organizations' websites in November 2004. The
38 information about risk assessment is included in recognition of the multi-disciplinary
nature of nutrient risk assessment and hence the different expertise being brought to the
40 workshop by the participants. It is intended to assist participants with their preparation
for the workshop discussions and report development. Participants are encouraged to
42 consider the background information critically as they develop their scientifically valid
international model to establish upper levels of intake and conduct nutrient risk
44 assessment. It is anticipated that participants will revise definitions and other content as
appropriate to fulfil their charge.

46
Annex 1 contains an introduction and rationale for the workshop. Annex 2, a table that
48 compares the risk assessments of one nutrient (pre-formed vitamin A) as reported by
three national/regional authorities, illustrates that there are differences among the
50 approaches used at the national/regional level for nutrient risk assessment.. Annex 3
contains two glossaries: the first covers generic terms in hazard and risk assessment, and
52 the second covers risk analysis terms related to food safety. Annex 4 contains
information about 'classic' nutrient risk assessment processes as developed for non-
54 nutrient substances as it has been conducted at national and regional levels. Annex 5
highlights characteristics of good risk assessment as developed for the purposes of food
56 safety. Annexes 6, 7, and 8 each contain tables that compare various nutrient risk
assessment approaches and results among the national/regional workgroups

58
In addition to the information in this concept paper, workshop participants also will have
60 available four discussion papers (DP). The papers serve the purpose of critically
evaluating certain key issues relevant to the workshop discussions and have been
62 prepared by the participants selected to serve as discussion paper authors (or drafting

experts). The discussion papers cover some but not all of the topics germane to the
 64 workshop. They stem primarily from the topics identified as challenges in the
 Background Paper (4). The discussion papers focus on:

- 66 - review of the evidence that takes place during the hazard identification step
 (Discussion Paper 1);
- 68 - use of uncertainty and adjustment factors during the hazard characterization step
 (Discussion Paper 2);
- 70 - approaches for dietary exposure assessment (Discussion Paper 3);
- considerations for the process of risk characterization (Discussion Paper 4).

72

These papers may be used by participants to stimulate their discussions. In addition, as
 74 appropriate and directed by participants, components may be included in the final report
 of the workshop.

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78 **II. CHARGES TO THE WORKSHOP**

Workshop participants are charged with the following general tasks and also are asked to
 80 be responsive to the questions highlighted in the remainder of this document.

*Workshop participants will specify a scientifically valid international model to establish
 82 upper levels of intake and conduct nutrient risk assessment. As part of this process
 participants will:*

- 84 ▪ *As a starting point consider the existing national models for nutrient risk
 assessment developed at the national and regional level (note: other models or
 86 frameworks that are available in the public domain also may be taken into
 account);*
- 88 ▪ *Develop the essential components/characteristics of hazard identification and
 hazard characterization to provide for a uniform approach to these activities
 90 internationally;*

- 92 ▪ *Identify general principles for harmonizing the process (rather than the outcome)*
of exposure assessment and risk characterization which by their nature vary from
94 *region to region because the relevant data vary from region to region;*
 ▪ *Check the model (and its application of the principles) by testing it using several*
96 *representative nutrients or substances, specifically Vitamin A, Iron and Vitamin*
 C/Antioxidant;
98 ▪ *Work within the initial context of a model relevant to adequately nourished*
 populations, and then identify the special considerations needed to apply the
100 *model to inadequately nourished populations.*

102 It is expected that, by the close of the workshop, the participants will have identified and
agreed upon a final report presenting the components of an international nutrient risk
104 assessment model, any needed caveats, and the identification of the nature of needed
modifications or adjustments pertaining to its use in various situations, such as with
106 inadequately nourished populations.

108 Inherent in the model development process is the task of checking the logic or
'satisfactory performance' of the model using selected substances of the types to be
110 addressed by the completed model. As part of the workshop activities, the model will be
checked using three nutrients: iron (a mineral), vitamin A (a fat-soluble vitamin), and
112 vitamin C/antioxidants (a water-soluble vitamin with the additional ability to act as an
antioxidant). These three nutrients reflect different challenges, such as narrow margins
114 between required intake and upper levels, and also are nutrients for which the three
national models differ in terms of their approaches and outcomes.

116
Nutrients and related substances differ from many other types of substances that
118 commonly are the subject of risk assessment in that they confer benefit as well as the
potential, at least in some cases, for risk. It is within the scope of the workshop to
120 consider these opposing characteristics (benefit and risk) when setting 'safety' factors or
other data corrections for uncertainty: the method used must ensure that an upper level of
122 intake will exceed the amount required for the benefit. However, it is outside the scope

of this workshop to consider other risk–benefit contexts as part of the model
 124 development.. These issues require exploration in a more comprehensive manner than
 can be accomplished during this workshop. They could be the subject of future research
 126 and of policy discussions among risk managers.

128 **III. AUDIENCE FOR WORKSHOP REPORT**

The audience for the outcomes of the workshop includes: (1) risk assessors who must
 130 quantify or otherwise determine upper levels of intake for nutrients and related
 substances and then characterize the risk; and (2) risk managers and those with related
 132 responsibilities and interests who need information from the nutrient risk assessment for
 their decision making. Information about the risk assessment process can help them
 134 develop the questions to ask of nutrient risk assessors.

136 **IV. TERMINOLOGY**

The definitions below may provide a basis for initial Workshop discussions and are taken
 138 from the work of WHO/IPCS and the Codex Alimentarius (see Annex 3). The source of
 the definition from Annex 3 is indicated. Additional terms that may be useful during
 140 preparation for the workshop and the initial workshop discussions appear in Annex 3 as
 well. The Workshop participants may rely on the WHO/IPCS and Codex Alimentarius
 142 terminology as a starting point, but they may modify these definitions to make them more
 suitable for the nutrient risk assessment model that they are developing.

144

General Definitions

- 146 ▪ Upper Level of Intake¹: A science-based quantitative level of total intake at which, or
 below, no risk is expected to occur assuming nutrient adequacy is met.
- 148 ▪ Risk (WHO/IPCS): The probability of an adverse effect in an organism, system or (sub)
 population caused under specified circumstances by exposure to an agent.
- 150 ▪ Risk (Codex Alimentarius): A function of the probability of an adverse health effect²
 and the severity of that effect, consequential to a hazard(s) in food.

¹ Originally included in the Background Paper (ref) as the following working definition: A quantitative level of total intake at which, or below, no harm is expected to occur assuming nutrient adequacy is met.

- 152 ▪ Hazard (WHO/IPCS): Inherent property of an agent or situation having the potential to
 154 cause adverse effects when an organism, system or (sub) population is exposed to that
 agent.
- 156 ▪ Hazard (Codex Alimentarius): A biological, chemical or physical agent in, or condition
 of, food with the potential to cause an adverse health effect.²
- 158 ▪ Adverse Effect (WHO/IPCS): Change in the morphology, physiology, growth,
 development, reproduction or life span of an organism, system, or (sub) population that
 160 results in an impairment of functional capacity, an impairment of the capacity to
 compensate for additional stress, or an increase in susceptibility to other influences. Used
 by some interchangeably with Adverse Health Effect.

162

Process Definitions

- 164 ▪ Risk Analysis (WHO/IPCS): A process for controlling situations where an organism,
 system or (sub) population could be exposed to a hazard. The process consists of three
 166 components: risk assessment, risk management and risk communication. [see also Codex
 Alimentarius definition in Annex 3]
- 168 ▪ Risk Assessment (WHO/IPCS): A process intended to calculate or estimate the risk to a
 given target organism, system or (sub) population, including the identification of
 170 attendant uncertainties, following exposure to a particular agent, taking into account the
 inherent characteristics of the agent of concerns as well as the characteristics of the
 172 specific target system. The process includes four steps: i) hazard identification; ii)
 hazard characterization; iii) exposure assessment; and iv) risk characterization. It is the
 174 first component in a risk analysis process. [see also Codex Alimentarius definition in
 Annex 3]
- 176 ▪ Risk Assessment Policy (Codex Alimentarius): Documented guidelines on the choice
 of options and associated judgements for their application at appropriate decision points
 178 in the risk assessment such that the scientific integrity of the process is maintained.

² The term *adverse health effect* is used by some but has not been defined by IPCS/WHO or Codex Alimentarius.

- 180 ▪ Risk Communication (WHO/IPCS): The interactive exchange of information about
(health or environmental) risks among risk assessors, managers, news media, interested
182 groups and the general public. [see also Codex Alimentarius definition in Annex 3]
- 184 ▪ Risk Management (WHO/IPCS): Decision-making process involving considerations of
political, social, economic, and technical factors with relevant risk assessment
information relating to a hazard so as to develop, analyze, and compare regulatory and
186 non-regulatory options and to select and implement appropriate regulatory response to
that hazard. [see also Codex Alimentarius definition in Annex 3].

188

190 **V. APPLICATIONS FOR AN INTERNATIONAL NUTRIENT RISK** **ASSESSMENT MODEL**

Annex 4 provides background information about risk assessment in general, including the
192 roles and tasks associated with the risk assessment process. The information provided
has been derived primarily from the work of Codex Alimentarius and on-going
194 workshops and consultancies convened by WHO and FAO. The annex also provides
general information about the nutrition context for risk assessment. Much of this
196 information was presented earlier in the Background Paper.³

The approaches highlighted in Annex 4 often operate in situations where there are
198 relatively specific or focused risk analysis needs and where there is likely to be the
opportunity for a highly iterative dialog between the risk assessor and the risk manager.
200 An international nutrient risk assessment model that specifies upper levels (ULs) of
intake for nutrients and related substances is expected to be most useful to others in the
202 future if it serves a range of purposes and applications. With this in mind, Workshop
participants may require some background information about the applications for which
204 the nutrient risk assessment (ULs and associated risk characterizations) may be used.
This section provides some information in this regard, particularly with respect both to
206 the general policy options to which the model may be applied and to the interface
between nutrient risk assessors and nutrient risk managers. Workshop participants may
208 wish to consider the ways in which this background information may be relevant to the
development of a nutrient risk assessment model for international use.

³ http://www.who.int/ipcs/highlights/nutrientproject_april05/en/

210 Initially, it is helpful to outline the generally accepted roles for risk assessors and risk
managers. Because the risk assessor typically carries out tasks in response to a specific
212 request from the risk manager, risk management tasks are listed first. Among the general
tasks of risk managers are the following:

- 214 ▪ to define the problem and to articulate the goals of the risk analysis;
- 216 ▪ to specify the questions to be answered by the risk assessment (identifying available
policy options) and to ask the risk assessor to provide information based on the
218 examination of available scientific evidence and professional expertise concerning the
nature and level of risk associated with the intake of the nutrient or related substance;
- 220 ▪ to consider the risk assessment, especially the risk characterization, along with other
relevant information to decide which policy option, if any, is most suitable for
implementation.

222 The following general tasks characterize the work of risk assessors:

- 224 ▪ to analyze the relevant scientific evidence systematically utilizing the steps of risk
assessment;
- 226 ▪ to structure the information about each component of a risk assessment step in a
logical sequence based on usual language, for example nutrition science and/or
toxicology language;
- 228 ▪ to indicate when and where scientific uncertainties exist and how the assessment of
the risk may incorporate correction factors for uncertainties as well as adjustments
230 and needed extrapolations;
- 232 ▪ to indicate differences in risk among different population groups as indicated by the
scientific evidence, uncertainties, and (when appropriate) the application of scientific
judgement;

- 234 ▪ to address the question(s) posed by the risk manager (e.g. establish a UL) or provide
reasons for not doing so;
- 236 ▪ to frame the risk characterization in a way that provides the needed information for
the available policy options identified by the risk manager and links it to the relevant
238 component of the risk assessment.

Turning more specifically to the general applications of a nutrient risk assessment model,
240 first in the context of nutrient risk assessment for upper levels of intake, it is likely that
risk management activities would have specified a problem statement such as the
242 following:

*To identify and characterize the risk associated with upper levels of intake for
244 nutrient(s) X or for related substance(s) Y, to be used by the risk manager in
making policy decisions relative to food products Z (as within their regulatory
246 purview).*

Essentially, the application of the general international model is related to its ability to
248 provide information to the risk manager so that he/she can evaluate the best course of
action (policy options), select all those that are appropriate, and follow through with risk
250 management. A general model, therefore, is predicated on the need to provide 'all-
purpose' data to cover the range of policy options that the model may be called upon to
252 address. Tables 1 through 4 below illustrate the application of the nutrient risk
assessment in the context of its providing the information relevant to a number of policy
254 options that may be available to the risk manager for nutrients and related substances.
The examples for the policy options are: Timing of Response, Product Formulation,
256 Labeling, and Education.

258 **Table 1. Elements of risk analysis for the policy option 'timing of response'** Note: decision may be 1) immediate action, 2) no action but close vigilance/monitoring, or 3) no action

RISK ASSESSMENT Data provided by risk assessor to inform the policy option decision	RISK MANAGEMENT Information developed by risk managers to make policy option decisions
<ul style="list-style-type: none"> • Nature of adverse effects <ul style="list-style-type: none"> ○ Severity ○ Vulnerable age/sex/life-stage groups ○ Specify if for all forms of nutrient/substance (i.e. total intake) or if for certain form (e.g. folic acid vs food folate; pre-formed vitamin A vs. beta-carotene) • Derivation of UL for vulnerable groups (including basis for UL, e.g. total intakes or particular nutrient form) • Status of vulnerable groups relative to UL: <ul style="list-style-type: none"> ○ Intake distributions of appropriate nutrient form relative to the UL: <ul style="list-style-type: none"> ▪ Percentage exceeding the UL ▪ Distribution approaching UL and at risk of exceeding UL with relatively small changes in intake ○ Magnitude of intakes exceeding UL (Level of intake compared with the UL; Narrowness between intake and UL) ○ Percentage exceeding UL • Other at-risk groups (e.g. malnourished, persons using certain drugs, certain diseases) and nature of their risk. • If appropriate, reasons why UL could not be established (e.g. insufficient data quality and/or quantity; risk present but not able to identify a threshold level) • <i>Description of uncertainties involved in each of the information needs above.</i> 	<ul style="list-style-type: none"> • Gathering of additional data needed to clarify immediacy of issue, and as appropriate requests to risk assessors for scientific evaluation of impact (e.g. manufacturing data, feasibility of change, existing regulatory authorities and limitations, cost, etc) • For other groups at risk (e.g. diseased populations):^a <ul style="list-style-type: none"> ○ percentage exceeding UL or the appropriate risk intake level if different from the UL for the general population ○ Magnitude of intakes exceeding UL (how close or far away from UL) ○ Numbers of people in these groups exceeding UL • If no UL because there is no threshold dose, identification of intake level at which adequacy is met^b • Determination of implementation terminology as needed or as appropriate vis a vis 'tolerable upper level' or 'safe upper level' etc.

260 ^a Because this information initially would have been outside the scope of that considered by risk assessors, the task may fall to risk managers. However, risk managers may consider options for engaging risk assessors in relevant scientific evaluations pertaining to such information.

262 ^b Because such data needs could not be necessarily anticipated prior to the risk assessment, the evaluation of the issues likely will take on an iterative aspect between nutrient risk managers and risk assessors.

266 **Table 2. Elements of risk analysis for the policy option 'product formulation /**
 268 **presence-absence of substance in food supply.'** Note: decision may be 1) limit amounts
 270 of nutrient/substances available to consumers, 2) require concurrent adjustment in other
 272 nutrients or substances that may adversely interact with subject nutrient/substance, 3)
 limit or ban use of certain forms or sources of nutrient/substance, limit or ban addition of
 the subject nutrient/substance to certain types of foods

<p style="text-align: center;">RISK ASSESSMENT</p> <p style="text-align: center;">Data provided by risk assessor to inform the policy option decision</p>	<p style="text-align: center;">RISK MANAGEMENT</p> <p style="text-align: center;">Information developed by risk managers to make policy option decisions</p>
<ul style="list-style-type: none"> • Form of nutrient associated with risk, all forms (total intake) or specific forms of nutrient/substance; or total intakes? • Role of bioavailability in risk and factors affecting bioavailability (e.g. nutrient form; interactions with other meal or food components) • Description of any nutrient-nutrient adverse interactions. • Description of uncertainties involved in information provided 	<ul style="list-style-type: none"> • Gathering of additional data needed to clarify outcome of policy decisions such as the relative contribution of particular product types or classes to total daily intakes, or—if staple product is source of exposure—exploration of whether a substitute staple product that contains a smaller amount of the substance can be made available.^a • Development of 'what-if scenarios' such as 1) the likely impact if amounts or types of nutrients were changed in specific types of foods, or 2) the impact of using nutrient requirements (or some level thereof) as a starting point for setting limits on amounts in food so as to limit exposure to degree possible. As appropriate or possible, request evaluation of scientific issues by risk assessor.

274 ^a As appropriate, risk managers may engage risk assessors for scientific evaluation of such data

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280

282 **Table 3. Elements of Risk Analysis for the Policy Option 'Labeling.'** Note: decision
 284 use may be 1) warning label, 2) allow addition of subject nutrient/substance to food products
 targeted and labelled for use by groups not at risk, 3) provide label directions for 'safe'
 use

RISK ASSESSMENT Data provided by risk assessor to inform the policy option decision	RISK MANAGEMENT Information developed by risk managers to make policy option decisions
<ul style="list-style-type: none"> • Ability of individuals within groups at risk to self-identify their risk • Use conditions likely to increase or decrease risk (e.g. consume with or without meals, bolus v. continual exposures) • Description of uncertainties involved in the information provided 	<ul style="list-style-type: none"> • Evaluate likelihood that vulnerable groups use food products containing the substance • Evaluate likelihood that vulnerable groups are able to control conditions of use to decrease risk • Evaluate utility and understandability of label information by high risk groups

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288 **Table 4. Elements of risk analysis for the policy option 'education.'** Note: decision
 290 may be 1) avoidance and/or reduced use for consumers, 2): Advice to health
 professionals to monitor the patient population at risk if consume 3) quality control and
 other procedures by industry to ensure that subject substance is unlikely to reach
 292 vulnerable groups.

RISK ASSESSMENT Data provided by risk assessor to inform the policy option decision	RISK MANAGEMENT Information developed by risk managers to make policy option decisions
<ul style="list-style-type: none"> • Ability of individuals within groups at risk to identify their risk • <i>Description of uncertainties involved in each of the information needs above.</i> 	<ul style="list-style-type: none"> • Conduct consumer studies on components of and effectiveness of educational programs • Consultation with health professional and industry groups

294

296 These examples are not comprehensive; however, they help to illustrate the role of
 nutrient risk assessors. Moreover, they demonstrate how the policy options may define

298 the questions asked of risk assessors, and they highlight the defining role the policy
options may have in setting the stage for risk assessment.

300

Importantly, these examples relate to a general model and therefore may not encompass
302 all tasks of the risk assessor and risk manager. Clearly, the relationship between risk
assessors and risk managers may include additional or different interactions, particularly
304 when carried out at the national or regional level. For instance, ‘what-if scenarios’ are
difficult to specify ahead of the risk assessment, but at some point the risk manager may
306 be in a position to identify certain regulatory changes or possible decisions that require
further scientific evaluation before their impact can be fully taken into consideration. In
308 this case, the risk manager may re-engage the risk assessor. The risk assessor, in turn,
would take on the task of answering scientific questions relevant to the policy scenarios
310 so that the risk manager can make a more informed policy choice. By its nature, nutrient
risk assessment is an iterative process.

312

VI. MODEL DEVELOPMENT: QUESTIONS

314 The questions below have been provided to assist and enrich the workshop discussions.

316 They pertain to the development of an international nutrient risk assessment model that is
assumed to have multiple policy applications and to be in a format that will foster
318 consistency across a broad range of nutrients. Risk managers may be required to use the
outcomes of the nutrient risk assessment model for many purposes. For example, they
320 may need UL-related information from the risk assessor pertaining to the food supply (e.g.
overall fortification policies) and to products that may be targeted to specified life-stage
322 groups (e.g. supplements, fortified foods for special dietary uses). Moreover, the
information provided by the assessment is needed in a form that allows application to a
324 range of policy options (e.g. composition, labeling, education). This interest in
addressing a multi-purpose international model underlies, in part, the nature of the
326 questions asked. The questions proceed sequentially through the various steps of general
risk assessment models and are intended to elicit identification of the basic components
328 of nutrient risk assessment to be used at the international level. They are also intended to

provide guidance and criteria for many of the decisions needed to implement a nutrient
 330 risk assessment model with international applicability.

332 **A. Background and definitions**

1. Defining UL

334 The Background Paper for this workshop defined UL as follows: '*A quantitative*
level of total intake at which, or below, no risk is expected to occur assuming
 336 *nutrient adequacy is met.*' (Note: three national/regional models have also each
 provided a definition for 'UL.'^{4, 5, 6}).

338

Q 1: For international nutrient risk assessment purposes, what is the appropriate
 340 definition of a UL? Should the definition of the UL be based on (i) 'a level at
 which, or below, no harm is likely to occur' or (ii) 'a level above which there is the
 342 potential for harm'?

344 **2. Time period for UL**

Q 2: What guidance can be provided relative to terminology and criteria for the
 346 time periods for the UL?

- a. For long term intakes (e.g. chronic, usual, lifetime)?
- 348 b. For short term intakes (e.g. acute, bolus)?

⁴ EU/EFSA/SCN: The Tolerable Upper Intake Level (UL) is 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 judgment as determined by assessment of risk, i.e. the probability of an adverse effect occurring at some specified level of exposure. The UL is not a recommended level of intake. It is an estimate of the highest level of intake which carries no appreciable risk of adverse health effects.

⁵ UK/EVM: The determination of a Safe Upper Level (SUL) entails determination of doses of vitamins and minerals that potentially susceptible individuals could take daily on a life-long basis, without medical supervision in reasonable safety. The setting of these levels provides a framework within which the consumer can make an informed decision about intake, having confidence that harm should not ensue. The levels so set will therefore tend to be conservative, and it is possible that for some vitamins and minerals larger amounts could be consumed for shorter periods without risk to health.

⁶ US/IOM: The Tolerable Upper Intake Level (UL) is the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population. As intake increases above the UL, the risk of adverse effects increases. The term 'tolerable' was chosen because it connotes a level of intake that can, with high probability, be tolerated biologically by individuals; it does not imply acceptability of that level in any other sense.

350 **3. Sub-groups for UL**

352 **Q 3:** What guidance can be provided for identifying the subgroups for which UL
information is needed?

- 354 **a.** What are the advantages and disadvantages of having consistency
between UL subgroups and subgroups for recommended intakes?
- 356 **b.** What are the advantages and disadvantages of using biological
differences relative to the adverse effect as the basis for defining
subgroups for ULs (including consideration of homeostatic mechanisms
358 that may differ among age and life-stage groups)?

360 **4. Limited data**

362 **Q 4:** What guidance can be provided for decisions as to whether or not to set a
UL when available data are very limited?

- 364 **a.** How can the risk assessor deal with situations where there is a need to
balance public health needs for a UL against a situation in which the
available data are very limited (e.g. a situation where a public health risk
366 is documented and the risk manager has no choice but to take some type of
action; a situation where the range between adequacy and risk is very
368 narrow)?
- 370 **b.** If in the context above a UL is established, what guidance can be
provided to ensure that the uncertainties surrounding this UL are clearly
communicated to potential users of the UL?
- 372 **c.** What criteria are appropriate to justify not setting a UL?

374 **5. Comparability of UL with other safety reference values**

376 **Q 5:** Is the concept of a nutrient UL synonymous with an Acceptable Daily
Intake (ADI)?

- 378 **a.** What are the similarities and differences?
- b.** Are there similarities or differences to other relevant concepts?

380

382 **B. 'Box 1' Hazard identification**

384 **Q 6:** What are the basic components and output of the hazard identification step
relative to an international risk assessment model?

386 **1. Definition and nature of adverse effects**

388 **Q 7:** What guidance/criteria can be provided for determining the appropriateness
of an outcome or biomarker as a sufficient indicator of an adverse effect?

390 **a.** What characteristics of a biomarker or adverse outcome would make
them potentially useful as a basis for setting a UL?

392 **b.** What criteria would justify not using a biomarker or adverse outcome
as a potential basis for setting a UL?

394 **2. Nature of review of evidence**

396 **Q 8:** Given that reviews of the scientific evidence can range from very
comprehensive searches that include identification of possible adverse effects of
high intakes to more abbreviated and focused reviews when the adverse effects
398 are generally recognized and known by the scientific community, what
criteria/guidance can be provided to decide on the type and scope of the scientific
400 review that is needed?

402 **Q 9:** Overall, what is the general research question that should guide the
scientific evaluation for the purposes of identifying an appropriate UL?

404 **a.** What is the appropriate population (e.g. 'healthy', 'general')?

406 **b.** What is the appropriate intake for which information is needed (e.g.
intakes above the recommended intake; duration of intake)?

408 **c.** What is the appropriate comparator (e.g. levels at or slightly above the
recommended intake)?

410 **d.** What are the appropriate types of health outcomes (e.g. biomarkers or
outcomes that meet the criteria in response to Q7 above)

412 **Q 10:** How should the general research question in Q9 above be modified to
414 identify potentially vulnerable high risk groups that are outside the scope of the
UL but need to be identified and discussed as part of the risk assessment process?

- 416 a. Inadequately nourished populations?
- 418 b. Populations which may represent significant proportions of the total
420 population but outside the scope of the UL population definition (e.g.
422 groups at risk of, or diagnosed with, common chronic diseases;
patients on prescription drugs that may adversely interact with the
nutrient of interest)?
- 424 c. Risks that are serious but are limited to a relatively small proportion of
the total population (e.g. iron overload, patients with diseased livers
due to etiologies other than excessive nutrient intakes)?

426 **Q 11:** What guidance can be provided to help risk assessors in deciding what
428 types of data are needed for a particular nutrient risk assessment (e.g. human only
vs. also animal and in vitro)?

430 **Q 12:** In general what are the inclusion and exclusion criteria for Q9 and Q10
432 above? What guidance can be provided to risk assessors for making these
434 decisions?

436 **Q 13:** What guidance can be provided to nutrient risk assessors for grading and
438 synthesizing the evidence?

440 **Q 14:** What information needs to be included in summary tables of the results of
442 the literature review in order to provide the information needed in the hazard
characterization, exposure assessment, and risk characterization steps of the
process?

C. 'Box 2' Hazard characterization

444 **Q 15:** What are the basic components and output of the hazard characterization
step relative to an international risk assessment model?

446

1. Dose–response

448 **Q 16:** What are the strengths and weaknesses of different approaches that can be
used in establishing dose–response relationships for nutrients given that they are
450 subject to physiological adaptation and homeostatic mechanisms at varying intake
levels (e.g. single point estimates such as NOAELs or LOAELs vs. approaches
452 that use the entire dose–response curve (e.g. benchmark dose–response))? What
criteria can be developed to guide this decision on a nutrient-by-nutrient basis?

454

Q 17: What are the types of uncertainties associated with dose–response
456 curves? (e.g. need for extrapolations from high to low doses? extrapolations
from short-term doses to chronic effects? bioavailability issues?)

458

Q 18: Experience has shown that not all nutrient risk is consistent with a
460 threshold model (e.g. vitamin A and bone health, saturated fats and coronary heart
disease). In these types of cases, what approaches or guidance is appropriate for
462 risk assessment decisions?

2. Uncertainty

464 **Q 19:** For the purposes of nutrient risk assessment, are there other potential
466 sources of uncertainty in addition to intraspecies variability, interspecies
extrapolation, and extrapolation from LOAEL to NOAEL that should be taken
468 into account?

470 **Q 20:** Are there criteria that can be developed to guide the determination and
application of uncertainty factors?

472

474 **Q 21:** What components of the rationale underlying the selection and magnitude
of the uncertainty should be included in the documentation of the decisions made
relative to the use of uncertainty factors?

476

3. Adjustment

478 **Q 22:** What are the options for the adjustment (scaling) of the UL to different age
and life-stage groups? What are the pros and cons of each method of
480 scaling? What are the criteria needed to guide decisions on the requirement for
adjustment and on the choice of an appropriate option?

482

4. Synthesis of all data and articulation of 'scientific judgement'

484 **Q 23:** What guidance is required to ensure full documentation of the final
weighing of all data (usually by nature a heterogeneous collection of information)
486 and the subsequent scientific judgement that takes place; and what form should
the guidance take?

488

D. 'Box 3' Dietary exposure estimation

490 **Q 24:** What are the basic components and output of the dietary exposure
estimation step relative to an international risk assessment model?

492

1. Consumption data

494 **Q 25:** For each major type of consumption database used for estimating the
consumption of foods and beverages, drinking water, and supplements, (i) What
496 are the strengths and weakness? and (ii) What are the biases and uncertainties?

498

2. Nutrient composition data

Q 26: If a choice of composition databases is available, what factors should be
considered in choosing among them? What are particular strengths, weaknesses,
500 biases, and uncertainties of composition databases that merit special attention?

502

Q 27: If modifications to the composition databases are needed,

504 **a.** If the composition data are incomplete, what approaches, if any, can be
 506 used to make reasonable estimates of composition for the purposes of
 506 nutrient risk assessment? Similarly, if some of the data are inaccurate or
 508 out of date, how can reasonable adjustments be made?

508 **b.** What approaches can be applied to composition databases to deal with
 510 bioavailability factors?

510

3. Analysis and intake summaries

512 **Q 28:** What are the options available to obtain estimates of intake distributions?
 514 What are the strengths and weaknesses of each option? What uncertainties and
 514 biases need to be addressed for each?

516 **Q 29:** If a database that will produce distributions of intake is lacking, what are
 518 the options for calculating intake estimates of “high consumers”? What are the
 518 strengths and weaknesses, biases, and uncertainties of each approach?

520 **Q 30:** If a total intake can be estimated only by combining data from several
 522 databases, what are the options for calculating intake estimates of “high
 522 consumers”? What are the strengths and weaknesses, biases and uncertainties of
 524 each approach?

524

4. General Principles

526 **Q 31:** What are the general principles needed to assist in harmonizing the risk
 528 assessor's approach to estimating dietary exposure?

528

E. ‘Box 4’ Risk characterization

530 **Q 32:** What are the basic components and output of the risk characterization step
 532 relative to an international risk assessment model?

532

534 **Q 33:** What can be learned from the experience of the existing national/regional
 534 models for nutrient risk assessment?

536 **Q 34:** What guidance can an international model provide about nutrient risk
characterization considerations beyond the basic components, such as
538 interpretative statements or 'other useful information'?

Q 35: Given the many different applications for which the nutrient risk manager
540 may use the outcomes of the risk assessment, what types of information should be
included in the nutrient risk characterization step of a generally-applicable
542 international model to allow the evaluation of policy options by those responsible
for such decisions?

544 **Q 36:** What are the overall principles and characteristics of a useful nutrient risk
characterization? Are there key aspects of its final presentation that aid in its
546 utility and assist in its role of providing the scientific information to be used by
others for decision making?

548

F. Presentation and communication of the assessment

550 **Q 37:** Given the policy decisions that the manager must make, a summary of the
sequence of the evaluation process used by the risk assessor may not be the most
552 effective way to communicate the results of the risk assessment to the user. If so,
what is the 'logical framework' that best presents and communicates the outcomes
554 and makes the process transparent and accountable?

VII. MODEL APPLICATION AND ADJUSTMENT: QUESTIONS

A. Testing and general application of the model

558 **Q 38:** Did the 'check' or 'test' nutrients demonstrate the utility and flexibility of
the model? What special issues were identified?

560

Q 39: What can be specified in terms of modifications or adjustments for the
562 model's use among different categories of nutrients and related substances (e.g.
vitamins/minerals versus macronutrients)?

564

B. Application of the model to inadequately nourished populations

566 **Q 40:** What are the considerations and needed adjustment for the model when it
is to be used for risk assessment for inadequately nourished populations?

568

VIII. FUTURE RESEARCH NEEDS

570 **Q 41:** What are the major research needs and data gaps?

572

574 **IX. REFERENCES**

- 576 1. European Commission. *Guidelines of the Scientific Committee on Food for the
development of tolerable upper intake levels for vitamins and minerals.*
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- 580 2. Expert Group on Vitamins and Minerals. *Safe Upper Levels for Vitamins and
Minerals.* London: Food Standards Agency Publications, May 2003.
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- 584 3. Food and Nutrition Board Institute of Medicine. *Dietary Reference Intakes: A Risk
Assessment Model for Establishing Upper Intake Levels for Nutrients.* Washington, D.C.:
586 National Academy Press, 1998.
- 588 4. FAO/WHO Background Paper. 1 November 2004.
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590

ANNEX 1

592

INTRODUCTION AND WORKSHOP RATIONALE

594 There is an increasing need for science-based determinations of upper levels of intake at
which some, if not all, nutrients and related substances may cause an adverse effect or
596 present risk⁷ to the human body. The increasing use of fortified foods, fortified
beverages, special dietary products, and dietary supplements results in the potential for
598 excessive intakes of nutrients and related substances. Thus, the subjects of this workshop
include 1) the development of a harmonized approach for determining the levels of intake
600 that if exceeded have the potential to cause an adverse effect, 2) the identification of
consistent methods to assess a population's exposure to the nutrient or related substance
602 using the best data available, and 3) characterization of the risks that would be posed by
exceeding an upper level of intake.

604

Risk managers, including those associated with the Codex Alimentarius, must evaluate
606 whether or not there is a need for policy initiatives for food products with relatively high
nutrient contents. Moreover, risk managers have standard-setting responsibilities: they
608 must ensure that food fortification practices safely provide the desired nutriture and that
dietary supplements and highly formulated special dietary products—as well as infant
610 formulas and medical foods—do so as well. To help inform the policy decisions tied in
with fulfilling these responsibilities, risk managers need science-based and well described
612 quantitative upper intake levels. Together with exposure estimates and information
relative to characterizing the risk, well-documented upper intake levels enable risk
614 managers to decide whether public health policies are needed across a broad range of
food products and, if so, which policy options are likely to be most effective and feasible.

616

⁷ For the purposes of initiating this workshop, the term 'adverse effect' and 'risk' are used. An *adverse effect* is defined in Annex 3 as: Change in the morphology, physiology, growth, development, reproduction or life span of an organism, system, or (sub) population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences. *Risk* is defined as the probability of an adverse effect in an organism, system or (sub) population caused under specified circumstances by exposure to an agent. Terms used by others include 'harm' and 'adverse health effect,' neither of which is defined.

618 An important first step in providing scientific advice concerning international upper
levels of intake for nutrients and related substances is to identify a valid international
approach or model for conducting nutrient risk assessment. Such a model must be
620 science-based, and it also must be adaptable for, and responsive to, the special
considerations presented by different types of nutrients and related substances. The
622 process of developing such a model will benefit from the knowledge gained from
previous efforts—especially from the experience and findings of those who have worked
624 to address nutrient risk assessment at national and regional levels. Several national
authorities and related bodies as well as some private groups and industry organizations
626 have addressed nutrient risk assessment. Their efforts have taken various forms ranging
from a comprehensive approach to approaches that address particular issues or concerns
628 only. Publications from such groups have been informative and sometimes ground-
breaking. Because the assessment approaches and outcomes for the same
630 nutrient/substances have differed, however, at this time no single approach can be
considered to have international application.

632

Valid upper intake levels are based on the review and analysis of data obtained from
634 available scientific studies using well-established methods. Therefore, it should be
possible to specify internationally applicable upper intake levels for nutrients and related
636 substances. International upper levels of intake would provide a sound basis for risk
managers to make policy decisions in the international arena, and they would have the
638 potential to assist with international fair trade practices. International upper levels also
could have utility for those countries or regions that have not addressed this topic
640 specifically yet would find such guidance helpful. And finally, an international model
also would present the opportunity to develop an approach to be used for adequately
642 nourished populations, and to modify the approach to address nutrient risk assessment for
inadequately nourished populations. The latter populations pose a special challenge since
644 they may be subject to high levels of fortification for certain nutrients or perhaps to large-
dose single or intermittent interventions.

646

648 FAO and WHO have a long history of providing scientific advice to Member Countries,
their subsidiary bodies, and the Codex Alimentarius Commission. An international model
to be used for nutrient risk assessment will provide scientific advice for use by Codex
650 Alimentarius but also by other nutrient risk assessors. The Codex Alimentarius
Commission has specified an immediate interest in upper levels of vitamins and minerals;
652 but certain types of fibers, amino acids, fatty acids, and dietary antioxidants also may be
subjects for nutrient risk assessment. There is reason to believe that the risk assessment
654 principles and decision points are the same or very similar for various categories of
nutrients and related substances. That is, the task at hand has the potential to be relevant
656 to all nutrients and related substances. Nonetheless, the development of an approach for
nutrient risk assessment generally must take into consideration the variability of the
658 endpoints of interest across the different types of nutrient categories (e.g. macronutrients,
vitamins, minerals). This means that it will be important for workshop efforts to include
660 identification of 1) the components of the approach that will vary depending upon the
target nutrient category and 2) the nature of the adaptations or modifications that are
662 needed for the various nutrient categories.

664 The workshop is charged with developing a model that can be used by risk assessors in
an international setting to establish upper levels of intake for nutrients and related
666 substances. It also is charged with addressing other aspects of nutrient risk assessment by
identifying consistent methods to 1) assess a population's exposure to the nutrient or
668 related substance using the best data available and 2) characterize the risks that would be
posed by exceeding an upper level of intake. In short, the workshop is to focus on the
670 steps, decision points, and key considerations associated with nutrient risk assessment.

672

ANNEX 2

674

NATIONAL MODEL GENERAL COMPARISON (VITAMIN A)

676

The table is listed below and was developed by WHO staff to facilitate an understanding
678 as to how and in what ways three existing national/regional nutrient risk assessment
models are similar or differ. This comparison is limited in that it was conducted for only
680 one nutrient (preformed vitamin A) and may not be comprehensive, but it may be of
some interest to workshop participants.

682

Context Paper

ANNEX 2. National model comparison: Vitamin A

TABLE 1. Vitamin A: comparisons for derivation of upper level (UL) among three approaches

Approach	EU-SCF (2002)¹	UK-EVM (2003)²	US-IOM (2001)³
Chemical Definition	Retinoids; “preformed” vitamin A; not provitamin A carotenoids (e.g. β-carotene)	Retinoids; “preformed” vitamin A; not vitamin A precursors (e.g., β-carotene).	Retinoids; “preformed vitamin A; not provitamin A carotenoids (e.g., β-carotene)
Applicability of Upper Limit (UL)⁴	<ul style="list-style-type: none"> • Intake from all sources (dietary and supplemental) • Short-term and long-term intakes 	<ul style="list-style-type: none"> • Long term intake from all sources 	<ul style="list-style-type: none"> • Food, fortified food, and/or supplements • Chronic intakes
Adverse Effect/Hazard: Considerations and Selections <ul style="list-style-type: none"> • Teratogenicity 	<p>√ Selected for UL for:</p> <p>Women of childbearing age Severe and irreversible toxicity occurs at intakes >3000 µg RE/d. Toxicity unrelated to pre-existing liver stores or nutritional status of mother. Critical period is during first 2 months of pregnancy and may occur with a single or limited number of dosages.</p>	<p>Discussed in section on establishment of a guidance level:</p> <p>Women who are pregnant or wish to become pregnant Epidemiological studies have indicated that exposure to high levels of vitamin A during pregnancy might increase the risk of birth defects. Vitamin A has also been shown to be teratogenic in animals. The available data do not allow identification of a threshold dose, although one epidemiological study has suggested that effects may occur at modest intakes (>3000 µg RE/d from supplements). Other studies indicate that the threshold may be higher. However, given the severity of the effect, it is prudent to take 3000 µg RE/d as the threshold for teratogenicity.</p>	<p>√ Selected for UL for:</p> <p>Women of Reproductive Age (14 – 50 yr, pregnant, lactating) A causal relationship between high vitamin A intakes and birth defects is based on unequivocal demonstration of human teratogenicity of 13-<i>cis</i>-retinoic acid and results from numerous animal and epidemiological studies. The critical period for susceptibility is the first trimester of pregnancy. The threshold at which risk occurs remains a matter of debate. Selected as the critical adverse effect based on considerations of causality, quality and completeness of the database.</p>

¹ European Commission, Scientific Committee on Food. *Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Preformed Vitamin A (retinol and retinyl esters)*. October 2002.

² United Kingdom, Food Standards Agency, Expert Group on Vitamins and Minerals. *Risk Assessment: Vitamin A (Retinol)* in “Safe Upper Levels for Vitamins and Minerals”. May 2003.

³ Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*. National Academy Press, Washington, DC. 2001.

⁴ EFSA and IOM refer to ULs as “Tolerable Upper Limits (ULs)”. These represent the maximum level of total chronic daily intake of a nutrient judged to be unlikely to pose a risk of adverse health effects to humans. EVM refers to ULs as Safe Upper Levels (SULs).

Approach	EU-SCF (2002) ¹	UK-EVM (2003) ²	US-IOM (2001) ³
<p>Adverse Effect/Hazard: Considerations and Selections</p> <ul style="list-style-type: none"> Hepatotoxicity; liver abnormalities 	<p>√Selected for:</p> <p>Men and Children Causally linked to high intakes of vitamin A over long time periods. One of most severe outcomes of chronic intake of high doses. Toxicity not always reversible after withdrawal of vitamin A.</p>	<p>(Some discussion but not selected)</p>	<p>√Selected for:</p> <p>Adults ≥ 19 yr (excluding women of childbearing age) There is a strong causal association shown by human and animal data between excess vitamin A intake and liver abnormalities. Abnormal liver pathology characteristic of vitamin A intoxication (or grossly elevated hepatic vitamin A levels) was used rather than liver enzymes because of uncertainties regarding other possible causes of enzyme changes.</p>
<p>Adverse Effect/Hazard: Considerations and Selections</p> <ul style="list-style-type: none"> Bone metabolism; reduced bone mineral density; bone toxicity 	<p>√Special note for:</p> <p>Postmenopausal women Several major epidemiology studies indicate an increased risk of bone fracture over an intake range similar to that normally consumed from food and supplements. This occurs at lower doses than other adverse effects. Available data do not establish causality and were therefore not appropriate for establishing a tolerable upper level. Not clear if the same dose response would apply to men.</p>	<p>√ Discussed in section on guidance level:</p> <p>Risk of bone fracture Recent epidemiological studies have indicated that post-menopausal women with long-term high intakes of vitamin A have an increased risk of hip-bone fracture. Other supporting epidemiological data have indicated that this effect may occur in men as well as women. These findings are supported by animal data, which have indicated that retinol has a direct effect on bone. Damage to the bone may be permanent.</p> <p>The risk of hip fracture is a continuous graded response associated with exposure levels that include average dietary intakes. It is not possible to identify an intake that is without some degree of risk. However, the available data indicate that total intakes greater than 1500 µg RE/day may be inappropriate.</p>	<p>Chronic, excessive vitamin A intake has been shown to lead to bone mineral loss in animals. The findings from four epidemiological studies are provocative but conflicting, and therefore are not useful for setting a UL for vitamin A.</p>

Approach	EU-SCF (2002) ¹	UK-EVM (2003) ²	US-IOM (2001) ³
<p>Adverse Effect/Hazard: Considerations and Selections</p> <ul style="list-style-type: none"> Hypervitaminosis A (e.g., bulging fontanel; intracranial pressure) 	<p>Rapidly reversible bulging fontanel that is not associated with adverse growth or developmental sequelae has been observed in infants receiving high doses of vitamin A. In older children and adults, excessive vitamin A intakes are linked to increased intra-cranial pressures.</p>	<p>Acute toxicity (e.g., bulging of fontanels in neonates and infants) is associated with doses well in excess of 100,000 µg RE. Infants <6 months develop acute symptoms following a single dose of 7500 – 15000 µg RE whereas a dose of 30,000 µg RE is well-tolerated in older infants (6 and 9 months). Acute toxicity in humans is rare. Most manifestations of chronic vitamin A toxicity are reversible on cessation of dose.</p>	<p>√ Selected for: <i>Boys 14-18y, Children 9-13y, Children 4-8y, Children 1-3y, Infants 0-12m</i> Intracranial (bulging fontanel) and skeletal abnormalities can result in infants given vitamin A doses of 5500 to 6750 µg/day.</p>
<p>Adverse Effect/Hazard: Considerations and Selections</p> <ul style="list-style-type: none"> Lipid metabolism 	<p>Patients ingesting 7500 µg RE/d for 4 years had small increases in cholesterol concentration (2-3%); not observed in patients on 4500 µg RE/d for 12 years.</p>		
<p>NOAEL (no observed adverse effect level)</p>			<p><i>Women of Reproductive Age (14-50 yr, pregnant, lactating) :</i> <i>4,500 µg/day</i> No adverse effects below 3000 µg/day from <i>supplemental</i> vitamin A. Significantly increased risk above 4500 µg/day from <i>food plus supplements</i>. Most data involve doses ≥ 7800 µg/day. 4500 µg/d represents a conservative value in light of evidence of no adverse effects at or below that level.</p>

Continues

Approach	EU-SCF (2002) ¹	UK-EVM (2003) ²	US-IOM (2001) ³
LOAEL (lowest observed adverse effect level)	<p>Bulging fontanel <u>7500 µg RE</u> (as a single dose in infants)</p> <p>Hepatotoxicity <u>7500 µg RE/day</u> for 6 yr</p> <p>Bone density/fracture <u>1500 µg RE/day</u> (no threshold)</p> <p>Lipid metabolism <u>7500 µg RE/day</u> for 4 yr (minor change only)</p> <p>Teratogenicity <u>>3000 µg RE/day</u> (based on Rothman et al., 1995)</p>		<p>Adults ≥ 19 y (excluding women of childbearing age): <u>14,000 µg/day</u></p> <p>Hepatotoxicity was reported at doses of 14,000 µg/day. Reports of hepatotoxicity at doses less than 14,000 µg/day were also found, but these studies failed to provide information on other predisposing or confounding factors such as alcohol intake, drugs and medications used, and history of viral hepatitis infection.</p> <p>Infants 0-12m: <u>6,000 µg/day</u> 6,460 µg/day (rounded to 6,000) identified by averaging the lowest doses of 4 case reports of hypervitaminosis A.</p>
Uncertainty Factors (UF)	<p>Not considered necessary because:</p> <ul style="list-style-type: none"> the true threshold intake for teratogenicity is likely at or higher than the LOAEL of 3000 µg RE/d. the LOAEL of 7500 µg RE/d for hepatotoxicity is 2.5-fold higher than the LOAEL of 3000 µg RE/d for teratogenicity. <p>Therefore, a level of >3000 µg RE/d covers both the risk of hepatotoxicity and teratogenesis and also applies to pregnancy and lactation.</p>		<p>Women of reproductive age (14-50 y, pregnant, lactating) :</p> <p>Interindividual variability in susceptibility (higher factor not justified because substantial data showing no adverse effects at doses ≥ 3000). UF = <u>1.5</u></p> <p>Adults ≥ 19 y (excluding women of childbearing age):</p> <p>Severe, irreversible nature of adverse effect + Extrapolation from LOAEL to NOAEL + Interindividual variation in sensitivity. UF = <u>5.0</u>*</p> <p>Infants 0-12m:</p> <p>Uncertainty of extrapolating LOAEL to NOAEL for non-severe and reversible effect (bulging fontanel) + Interindividual variability in sensitivity. UF = <u>10</u>*</p> <hr/> <p>*Note: UF value presented only as conglomerate; values assigned to specific factors not specified.</p>

<p>Upper Limits (ULs) or Guidance Levels</p>	<p>ULs:</p> <p><i>Adults (women of child-bearing age and men)</i> → <u>3000</u> ug RE/day</p> <p><i>15-17y*</i> → <u>2600</u> ug RE/day</p> <p><i>11-14y*</i> → <u>2000</u> ug RE/day</p> <p><i>7 - 10y*</i> → <u>1500</u> ug RE/day</p> <p><i>4 - 6y*</i> → <u>1100</u> ug RE/day</p> <p><i>1 - 3y*</i> → <u>800</u> ug RE/day</p> <p>Advice for Postmenopausal Women -- Upper level does not apply to postmenopausal women who represent group at greatest risk of bone fracture as it may not provide an adequate margin of safety in relation to the possible decrease in bone density and risk of bone fracture. Because of the relatively high risk for osteoporosis and fracture in postmenopausal women, it is recommended that these women should restrict their intakes to 1500 µg RE/d.</p> <hr/> <p>*The UL for children is based on the value of 3000 µg RE/day for adults, with correction for differences in basal metabolic rate compared to adults using scaling according to body surface area (body weight^{0.75}).</p>	<p>Guidance Levels: Evidence base inadequate to establish a UL.</p> <p>Teratogenicity: <u>3000</u> µg RE/day. Women who are pregnant or wish to become pregnant should not take dietary supplements containing vitamin A except on medical advice.</p> <p>Risk of bone fracture: Total intakes greater than <u>1500</u> µg RE/day may be inappropriate.</p>	<p>ULs:</p> <p><i>Women 19-50y, Pregnant 19-50y, Lactating 19-50y</i> → <u>3000</u> µg/day = 4500/1.5</p> <p><i>Girls 14-18y, Pregnant 14-18y, Lactating 14-18y</i> → <u>2800</u> µg/day *</p> <p><i>Adults ≥ 19 yr (excluding women of childbearing age)</i> → <u>3000</u> ug/day = 14000/5.0</p> <p><i>Boys 14-18y</i> → <u>2800</u> µg/day**</p> <p><i>Children 9-13y</i> → <u>1700</u> µg/day**</p> <p><i>Children 4-8y</i> → <u>900</u> µg/day**</p> <p><i>Children 1-3y</i> → <u>600</u> µg/day**</p> <p><i>Infants 0-12m</i> → <u>600</u> µg/day = 6000/10</p> <hr/> <p>In absence of NOAEL/LOAEL, the UL values for children are adjusted from those established for adults on the basis of relative body weight with use of reference weights</p> <p>*body wt adjustment of 3000 ug/day from women/pregnant/lactating 19-50y **body wt adjustment of 3000 ug/day from men 19+y/women 51+y</p>
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ANNEX 3
GLOSSARY OF TERMS
Alphabetical List of Selected Generic Terms
in Hazard and Risk Assessment and their Definitions¹

Term	Description
Acceptable Daily Intake	Estimated maximum amount of an agent, expressed on a body mass basis, to which an individual in a (sub) population may be exposed daily over its lifetime without appreciable health risk. Related terms: <i>Reference Dose, Tolerable Daily Intake</i>
Acceptable Risk	This is a risk management term. The acceptability of the risk depends on scientific data, social, economic, and political factors, and on the perceived benefits arising from exposure to an agent.
Adverse Effect	Change in the morphology, physiology, growth, development, reproduction or life span of an organism, system, or (sub) population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences.
Analysis	Detailed examination of anything complex, made in order to understand its nature or to determine its essential features.
Assessment	Evaluation or appraisal of an analysis of facts and the inference of possible consequences concerning a particular object or process.
Assessment Endpoint	Qualitative/Quantitative expression of a specific factor with which a risk may be associated as determined through an appropriate risk assessment.
Assessment Factor	Numerical adjustment used to extrapolate from experimentally determined (dose response) relationships to estimate the agent exposure below which an adverse effect is not likely to occur. Related terms: <i>Safety Factor, Uncertainty Factor</i> .
Concentration	Amount of a material or agent dissolved or contained in unit quantity in a given medium or system.
Concentration-Effect Relationship	Relationship between the exposure, expressed in concentration, of a given organism, system or (sub) population to an agent in a specific pattern during a given time and the magnitude of a continuously-graded effect to that organism, system or (sub) population. Related terms: <i>Effect Assessment, Dose-Response Relationship</i>

¹ IPCS (International Programme on Chemical Safety). *Descriptions of Selected Key Generic Terms Used In Chemical Hazard/Risk Assessment: Joint Project with OECD on the Harmonisation of Hazard/Risk Assessment Terminology*. Access online: http://www.who.int/ipcs/publications/methods/harmonization/definitions_terms/en/

Dose	Total amount of an agent administered to, taken up or absorbed by an organism, system or (sub) population.
Dose-Effect Relationship	Relationship between the total amount of an agent administered to, taken up or absorbed by an organism, system or (sub) population and the magnitude of a continuously-graded effect to that organism, system or (sub)population. Related terms: <i>Effect Assessment, Dose-Response Relationship, Concentration-Effect Relationship.</i>
Dose-Related Effect	Any effect to an organism, system or (sub) population as a result of the quantity of an agent administered to, taken up or absorbed by that organism, system or (sub)population.
Dose Response	Relationship between the amount of an agent administered to, taken up or absorbed by an organism, system or (sub) population and the change developed in that organism, system or (sub) population in reaction to the agent. Synonymous with Dose-response relationship. Related Term: <i>Dose-Effect Relationship, Effect Assessment, Concentration-Effect Relationship.</i>
Dose-Response Assessment	Analysis of the relationship between the total amount of an agent administered to, taken up or absorbed by an organism, system or (sub)population and the changes developed in that organism, system or (sub)population in reaction to that agent, and inferences derived from such an analysis with respect to the entire population. Dose-Response Assessment is the second of four steps in risk assessment. Related terms: <i>Hazard Characterisation, Dose-Effect Relationship, Effect Assessment, Dose-Response Relationship, Concentration-Effect Relationship.</i>
Dose-Response Curve	Graphical presentation of a dose-response relationship.
Dose-Response Relationship	Relationship between the amount of an agent administered to, taken up or absorbed by an organism, system or (sub) population and the change developed in that organism, system or (sub) population in reaction to the agent. Related Term: <i>Dose-Effect Relationship, Effect Assessment, Concentration-Effect Relationship.</i>
Effect	Change in the state or dynamics of an organism, system or (sub) population caused by the exposure to an agent.

Effect Assessment	Combination of analysis and inference of possible consequences of the exposure to a particular agent based on knowledge of the dose-effect relationship associated with that agent in a specific target organism, system or (sub) population.
Expert Judgement	Opinion of an authoritative person on a particular subject.
Exposure	Concentration or amount of a particular agent that reaches a target organism, system or (sub) population in a specific frequency for a defined duration.
Exposure Assessment	Evaluation of the exposure of an organism, system or (sub) population to an agent (and its derivatives). Exposure Assessment is the third step in the process of Risk Assessment.
Exposure Scenario	A set of conditions or assumptions about sources, exposure pathways, amount or concentrations of agent(s) involved, and exposed organism, system or (sub) population (i.e. numbers, characteristics, habits) used to aid in the evaluation and quantification of exposure(s) in a given situation.
Fate	Pattern of distribution of an agent, its derivatives or metabolites in an organism, system, compartment or (sub) population of concern as a result of transport, partitioning, transformation or degradation.
Guidance Value	Value, such as concentration in air or water, which is derived after allocation of the reference dose among the different possible media (routes) of exposure. The aim of the guidance value is to provide quantitative information from risk assessment to the risk managers to enable them to make decisions. (See also: reference dose)
Hazard	Inherent property of an agent or situation having the potential to cause adverse effects when an organism, system or (sub) population is exposed to that agent.
Hazard Assessment	A process designed to determine the possible adverse effects of an agent or situation to which an organism, system or (sub) population could be exposed. The process includes hazard identification and hazard characterization. The process focuses on the hazard in contrast to risk assessment where exposure assessment is a distinct additional step.

Hazard Characterization	<p>The qualitative and, wherever possible, quantitative description of the inherent properties of an agent or situation having the potential to cause adverse effects. This should, where possible, include a dose–response assessment and its attendant uncertainties.</p> <p>Hazard Characterisation is the second stage in the process of Hazard Assessment, and the second step in Risk Assessment.</p> <p>Related terms: <i>Dose-Effect Relationship, Effect Assessment, Dose–Response Relationship, Concentration -Effect Relationship.</i></p>
Hazard Identification	<p>The identification of the type and nature of adverse effects that an agent has as inherent capacity to cause in an organism, system or (sub) population.</p> <p>Hazard identification is the first stage in hazard assessment and the first step in the process of Risk Assessment</p>
Margin of Exposure	<p>Ratio of the no-observed-adverse-effect level (NOAEL) for the critical effect to the theoretical, predicted or estimated exposure dose or concentration.</p> <p>Related term: <i>Margin of Safety</i></p>
Margin of Safety	<p>For some experts the Margin of Safety has the same meaning as the Margin of Exposure, while for others, the Margin of Safety means the margin between the reference dose and the actual exposure dose or concentration.</p> <p>Related term: <i>Margin of Exposure</i></p>
Measurement Endpoint	<p>Measurable (ecological) characteristic that is related to the valued characteristic chosen as an assessment point.</p>
Reference Dose	<p>An estimate of the daily exposure dose that is likely to be without deleterious effect even if continued exposure occurs over a lifetime.</p> <p>Related term: <i>Acceptable Daily Intake.</i></p>
Response	<p>Change developed in the state or dynamics of an organism, system or (sub) population in reaction to exposure to an agent.</p>
Risk	<p>The probability of an adverse effect in an organism, system or (sub) population caused under specified circumstances by exposure to an agent.</p>
Risk Analysis	<p>A process for controlling situations where an organism, system or (sub) population could be exposed to a hazard.</p> <p>The Risk Analysis process consists of three components: risk assessment, risk management and risk communication.</p>

Risk Assessment	<p>A process intended to calculate or estimate the risk to a given target organism, system or (sub)population , including the identification of attendant uncertainties, following exposure to a particular agent, taking into account the inherent characteristics of the agent of concern as well as the characteristics of the specific target system.</p> <p>The Risk Assessment process includes four steps: hazard identification, hazard characterisation (related term: dose–response assessment), exposure assessment, and risk characterization. It is the first component in a risk analysis process.</p>
Risk Characterization	<p>The qualitative and, wherever possible, quantitative determination, including attendant uncertainties, of the probability of occurrence of known and potential adverse effects of an agent in a given organism, system or (sub)population, under defined exposure conditions.</p> <p>Risk Characterisation is the fourth step in the Risk Assessment process.</p>
Risk Communication	<p>Interactive exchange of information about (health or environmental) risks among risk assessors, managers, news media, interested groups and the general public.</p>
Risk Estimation	<p>Quantification of the probability, including attendant uncertainties, that specific adverse effects will occur in an organism, system or (sub)population due to actual or predicted exposure.</p>
Risk Evaluation	<p>Establishment of a qualitative or quantitative relationship between risks and benefits of exposure to an agent, involving the complex process of determining the significance of the identified hazards and estimated risks to the system concerned or affected by the exposure, as well as the significance of the benefits brought about by the agent.</p> <p>It is an element of risk management. Risk Evaluation is synonymous with Risk-Benefit evaluation</p>
Risk Management	<p>Decision-making process involving considerations of political, social, economic, and technical factors with relevant risk assessment information relating to a hazard so as to develop, analyse, and compare regulatory and non-regulatory options and to select and implement appropriate regulatory response to that hazard.</p> <p>Risk management comprises three elements: risk evaluation; emission and exposure control; risk monitoring.</p>
Risk Monitoring	<p>Process of following up the decisions and actions within risk management in order to ascertain that risk containment or reduction with respect to a particular hazard is assured.</p> <p>Risk monitoring is an element of risk management.</p>

Safety	Practical certainty that adverse effects will not result from exposure to an agent under defined circumstances. It is the reciprocal of risk.
Safety Factor	Composite (reductive) factor by which an observed or estimated no-observed-adverse effect level (NOAEL) is divided to arrive at a criterion or standard that is considered safe or without appreciable risk. Related terms: <i>Assessment Factor, Uncertainty Factor.</i>
Threshold	Dose or exposure concentration of an agent below that a stated effect is not observed or expected to occur.
Tolerable daily Intake	Analogous to Acceptable Daily Intake. The term Tolerable is used for agents which are not deliberately added such as contaminants in food.
Tolerable Intake	Estimated maximum amount of an agent, expressed on a body mass basis, to which each individual in a (sub) population may be exposed over a specified period without appreciable risk.
Toxicity	Inherent property of an agent to cause an adverse biological effect.
Uncertainty	Imperfect knowledge concerning the present or future state of an organism, system or (sub) population under consideration.
Uncertainty Factor	Reductive factor by which an observed or estimated no-observed-adverse effect level (NOAEL) is divided to arrive at a criterion or standard that is considered safe or without appreciable risk. Related terms: <i>Assessment Factor, Safety Factor.</i>
Validation	Process by which the reliability and relevance of a particular approach, method, process or assessment is established for a defined purpose. Different parties define "Reliability" as establishing the reproducibility of the outcome of the approach, method, process or assessment over time. "Relevance" is defined as establishing the meaningfulness and usefulness of the approach, method, process or assessment for the defined purpose.

**Glossary: Risk Analysis Terms Related to Food Safety
for the Purposes of the Codex Alimentarius²**

Hazard: A biological, chemical or physical agent in, or condition of, food with the potential to cause an adverse health effect.

Hazard Identification: The identification of biological, chemical, and physical agents capable of causing adverse health effects and which may be present in a particular food or group of foods.

Hazard Characterization: The qualitative and/or quantitative evaluation of the nature of the adverse health effects associated with biological, chemical and physical agents which may be present in food. For chemical agents, a dose–response assessment should be performed. For biological or physical agents, a dose–response assessment should be performed if the data are obtainable.

Dose–Response Assessment: The determination of the relationship between the magnitude of exposure (dose) to a chemical, biological or physical agent and the severity and/or frequency of associated adverse health effects (response).

Exposure Assessment: The qualitative and/or quantitative evaluation of the likely intake of biological, chemical, and physical agents via food as well as exposures from other sources if relevant.

Risk: A function of the probability of an adverse health effect and the severity of that effect, consequential to a hazard(s) in food.

Risk Analysis: A process consisting of three components: risk assessment, risk management and risk communication.

² Codex Alimentarius Commission. Joint FAO/WHO Food Standards Programme: Procedural Manual. Thirteenth edition. Rome: Food and Agriculture Organization of the United Nations and World Health Organization, 2004.

Risk Assessment: A scientifically based process consisting of the following steps: (i) hazard identification, (ii) hazard characterization, (iii) exposure assessment, and (iv) risk characterization.

Risk Assessment Policy: Documented guidelines on the choice of options and associated judgements for their application at appropriate decision points in the risk assessment such that the scientific integrity of the process is maintained.

Risk Characterization: The qualitative and/or quantitative estimation, including attendant uncertainties, of the probability of occurrence and severity of known or potential adverse health effects in a given population based on hazard identification, hazard characterization and exposure assessment.

Risk Communication: The interactive exchange of information and opinions throughout the risk analysis process concerning risks, risk-related factors and risk perceptions, among risk assessors, risk managers, consumers, industry, the academic community and other interested parties, including the explanation of risk assessment findings and the basis of risk management decisions.

Risk Estimate: The quantitative estimation of risk resulting from risk characterization.

Risk Management: The process, distinct from risk assessment, of weighing policy alternatives, in consultation with all interested parties, considering risk assessment and other factors relevant for the health protection of consumers and for the promotion of fair trade practices, and, if needed, selecting appropriate prevention and control options.

Risk Profile: The description of the food safety problem and its context.

ANNEX 4

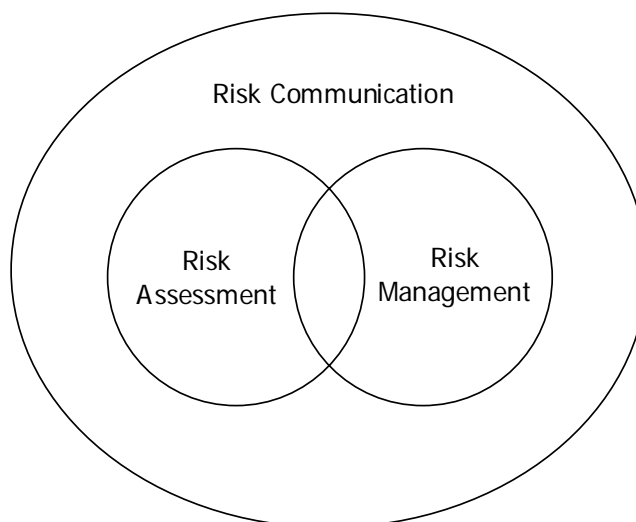
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NUTRIENT RISK ASSESSMENT: BACKGROUND**4 1 General process of risk assessment**

The process of risk assessment is a component of the larger process of risk analysis. The overall process is applicable whether the interest is a nutrient or a non-nutrient. The schematic in Figure 1 is commonly used to illustrate the relationships among the risk analysis components.

10

Figure 1: Components of risk analysis



12

Regarding food safety and non-nutrients, a number of organizations have considered models for risk analysis and, in turn, risk assessment. FAO and WHO in particular have played a role in the development of international food safety risk analysis. A conference sponsored by FAO/WHO recommended in 1991 that the Codex Alimentarius Commission incorporate risk assessment principles into its decision-making process, and Codex adopted such principles in 1991 and 1993. Currently, the Procedural Manual of the Codex Alimentarius Commission includes *Working Principles for Risk Analysis for*

20 *Application in the Framework of the Codex Alimentarius*(1). Much can be gleaned from
these efforts, and they provide an important foundation for nutrient risk assessment
22 considerations.

24 Risk assessment addresses the relationships between exposure to a substance and the
likelihood that an adverse effect will occur in the exposed population. In essence, risk
26 assessment is a scientific undertaking to characterize the nature and likelihood of harm
resulting from human exposure to "agents in the environment." The process of classic
28 risk assessment involves objective data review followed by scientific judgments and
decisions made during a four-step process. Uncertainties and variability in the data
30 available are identified and discussed as part of the risk assessment. The uncertainties
may be due to questions about the available data, questions about the appropriateness of
32 inferences made in the absence of sufficient data, or other factors. Adjustment factors
may be used to correct for the uncertainties.

34

Although problem formulation precedes the conduct of risk assessment, some view the
36 formulation as the first step of risk assessment. However, the four classically recognized
steps or 'boxes' of a risk assessment are:

38

- | |
|--|
| (1) hazard identification |
| (2) hazard
characterization |
| (3) exposure assessment |
| (4) risk characterization |

40

42 A key quantitative outcome resulting from the hazard characterization step is the
specification of a level of intake—usually referred to as an *upper level* (UL)—at which,
44 or below, no harm is likely to occur. Alternatively, the UL is the intake level above
which there is the potential for harm. Since nutrients and related substances may also

46 'cause risk' if their intake levels are too low, a possible addition to the definition would
be the assumption that the intake needs for nutrient or substance are adequately met.
48 Notably, the UL is neither a recommended intake nor a level for fortification or
supplementation. A UL is not a regulatory limit. Rather, a UL is a piece of information
50 to assist in decision-making.

52 Depending upon the data available, the UL may be specified for different life-stage and
age/sex groupings. Also, depending upon the data available, the UL may reflect intake
54 from all sources or intake from selected sources only. Ideally, nutrient risk assessment is
based on intake from all sources of the form or forms of the nutrient that is of concern.
56 ULs are starting points in that they represent scientific information that the risk manager
can use, among other considerations, in the development of policies and standards. In
58 most cases, the uncertainty around the UL is specified. Some distinguish between a UL
and a guidance level, with the guidance level established in those cases when the data are
60 too limited to establish a UL. In short, more uncertainty is associated with a guidance
level than with a UL.

62

Strictly speaking, the risk assessor does not place the UL within the context of being
64 tolerable or safe in terms of its application to food standards or related activities. This is
a definitional task that falls within the domain of the risk manager. In practice, however,
66 risk assessors have used a variety of terms (not all synonymous) including *tolerable*
upper levels, *tolerable daily intake*, *safe upper levels*, and *upper range of safe intake*.

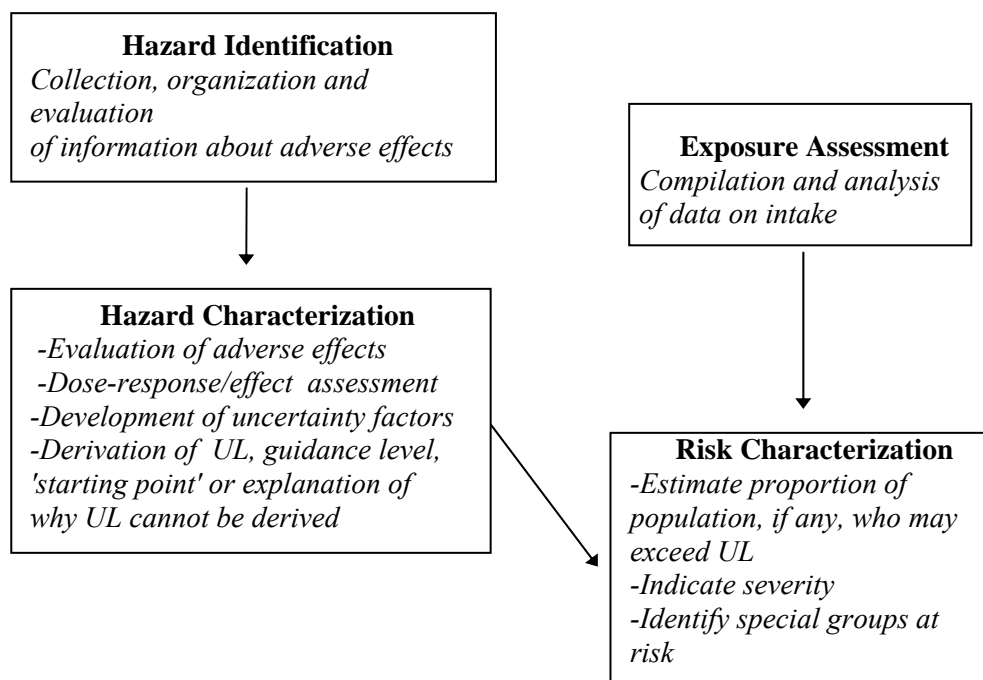
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Many risk assessors who deal with non-nutrients are familiar with the term Acceptable
70 Daily Intake (ADI), which is defined as the estimated maximum amount of an agent,
expressed on a body mass basis, to which an individual in a (sub) population may be
72 exposed daily over its lifetime without appreciable health risk. This term has not been
extensively used in nutrient risk assessment. Likewise the term Tolerable Intake
74 (estimated maximum amount of an agent, expressed on a body mass basis, to which each
individual in a (sub) population may be exposed over a specified period without
76 appreciable risk) is not associated with nutrient risk assessment.

78 At its most basic, risk assessment proceeds as shown in Figure 2 (below).

80

Figure 2. Steps in risk assessment



82 In particular, hazard identification is followed by hazard characterization, and the result
 produces a UL. An exposure assessment is conducted to compile and analyze
 84 information about the exposure within the population of interest. The information
 obtained from the exposure assessment is combined with the UL and other hazard
 86 characterization information to produce a risk characterization. Risk characterization
 identifies the proportion of the population likely to exceed the UL and highlights
 88 important considerations, including the severity and nature of the adverse effect, a
 description of uncertainties, and the identification of any special groups at risk.

90

2 The nutrition context for risk assessment

2.1 General

92 While the development of a nutrient risk assessment approach can make considerable use
 94 of models for non-nutrients as a starting point, these models are not fully applicable

because nutrients and related substances are unlike non-nutrients in that they provide health benefits. Thus, nutrient risk assessment requires special attention to uncertainty factors. For the risk assessment of non-nutrients, standard safety factors have been developed to ensure toxicological safety in the face of data uncertainties (2). Using those safety factors in nutrient risk assessment could result in UL values that are the same or less than the levels required for nutrient adequacy, a nonsensical outcome. In evaluations concerning several substances purported to have nutritional benefit, the FAO/WHO Joint Expert Committee on Food Additive (JECFA) applied the approach used for food additive safety assessment. The approach used the no-observed-adverse-effect level (NOAEL) or lowest-observed-adverse effect level (LOAEL) from human or animal studies with a safety or uncertainty factor to arrive at an ADI. The standard default safety factor is 100. JECFA determined that, in the case of nutrients and other substances necessary for health and well-being, the use of a lower safety factor may be appropriate to make sure that the upper level of nutrient intake is high enough to satisfy nutritional needs and to maintain health.

110

The application of risk assessment to nutrients and related substances is complicated by the fact that ‘harm’ relative to nutrient intake has two aspects: harm resulting from excessive intakes and harm resulting from intakes that are too low. Between these two points is the ‘acceptable range of intake.’ The two-tailed aspect of the potential for harm associated with nutrients and related substances is illustrated in Figure 3. The WHO International Programme on Chemical Safety has developed an approach for the assessment of risk from essential trace elements that uses an acceptable-range-of-oral intake (AROI)(3).

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124

Figure 3. Two-tailed 'risk' for nutrients: Inadequacy and toxicity¹⁰

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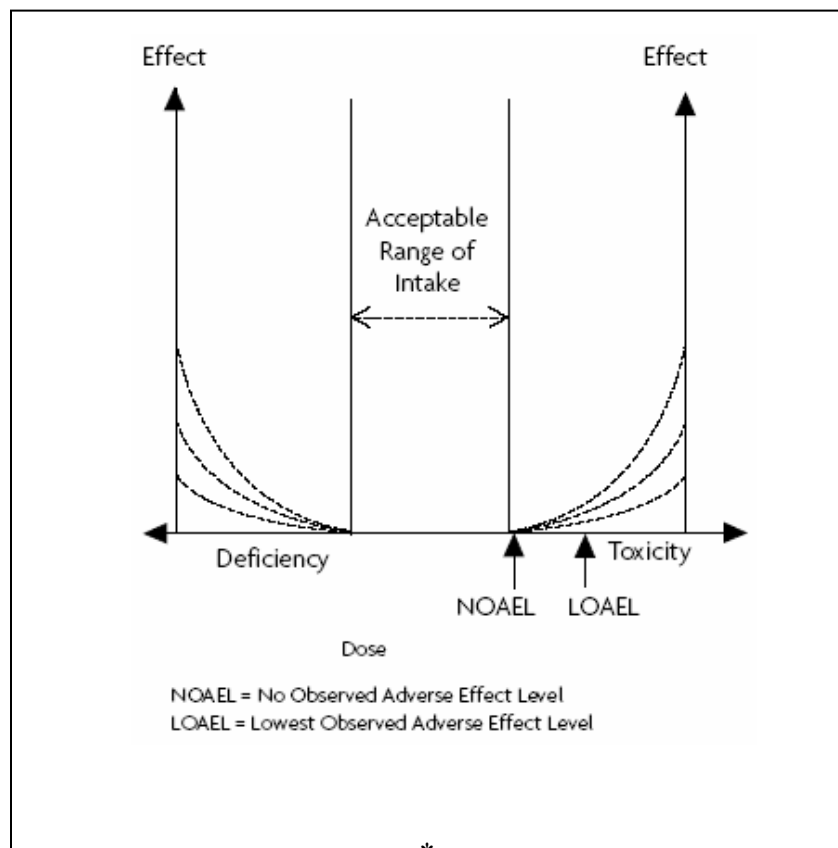
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* Note: Current practice usually involves setting a level of adequacy (recommended intake level) that takes into account the promotion of health as well as deficiency prevention.

144

While a graphic representation such as that found in Figure 3 above is helpful in making the point about the two-tailed potential for harm, the relationships themselves may not be symmetrical. The dotted lines in the figure are meant to indicate that the shape of the curves may differ.

The acceptable range of intake is not specifically defined except as a range of intake believed to be 'safe.' The definition of 'nutrient adequacy', which is included in the lower end of the acceptable range of intake (as shown with an asterisk in the figure), is not universally agreed upon,¹¹ but the current practice is to refer to it as a level of intake that

¹⁰ Modified from ref (5), page 21

¹¹ Some nations or regions define adequacy based on levels to prevent deficiency.

154 maintains life and/or promotes health.¹² However, in what ways these considerations
156 affect nutrient risk assessment is unclear.

2.2 Overview of the four steps

158 To illustrate the four steps of nutrient risk assessment, it can be useful to refer to the
160 discussions provided in reports from workgroups concerning models already in use at
162 national or regional levels. Sources of relatively comprehensive reports of quantitative
164 models were identified, and three of them reflect the deliberations and conclusions of an
166 expert body convened at the request of a government authority or related body. The
168 initial focus has been placed on models from governments or related bodies since the
170 models are most likely to be designed for use within a regulatory setting and appear to
172 have targeted their outcomes to a general (sometimes referred to as 'healthy') population.
174 Additional descriptions of risk assessment approaches are available in the public domain
176 and may be considered by workshop participants.

168 The following national/regional models serve as a starting point for the workshop: EU-
170 SCF/EFSA: European Union, Scientific Committee on Food (Note: Activities formerly
172 the responsibility of SCF now rest with the European Food Safety Authority) (4); UK-
174 EVM: Expert Group on Vitamins and Minerals, United Kingdom, Food Standards
176 Agency (5); and US-IOM: Institute of Medicine, United States of America, National
178 Academies of Science (also relevant to Canada) (6). It should be noted that while
180 providing much information about nutrient risk assessment, they were not designed to
182 make specific provisions for populations that may be inadequately nourished as might be
184 encountered in the use of an international model.

2.2.1 Hazard identification

180 This step involves the collection, organization, and evaluation of all information
182 pertaining to the adverse effects associated with a given nutrient or related substance. It
184 provides an overview of the ability of the nutrient or related substance to cause one or

¹² Also referred to as 'optimal health'

184 more types of 'toxicity' in humans. Usually the process includes the selection of the most
critical or sensitive endpoint (or adverse effect) upon which to base the assessment.

186 The three workgroup reports used essentially the same databases for their risk
assessments. The timing of the reports varied enough, however, that some more recent
188 studies of adverse effects of nutrients could be used only by later panels. The three
panels sometimes identified different hazards and/or weighted them differently. This
190 includes cases that appear not to be due to differences in the timing of the nutrient risk
assessment. The differences—beyond those attributable to information from newer data
192—likely reflect the necessary reliance on scientific judgement. This, of course, occurs
because of the substantial inadequacies in and uncertainties arising from the published
194 studies that address the adverse effects and related information for nutrients and related
substances.

196
One workgroup (UK-EVM) noted that the overall quality of the database for evaluating
198 nutrient safety generally was poor as compared to databases available for non-nutrients
such as food additives. Their report commented that both human and animals studies
200 usually were not designed for evaluating adverse effects or toxicities. Instead, they were
designed to evaluate beneficial or metabolic effects of nutrients and related substances.
202 Since information on potential hazards was not developed systematically and objectively,
it tended to be incomplete and difficult to interpret. Data on vulnerable groups (e.g.
204 young children, elderly) were particularly scarce. Most animal studies were of an
investigative nature and intended to evaluate a very specific question. As such, they did
206 not result in the comprehensive set of toxicology studies normally done to support
regulatory requirements.

208
For reasons such as these, the evaluation of the data available for nutrient risk assessment
210 can be quite challenging. Moreover, while national and regional authorities have
addressed nutrient risk assessment on a more or less 'as-needed' basis, a formal
212 systematic methodology for use across nutrients and across reports is lacking

internationally. The development of such a systematic review method for the purposes of
214 hazard identification, while challenging, would be useful.

216 *2.2.2 Hazard characterization*

Hazard characterization is the detailed evaluation of the nature of the adverse effects
218 associated with the nutrient or related substance. It rests largely on the assessment of a
dose–response, sometimes referred to as dose–effect assessment. In fact, some groups
220 refer to hazard characterization as 'dose–response assessment.' A dose–response
assessment is a process whereby scientific evidence (experimental/medical) is used to
222 specify the relationship or 'data curve' between increasing intake and increasing
likelihood of a response or adverse effect. Based on these evaluations, a UL is derived
224 taking into account uncertainties such as those related to the available and likely limited
data including those associated with variability between species and individuals.

226

The three workgroups laid out similar general approaches and criteria for evaluating and
228 weighing the overall scientific evidence and had access to many, but not all, of the same
studies. Nonetheless, taking into account adjustments in outcomes that may have resulted
230 from newer data available to certain panels, they sometimes came to different
conclusions as to the nature and adequacy of the database for selecting specific hazards as
232 critical endpoints and threshold levels (LOAEL or NOAEL). In short, there were
decision points at which the panels diverged. This resulted, in some cases, in differences
234 in conclusions emerging from their nutrient risk assessments.

236

2.2.3. Exposure Assessment

238 Exposure assessment or dietary intake assessment is the process of compiling and
analyzing data on the intake of the substance for the population of interest. Analyses
240 need to include estimates of the distributions of intakes so that the intakes of consumers
at the high end of the intake distribution curve can be evaluated in comparison to the UL.
242 Obtaining estimates of mean intake alone is not sufficient. Typically the analysis
includes the application of statistical adjustment factors and other intake assessment tools

244 that allow conclusions about the distribution of the amount of a substance being
consumed on a 'usual' basis—without inflating the estimates.

246

The many difficulties associated with collecting accurate and representative food intake
248 data reflect methodological challenges that in turn cause uncertainties. These include
inadequate composition tables by which to estimate the intakes of specific nutrients from
250 foods (particularly as related to changes in fortified foods in the market place), in the
need for data to estimate usual intakes, and inaccuracies in reporting the types and
252 amounts of foods consumed.

254 Additionally, there are only limited data on intakes from dietary supplements.

Compositional data for dietary supplements and some fortified foods usually are based on
256 declared label values, which may represent significant underestimates: manufacturers
typically add overages.¹³ Moreover, formulations can be changed easily to meet market
258 demand. The intake data on dietary supplement use usually differ from the intake data
available for foods. For example, they may cover different time periods or they are
260 obtained from different surveys. This complicates the estimation of total intakes. When
separate intake estimates are given for diets and supplements, it generally is inappropriate
262 to add the intakes. A consistent approach for arriving at total nutrient intake estimates
from foods and supplements has not been specifically identified.

264

¹³ Ref (5), page 341, Table 7. The table reports over-formulations for an array of nutrients ranging from 30-100%.

2.2.4 Risk Characterization

266 This final step pulls together all the previous steps of risk assessment in order to
characterize and describe the risk. Some refer to risk characterization as advice for
268 decision-making. The tasks focus on the integration of the hazard characterization and its
resulting UL with the intake/exposure assessments for the general population of interest
270 or vulnerable population subgroups (e.g. children). Therefore, in risk characterization,
the proportion of the population who may have intakes that exceed the UL is identified as
272 well as the degree to which their intakes exceed the UL. Usually there is a discussion of
the severity of the adverse effect and the likely reversibility of the potential harm if
274 intakes are reduced below the UL. Some risk characterizations may include indications
as to the overall public health significance of the possible harm to selected population
276 subgroups and the identification of other special groups 'at risk.' Any other scientific
information that could be taken into account in managing the problem is included in the
278 risk characterization. In short, the significance of the risk of excessive nutrient intake
carefully addresses all the topics described above.

280

Risk characterization is a step within risk assessment that illustrates readily the interface
282 between risk assessment and risk management. It could be described as a 'hand-off' from
the risk assessors to the risk managers. Along with the careful consideration of the
284 questions to be asked of risk assessors, the risk assessors must carefully consider what
constitutes a meaningful and useful set of scientific information to best inform risk
286 managers who must then proceed to make policy decisions.

288 **3 International considerations**

290 One of the goals of any international model or framework is to foster harmonization to
the extent possible. In the case of a model for nutrient risk assessment, an important
consideration is whether the outcomes of nutrient risk assessment can be harmonized.
292 That is, there is a need to identify the steps that could be considered globally and the
steps that may be less universal in scope. In this regard, the nature of the data to be used
294 during the execution of the specific steps provides a key. If the type of data inputted into
each step is used as a starting point, it is possible to divide the steps into two categories.

296

First, there are those steps that are based on the available scientific/medical literature and
298 intended to identify and interpret the biological, physiological and chemical evidence for
the relationship between intake and the potential for harm to humans. These data by their
300 nature are relevant across wide and diverse populations, i.e. they tend to reflect the
science pertaining to all humans. They have global relevance.

302

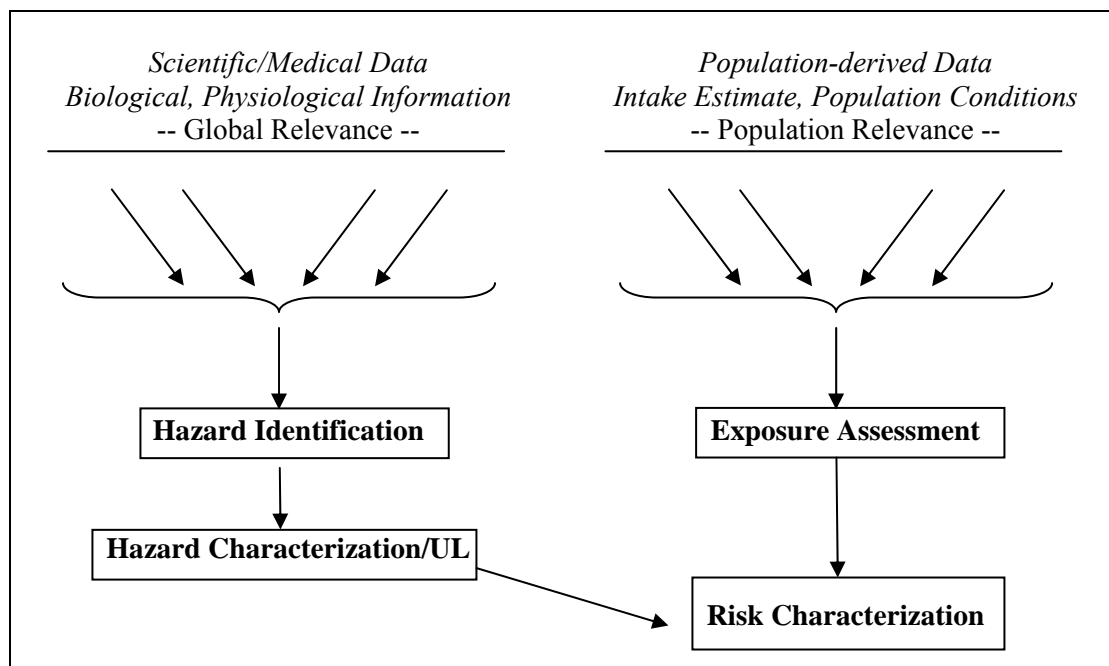
Second, there are those steps based on information about the population¹⁴ targeted for
304 risk assessment. This information would include data about dietary and supplement
consumption patterns and about the composition the food and supplements consumed,
306 which in turn underpin the exposure assessment step. The exposure assessment is
population relevant, i.e. is dependent on the types of foods and supplements consumed
308 and dietary patterns within a region or nation-state. Risk characterization includes
considerations of the globally relevant hazard characterization within the context of the
310 exposure assessment. This would cause risk characterization to be population relevant.

312 These differences are illustrated in Figure 4.

¹⁴ The term 'population' in discussions pertaining to nutrient risk assessment in the international context refers to nations/regions with a common food supply and dietary patterns and which would be expected to differ from other nations/regions in this respect. Elsewhere in this paper or in other documents the term 'subgroup' or 'population subgroup' may be used to refer to special or vulnerable groups such as children or women of childbearing age. The term (sub) population may refer to either a population or population subgroups.

314

Figure 4. Steps in risk assessment: Global versus population relevance



316

318 This consideration does not preclude an international nutrient risk assessment workshop
 addressing principles for all four steps of risk assessment. However, what it does suggest
 320 is that the use of the principles for hazard identification/characterization results in
 outcomes, notably the UL, that could be globally relevant. In the case of exposure
 322 assessment and risk characterization, the application of the principles produces outcomes
 that are population relevant. That is, risk characterizations—even when conducted in a
 324 consistent manner using internationally-applicable guiding principles—can inherently be
 different depending upon the target population.

326

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ANNEX 5

2

CHARACTERISTICS OF A GOOD RISK ASSESSMENT (FOOD SAFETY)¹⁵

4

A good risk assessment helps food safety regulators and other officials to make effective decisions about a food safety risk. It improves the quality of the decision-making process and informs the decision for which it was prepared. Although there is not one particular type of ‘best’ risk assessment, a good risk assessment has a number of essential characteristics:

10 • ***Clearly identifies the questions to be answered***

A good risk assessment ensures that both the questions asked and the responses identified are the most appropriate. Although the questions to be answered by the risk assessment come from the risk managers, risk assessors must spend time understanding, defining and, if necessary, clarifying and refining them together with risk managers. The questions to be answered should be documented and understood by all members of the risk analysis team.

12 • ***Is a collaborative and interdisciplinary team effort***

A good risk assessment involves a range of scientific and non-scientific experts working together in order to respond to the questions asked. The best teams are interdisciplinary ones where experts’ roles are complementary and their contributions together exceed the sum of their individual parts.

14 • ***Has adequate resources***

A good risk assessment has adequate resources (time, money, personnel and expertise) that reflect the importance of the food safety problem under consideration and that are sufficient to answer all the questions posed.

16 • ***Is based on scientific evidence and sound assumptions***

A good risk assessment is based on scientific evidence and clearly formulated, unbiased assumptions. Sound assumptions are important to help bridge data gaps. Risk assessors should try to clearly formulate implicit assumptions (i.e. ones that are

¹⁵ Reproduced with permission: FAO/WHO (Food and Agriculture Organization of the United Nations/World Health Organization). *Draft Version* (uncirculated): *Food Safety Risk Analysis: An Overview and Framework Manual*.

not expressed explicitly but reside inside thoughts or actions) as well as explicit ones (i.e. assumptions made knowingly). The assumptions used should be rigorously challenged and should clearly identify any weaknesses. Good assumptions are revised or discarded as necessary are based on the most likely outcomes rather than the worst-case scenarios.

6 • ***Uses the best available data***

8 A good risk assessment uses high-quality, accurate and reliable quantitative, qualitative and/or semi-quantitative data. Risk assessors need to be able to transform facts and evidence into useful information, which can be used to support, inform and guide decision-making. They should pay adequate attention to the collection, analysis and mining of data, and ensure the use of good conceptual and computer models. Risk assessors should also ensure that analysis is explicitly tied to existing evidence, clearly presented, and supported by references and bibliographic information.

14 • ***Explicitly acknowledges, identifies and addresses uncertainty***

16 A good risk assessment explicitly acknowledges, identifies, describes and addresses the magnitude, importance, types and sources of uncertainty. It seeks to eliminate uncertainty or reduce it to a minimum, and address any remaining uncertainty by the most appropriate means (e.g. expert knowledge, primary research, and qualitative and quantitative techniques such as sensitivity analysis, probabilistic techniques and Monte Carlo analysis). If necessary, variability is addressed separately and explicitly.

20 • ***Considers all the relevant risks***

22 A good risk assessment considers all the explicit and implicit risks that are relevant in any particular situation. It identifies and quantifies residual risks (i.e. the risk that remains after a management action is taken) as far as possible, and puts them into perspective. Good risk assessment also takes account of changes or transformation in risks due to management measures. For instance, chlorine in the water supply reduces microbial risks but increases chemical risks. Banning the use of antibiotics in animal feed reduces risks of antibiotic resistance but may increase the risk of food-borne illness. Risk assessors must ensure that when risks are transformed they are carefully explained so that proper risk-risk trade-offs can be made.

- ***Is objective, unbiased and transparent***

2 A good risk assessment is honest, unbiased, clear and objective. It should be based on
4 a scientific approach and carried out with objectivity and neutrality. Opinions or
6 value judgements (for instance on economic, political, legal or environmental aspects
of the risk) should not be allowed to influence the outcome of a risk assessment. A
good risk assessment should explicitly and openly identify and discuss any
controversies in the science or uncertainties in the analysis.

- ***Is clearly and comprehensively documented***

8 A good risk assessment should clearly document the assumptions, logic, models used,
10 calculations, and results obtained so that they are comprehensible to risk managers
and other stakeholders despite their complexity. The risk assessment process should
12 produce a coherent narrative report that puts risks into a proper perspective and
explains how they should be managed and why. It should be comprehensive and
14 detailed enough to meet all the risk managers' needs for decision-making.

- ***Is reviewed and evaluated***

16 A good risk assessment has a separate quality assurance process, which may include
some sort of peer or independent review. The results are estimates and should be
18 subject to independent evaluation and review. Good risk assessment is open to
evaluation and is flexible enough to change when opportunities for improvements are
20 identified.

- ***Has educational value***

22 A good risk assessment helps managers to understand food safety problems and learn
about related issues. It helps managers to identify the limits of knowledge and enables
24 resources to be directed towards narrowing information gaps. Good risk assessment is
conducive to learning and the process is as important as the result.

26

ANNEX 6

2

NATIONAL MODEL COMPARISON: ADVERSE EFFECTS

4

The tables are listed below and were developed by WHO staff to facilitate an understanding as to how and in what ways three existing national/regional nutrient risk assessment models are similar or differ in their considerations of adverse effects (i.e. endpoints). This comparison may not be comprehensive, but it may be of some interest to workshop participants.

10

Context Paper

ANNEX 6. National model comparison: adverse effects

Table 1. General approach to considering adverse effects in setting upper levels, by working group

Type of Statement	EU–SCF/EFSA	UK–EVM	US–IOM
Definition of upper 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. ‘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.	Safe upper levels (SULs) are doses of vitamins and minerals that potentially susceptible individuals could take daily on a life-long basis without medical supervision in reasonable safety. Guidance levels ^a have been given instead of SULs when the evidence base is inadequate to set an SUL	The highest level of daily nutrient intake that is likely to pose no risk of adverse health effects for almost all individuals in the general population. Different ULs may be developed for various life stage groups.
Definition of adverse effect	“Change in morphology, physiology, growth, development or life span of an organism which results in impairment of functional capacity or impairment of capacity to compensate for additional stress or increase in susceptibility to the harmful effects of other environmental influences (WHO, 1994). Decisions on whether or not any effect is adverse require expert judgement.”	Not specified	“any significant alteration in the structure or function of the human organism (Klaassen et al., 1986) or any impairment of a physiologically important function that could lead to a health effect that is adverse”
Additional considerations or comments		Levels tend to be conservative.	Adverse effects include the alteration in detrimental ways of the health benefits conferred by another nutrient, that is, adverse nutrient-nutrient interactions
Approach for determining which observed effects are adverse	Not all demonstrable structural or functional alterations represent adverse effects. Some alterations may be considered of little or self-limiting biological importance. Decisions on which observed effects are adverse are based on scientific judgements.	None indicated	Based on scientific judgements. Some demonstrable structural or functional alterations or nutrient-nutrient interactions may be considered of little or self-limiting biological importance

^a Guidance level is not expected to produce adverse effects in a majority of the people.

ANNEX 6. National model comparison: adverse effects

Table 2. Adverse effects considered and used in setting an upper level for vitamin A, by working group

Adverse Effect	EU-SCF (2002)	UK-EVM (2003)	US-IOM (2001)
Adults	---Information provided relative to the adverse effect---		
Decreased bone mineral density and increased risk of hip fracture	× Suggestive evidence that excess vitamin A intake may increase bone resorption and decrease bone formation. Vulnerable group: postmenopausal women	× Vulnerable groups: older people, those with osteoporosis	× Evidence is conflicting, data lacking to confirm findings of Melhus et al. (1998)
Teratogenicity	√ For women of childbearing age; in addition, UL set on this basis was discussed in relation to other subgroups	× A potential risk, especially in the first trimester of pregnancy	√ For women of childbearing age
Liver abnormalities, hepatotoxicity	√ Toxicity appears to depend on the dose taken and on the duration of intake	× Details not specified	√ For all other adults—specifically abnormal liver pathology that is characteristic of vitamin A intoxication, or grossly elevated hepatic vitamin A levels
Elevated serum cholesterol	× Small increase observed		
Chronic toxicity		× Signs described in animals and humans	
Infants and Children	UL based on the value for adults		
Intracranial and skeletal abnormalities, retarded growth	× Bulging fontanelle and intracranial hypertension discussed in relation to studies of high-dose vitamin A to prevent deficiency	×	√ Case reports of “hypervitaminosis A,” which included a wide variety of adverse effects
Various other signs including bone pain, desquamation, weight loss, vomiting, hepatomegaly			√
UL Established?	Yes	No. Report indicates that a guidance level ^a was set, but it was not found.	Yes
Other Comments	Narrow margin between the population reference intake and intakes associated with adverse effects	Several vulnerable groups listed, but not linked with a specific adverse effect.	

× denotes that the adverse effect was mentioned or reviewed in the hazard identification

√ denotes that the adverse effect was identified as providing a basis for setting a UL.

^a Guidance level is not expected to produce adverse effects in a majority of the people.

NOTE: Some differences may be due to differences in the publications available since reviews were conducted in different years.

ANNEX 6. National model comparison: adverse effects

Table 3. Adverse effects considered and used in setting an upper level for iron, by working group

Adverse Effect	EU-SCF (2002)	UK-EVM (2003)	US-IOM (2001)
Acute intoxication	× Young children especially at risk	× Mainly from accidental ingestion by children	× Mainly from accidental ingestion by children
Iron-zinc interactions		× Significance of the decreased serum zinc concentrations is unclear	× Significance of the decreased serum zinc concentrations is unclear
Gastrointestinal effects (e.g., constipation, vomiting, diarrhea)	× Vary with the delivery system	× Vary with the form of iron	√ Although not considered serious compared with other effects considered, this was the only one for which there was sufficient evidence on which to base a UL
Iron overload	× Susceptible groups include adults homozygous for hereditary haemochromatosis, those receiving long-term, high-dose medical treatment with iron, and those given repeated blood transfusions; a causative factor for Bantu siderosis. Poor correlation between iron intake and various indicators	× Parenteral iron and/or increased absorption rather than high oral intake typically involved	× Only one clear example of <i>dietary</i> iron overload (among South African and Zimbabwean blacks), and there may be a genetic component. Secondary iron overload discussed
Cardiovascular disease, type 2 diabetes	× Epidemiological evidence is contradictory and unconvincing	× Mentions problems of interpreting the data from epidemiological studies	× Body of evidence does not provide convincing support for a causal relationship between dietary iron intake and the risk for CHD.
Cancer	× Body of evidence is not consistent and does not demonstrate causality	× In the absence of chemical carcinogens, few studies on tumorigenesis in animals.	× Hepatic iron accumulation is a risk factor for hepatocellular carcinoma among those with hemochromatosis, but evidence for a relationship between dietary iron intake and cancer is inconclusive in the general population.
Reproductive and developmental toxicity		× None noted in animals	
UL Established?	No	No, however a guidance level ^a was set.	Yes
Other Comments		Guidance level does not apply to those with increased susceptibility to iron overload.	

× denotes that the adverse effect was mentioned or reviewed in the hazard identification

√ denotes that the adverse effect was identified as providing a basis for setting a UL.

^a Guidance level is not expected to produce adverse effects in a majority of the people.

NOTE: Some differences may be due to differences in the publications available since reviews were conducted in different years.

ANNEX 6. National model comparison: adverse effects

Table 4. Adverse effects considered and used in setting an upper level for vitamin C, by working group

Adverse Effect	EU-EFSA (2004)	UK-EVM (2003)	US-IOM (2000)
Gastrointestinal effects (e.g., distention, flatulence, diarrhea)	× The most clearly defined adverse effect at high intakes, but data on the dose-response relationship; are too limited to use as the bases for an upper level intake value.	× Associated with high doses; few controlled studies address this response. Data insufficient for a UL.	√ Effect attributed to osmotic effect of the unabsorbed vitamin. Data primarily from case-control studies
Metabolic acidosis	× Details not specified	× Details not specified	
Pro-oxidant effects	Details not specified	× Significance is uncertain for the general population	× No clear causal relationship shown
Changes in prothrombin activity	× Not sufficiently well documented or substantiated to be used as the basis for risk assessment	× Details not specified	
Systemic conditioning, 'conditioned need' scurvy	× Reported in guinea pigs; anecdotal evidence in humans, doesn't pose a significant risk	× Details not specified	× Evidence of an effect is scanty and conflicting both for infants and adults
Renal effects: stones, high oxalate or uric acid excretion	× Not sufficiently well documented or substantiated to be used as the basis for risk assessment	× Data are conflicting. Potentially vulnerable group: those with a predisposition to urinary or renal stones	× Cases of stones limited to a few subjects with renal disease. No clear causal relationship shown. Highly sensitive subpopulation: those with renal disorders
Excessive iron uptake from the gut	Small increase in iron absorption could be a problem for those with haemochromatosis or heterozygous for the condition	× Vulnerable group: those with disorders of iron metabolism or storage	× Highly sensitive subpopulation: those with haemochromatosis
Reduced vitamin B ₁₂ and copper status	× Not sufficiently well documented or substantiated to be used as the basis for risk assessment	× Details not specified	× No clear causal relationship shown
Reproductive effects		× None reported.	
Decreased growth		× Reported in guinea pigs	
Genotoxicity	× Current data do not allow adequate evaluation of the genotoxic potential of high intakes of the vitamin. Oxidative DNA damage observed <i>in vitro</i> and <i>in vivo</i> is of uncertain significance.	×	
Carcinogenicity	× Findings in animals not relevant to human health; conflicting evidence about the relationship with breast cancer	× Mixed results from <i>in vitro</i> studies	

Continues

Table 4, continued. Adverse effects considered and used in setting an upper level for vitamin C, by working group

Adverse Effect	EU-EFSA (2004)	UK-EVM (2003)	US-IOM (2000)
Increase in serum cholesterol concentration	× Evidence is conflicting		
Dental enamel erosion			× Single study, no clear causal relationship shown
Allergic response			× Single study, no clear causal relationship shown
Hemolysis			× Highly sensitive subpopulations: newborns with glucose-6-phosphate dehydrogenase deficiency, normal preterm infants
UL Established?	No	No, however a guidance level was set.	Yes

× denotes that the adverse effect was mentioned or reviewed in the hazard identification

√ denotes that the adverse effect was identified as providing a basis for setting a UL.

^a Guidance level is not expected to produce adverse effects in a majority of the people.

NOTE: Some differences may be due to differences in the publications available since reviews were conducted in different years.

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ANNEX 7

2

NATIONAL MODEL COMPARISON: INTAKE ASSESSMENT

4

The tables are listed below and were developed by WHO staff to facilitate an understanding as to how and in what ways three existing national/regional nutrient risk assessment models are similar or differ in their considerations of the assessment of intakes of food, supplements, and water. This comparison may not be comprehensive, but it may be of some interest to workshop participants.

10

Context Paper

ANNEX 7. National model comparison: Intake assessment

Table 1. Background: Data sources, methodologies, caveats

	EU–SCF/EFSA	UK-EVM	US-IOM
Intakes from foods	<p>Summary tables of intake data. Number and source of studies varied by nutrient. For nutrients described in table below, up to 15 publications for 8 countries were available:</p> <p><i>Methods used:</i></p> <p>7- and 8-day records:</p> <ul style="list-style-type: none"> ▪ 7 studies ▪ 1 household study (n = 2734) ▪ 6 studies with individuals (n= >11,510) <p>7-day weighed record</p> <ul style="list-style-type: none"> ▪ 1 study ▪ 2197 individuals <p>7-d weighed intake, 3-d weighed intake, 24 hr recall:</p> <ul style="list-style-type: none"> ▪ 1 study ▪ 4972 individuals <p>2-day records:</p> <ul style="list-style-type: none"> ▪ 1 study ▪ 5958 households <p>24-hour recall</p> <ul style="list-style-type: none"> ▪ 1 study ▪ 2488 individuals <p>Semi-quantitative FFQ (180 food items):</p> <ul style="list-style-type: none"> ▪ 1 study ▪ 2672 individuals <p>Computer assisted dietary interview</p> <ul style="list-style-type: none"> ▪ 1 study ▪ >4000 individuals <p>Methodology undefined:</p> <ul style="list-style-type: none"> ▪ 2 studies ▪ >1000 individuals 	<p>Three different types of nutritional surveys were considered:</p> <ul style="list-style-type: none"> • National Diet and Nutrition Survey 1986–1987 (NDNS): <ul style="list-style-type: none"> ▪ Generally used. ▪ Cross-sectional data ▪ Nationally representative samples of specific population age groups ▪ Uses a weighed 4- or 7- day dietary record kept by the participant ▪ Rolling program of detailed dietary surveys of individuals divided into specific population age groups. ▪ Caution – 1986/7 data do not reflect recent changes in use of supplements and fortified foods. ▪ Nutrients from food sources only (including beverages such as teas but excluding supplements and drinking water). ▪ Prone to under-reporting because of respondent burden ▪ Nutrient status information is collected via blood samples and physical measurements. ▪ Detailed interview information on SES, demographic and lifestyle characteristics. • The National Food Survey (NFS): <ul style="list-style-type: none"> ▪ Reports annually on household food purchases. ▪ Average nutrient intakes/person and population trends over time ▪ No information on age/gender sub-groups ▪ No information on distributions of nutrient intakes in the population ▪ Used when NDNS data not available. • The Total Diet Study (TDS): <ul style="list-style-type: none"> ▪ Continuous study ▪ Selected foods representing the average UK diet are analyzed ▪ Foods combined into 20 groups of similar foods for analysis ▪ Particularly useful for estimating intakes where food composition data are lacking and for trend analysis. ▪ Population level data only; no information on individuals. <p>Published literature used when survey data not available.</p>	<p><u>US:</u></p> <p>Major sources of data were 2 nationally representative surveys:</p> <ol style="list-style-type: none"> 1. National Health and Nutrition Examination Survey of 1988-94 (NHANES III): <ul style="list-style-type: none"> • 30,000 subjects • Ages 2 months and older • Single 24-h recall for all subjects + second recall for a 5% nonrandom sub-sample to allow statistical adjustment of intake estimates for day-to-day variation • Contains quantitative estimates of water and supplement consumption. 2. Continuing Survey of Food Intakes by Individuals (CSFII) for 1994-96: <ul style="list-style-type: none"> • 16,000 subjects • All ages • Statistical adjustment for day-to-day variations • Qualitative intake data for supplements <p>FDA’s Total Diet Study.</p> <ul style="list-style-type: none"> • Used for nutrients not covered by the two surveys above • A Market Basket Survey • 306 core foods representing the USDA food consumption survey data for 94-96 for numerous age/gender groups • Intake data were not adjusted for day-to-day variation. <p><u>Canada:</u></p> <p>Data collected in Québec and Nova Scotia. (The extent to which these data are applicable nationwide is not known).</p> <p><u>Estimates of nutrient intakes:</u></p> <ul style="list-style-type: none"> • Intake distributions for all age/gender/lifestage groups • Unreliable estimates flagged • Sometimes reported as a single distribution of total intakes (food + supplements + water,

	EU-SCF/EFSA	UK-EVM	US-IOM
Intakes from foods, continued		<p>Data Interpretation: All methods of estimating the amounts of food consumed are associated with some degree of error. For example:</p> <ul style="list-style-type: none"> • Dietary recording period may not be long enough to provide information about foods consumed occasionally • Subjects may mis-report foods consumed or change their habitual diet during the recording period • Data, even from most detailed surveys, may be out of date because of significant changes in eating habits and increases in supplement use in recent years. • Therefore, caution is needed in interpretation of dietary survey data. 	<p>where applicable); sometimes reported as separate intake distributions for foods and supplements.</p> <p><u>Discussion of Assessment Methods:</u></p> <ul style="list-style-type: none"> • Individuals under-report intakes; greater for obese • Quality of composition data variable • Large day-to-day variations require large numbers of days or statistical adjustments to approximate usual intakes
Intakes from Supplements	<p>Data bases varied as to whether supplements were included or excluded.</p> <p>Collected data on dietary supplements:</p> <ul style="list-style-type: none"> • 7 studies • 6 Individual and 1 household survey • > 13,000 individuals or households 	<p>Manufacturer-supplied data on single and multiple nutrient products:</p> <ul style="list-style-type: none"> • Label values for lowest, highest, and most common vitamin and mineral contents of products marketed as single nutrient and multi-nutrient products. • Similar data for products formulated for children • Sales (millions of units) <p>Potential exposure to vitamins and minerals from food supplements also estimated from OTC Directory 2001-2.</p> <p>These sources of information were used to provide a single estimate of maximum exposure from supplements.</p> <p>Label values do not reflect ‘overages’ used in the manufacture of food supplements (20 – 100% > label value).</p>	<p>NHANES III or 1986 National Health Interview Survey (NHIS)</p> <ul style="list-style-type: none"> • Each respondent asked how often used over a specified time period for each supplement product (i.e., for NHANES III, frequency of use over past 30 days) • Composition information based on label declaration • Intake = (frequency of use) x (label declaration of nutrient content) • Nutrient intake distributions by age/gender/lifestage group
Intakes from Water	<p>Where applicable, provide information on standards for maximum concentration of nutrients in drinking water.</p>	<p>Where applicable, assumed 2 L/d consumption and maximum permitted level of nutrient of interest (e.g., copper).</p>	<p>Distributions of reported intakes (mL/d) by age/gender/lifestage group</p>
Total Nutrient Intakes (foods + supplements + water)	<p>Summary table of means and 97.5th pctl from available studies.</p> <ul style="list-style-type: none"> • Indication as to whether intakes are for foods only or also include supplements. • As available, results presented for one of the following units: <ul style="list-style-type: none"> ○ Household ○ Individuals ○ Males and females 	<p>Data presented as a single value for each of these categories:</p> <ul style="list-style-type: none"> • Food: Mean and 97.5th pctl • Supplements: Maximum daily dose in marketed products • Water: Maximum allowable concentrations in 2L • Estimated maximum daily intake calculated by summing across the 3 sources above. 	<p>Where composition data are available from NHANES III, data presented as:</p> <ul style="list-style-type: none"> • Distributions by age/gender/lifestage group • For some nutrients, separate distributions are given for nutrient intakes from foods and from supplements; in other cases, distributions reported as combined intakes from foods+ supplements <p>Where UL is based on a form of nutrient (e.g., synthetic or added form), composition data may be adjusted appropriately to estimate intakes for specified form.</p>

Context Paper

ANNEX 7. National model comparison: Intake assessment

Table 2. Vitamin A comparison

	EU-SCF (2002)	UK-EVM (2003)	US-IOM (2001)
ULs	<p>Women of child-bearing age and men = 3000 µg RE/d</p> <p>Children 1 – 3 yr = 800 µg RE/d</p> <p>Children 4 – 6 yr = 1,100 µg RE/d</p> <p>Children 7 – 10 yr = 1,500 µg RE/d</p> <p>Children 11 – 14 yr = 2,000 µg RE/d</p> <p>Children 15 – 17 yr = 2,600 µg RE/d</p> <p>Advisable for postmenopausal women to restrict their intake to 1,500 µg/d.</p>	<p>None established.</p> <p>Discussed:</p> <ul style="list-style-type: none"> Prudent to take 3,000 µg RE/d as the threshold for teratogenicity. Intakes greater than 1,500 µg RE/d may be inappropriate relative to risk of hip fracture. 	<p>Women and Men, 19 + yr = 3,000 µg/d</p> <p>Girls and Boys, 14 - 18 yr = 2,800 µg/d</p> <p>Children 1-3 yr = 600 µg/d</p> <p>Children 4-8 yr = 900 µg/d</p> <p>Children 9 – 13 yr = 1,700 µg/d</p>
Intake Estimates	<p><u>Publications including foods and supplements:</u></p> <p>Means (3 studies):</p> <ul style="list-style-type: none"> Men: 1,277 – 2,020 µg/d Women: 1,133 – 1,790 µg/d Household: 759 µg/d <p>97.5th pctl (2 studies):</p> <ul style="list-style-type: none"> Men: 6,671 µg/d Women: 5,779 µg/d Household: 4,377 µg/d <p>Differences between the mean and median values indicated a skewed distribution of intakes, which arises from the non-uniform distribution of preformed retinol in the food supply and very high intakes by consumers of foods such as liver.</p>	<p><u>Food:</u></p> <ul style="list-style-type: none"> median = 520 µg RE/d (from 1986/87 NDNS) 97.5th pctl = 6,050 µg RE/d <p><u>Supplements:</u></p> <ul style="list-style-type: none"> Up to 2,400 µg RE/d (sales data) <p><u>Estimated maximum intake:</u></p> <ul style="list-style-type: none"> 6050 + 2400 = 8,450 µg RE/d <p>High intake groups include people who consume liver and liver products regularly.</p>	<p><u>Food:</u></p> <p>Highest median intake:</p> <ul style="list-style-type: none"> Lactating women = 1.050 µg/d <p>Highest 95th pctl intake:</p> <ul style="list-style-type: none"> Males 31 – 50 y = 1,965 µg/d <p><u>Supplements:</u></p> <p>95th pctl for adults:</p> <ul style="list-style-type: none"> Ranged from 1,500 to 3,000 µg/d. <p>< 5 % of pregnant women had dietary and supplemental levels exceeding the UL</p>
Discussion	<p><u>Risk characterization:</u></p> <p>The 97.5th pctl intake for adults in most of Europe is greater than the UL of 3,000 µg RE/d.</p> <p>Because alternations of embryogenesis may occur following a single or a small number of doses of vitamin A, for women of childbearing age the UL should be compared with intake estimates that reflect short-term, rather than long-term exposure.</p> <p>Because current intakes may exceed the TUL, careful consideration should be given to the appropriateness of the enrichment of human foods with vitamin A, and to the potential effects on human exposure of the addition of vitamin A to animal feed.</p>	<p><u>Discussion on Guidance Levels:</u></p> <p>Endorse current advice that women who are pregnant or who wish to become pregnant should not take dietary supplements containing vitamin A except on medical advice.</p> <p>High level consumers of liver and liver products and/or supplements may exceed intakes at which adverse effects have been reported.</p> <p>Dietary supplements may contain overages that are 20-100% more than label declaration. This may be particularly important given that the effect on fracture risk appears to be a graded response, with the risk of fracture increasing with increased intake.</p>	<p><u>Risk Characterization:</u> The risk of exceeding the UL for vitamin A appears to be small based on the intakes cited above.</p>

Context Paper

ANNEX 7. National model comparison: Intake assessment

Table 3. Iron comparison

	EU-EFSA (2004)	UK-EVM (2003)	US-IOM (2001)
ULs	ULs: None provided	ULs: None established <u>Guidance Level:</u> <ul style="list-style-type: none"> ○ A supplemental intake of approximately 17 mg/d (equivalent to 0.28 mg/kg/bw/d for a 60 kg adult) would not be expected to produce adverse effects in the majority of people. ○ This guidance level does not apply to the small proportion of the population who have increased susceptibility to iron overload. 	ULs: M & F ≥ 14 yr = 45 mg/d Children 1- 13 yr = 40 mg/d
Intake Estimates	Publications including foods and supplements: Means (5 studies): <ul style="list-style-type: none"> ○ Males: 13 – 22 mg/d ○ Females: 12 – 18 mg/d ○ Household: 13 mg/d 97.5 th pctl (5 studies): <ul style="list-style-type: none"> ○ Males: 27 – 41 mg/d ○ Females: 27 – 72 mg/d ○ Household: 22 mg/d 	<u>Food:</u> <ul style="list-style-type: none"> • Mean = 12 mg/d • 97.5th pctl = 24 mg/d (from 1986/7 NDNS) <u>Water:</u> <ul style="list-style-type: none"> • 0.4 mg/d (assuming 2 L/d at UK limit of 0.2 mg/L) <u>Supplements:</u> <ul style="list-style-type: none"> • 20 mg/d (up to 60 mg/d for particular conditions, e.g. pregnancy) (sales data) <u>Estimated maximum intake:</u> <ul style="list-style-type: none"> • 24 + 0.4 + 20 mg = 44 mg/d 	Food + Supplements (NHANES III): Highest intakes (excluding pregnant and lactating women): <ul style="list-style-type: none"> ○ Median: Men 31-50 y = 19 mg/d ○ 90th pctl: Men ≥ 51 y = 34 mg/d Pregnant and lactating women: <ul style="list-style-type: none"> • 50 – 75% of pregnant and lactating women consumed iron from food and supplements at a level greater than 45 mg/d, but iron supplement is usually supervised in pre- and postnatal care programs. • The 90 th pctl intakes are below the UL of 45 mg/d.
Discussion	<u>Risk Characterization:</u> Risk of adverse effects from high iron intake from food sources, including fortified foods in some countries, but excluding supplements, is considered to be low for the population as a whole. Intake from supplements in men and postmenopausal women may increase the proportion of the population likely to develop biochemical indicators of high iron stores. A particularly sensitive subpopulation (up to 0.5% of the population) are homozygotes for hereditary haemochromatosis, who are susceptible to iron overload even at normal dietary iron intakes. Such individuals should avoid iron-supplements and highly iron-fortified foods. The majority of homozygotes are not diagnosed or identified, and they are not aware of their greater susceptibility until sufficient iron has accumulated to produce adverse effects.		<u>Risk Characterization:</u> The risk of adverse effects from dietary sources appears to be low. Individuals taking iron salts at a level above the UL may encounter g.i. side effects, especially when taken on an empty stomach. 25% of men aged 31-50 years in US have ferritin concentrations greater than 200 µg/L which may be a risk factor for cardiovascular disease. This prevalence is higher in men older than 50 yr. The significance of high ferritin concentrations and their relationship to dietary iron intake is uncertain. Nevertheless, the association between a high iron intake and iron overload in sub-Saharan Africa makes it prudent to recommend that men and postmenopausal women avoid iron supplements and highly fortified foods.

Table 4. Vitamin C comparison

	EU-EFSA (2004)	UK-EVM (2003)	US-IOM (2000)
ULs	<u>ULs</u> : None provided.	<u>ULs</u> : None provided. <u>Guidance Level</u> : <ul style="list-style-type: none"> • A supplemental level of 1,000 mg/d would not be expected to have any significant adverse effects. • A guidance level for total vitamin C has not been estimated since adverse effects appear to follow supplemental, bolus doses rather than intake of vitamin C from food. • Higher levels of vitamin C may be without adverse effects in many individuals. 	<u>ULs</u> : Adults ≥ 19 yr = 2,000 mg/d Adolescents 14 – 18 yr = 1,800 mg/d Children 1-3 yr = 400 mg/d Children 4 – 8 yr = 650 mg/d Children 9 – 13 yr = 1,200 mg
Intake Estimates	<u>Publications including foods and supplements</u> : Means (5 studies): <ul style="list-style-type: none"> ○ Men: 101 – 168 mg/d ○ Women: 108 – 169 mg/d ○ Household: 113 mg/d 97.5 th pctl (5 studies): <ul style="list-style-type: none"> ○ Men: 309 – 1,056 mg/d ○ Women: 285 – 1,117 mg/d ○ Household: 268 mg/d 	<u>Food</u> : <ul style="list-style-type: none"> • Mean = 64 mg/d • 97.5th pctl = 160 mg/d (from 1986/7 NDNS) <u>Supplements</u> : <ul style="list-style-type: none"> • Up to 3,000 mg/d (sales data) <u>Estimated maximum daily intake</u> : <ul style="list-style-type: none"> • 160 + 3000 = 3,160 mg Vegetarians are a potential high intake group.	<u>Food + supplements</u> : Highest mean intake: <ul style="list-style-type: none"> • Males 51-70 y and females ≥ 51 yr: about 200 mg/d Highest 99 th pctl intake: <ul style="list-style-type: none"> • Males 31 – 70 y and females 51-70 y: > 1,200 mg/d
Discussion	<u>Risk Characterization</u> : These dietary intakes do not represent a cause for concern.	<u>Establishment of Guidance Level</u> : Potentially vulnerable groups include individuals who are heterozygous for haemochromatosis and thalassaemia or those with a predisposition to urinary or renal stones. Data on the possible adverse effects of vitamin C on these individuals are also conflicting, but appear to occur at intakes > 1 g/d.	<u>Risk Characterization</u> : The risk of adverse effects resulting from excess intake of vitamin C from food and supplements appears to be very low at the highest intakes.

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Table 5. Vitamin E comparison

	EU-SCF (2003)	UK-EVM (2003)	US-IOM (2002)
ULs	<p><u>ULs:</u> Adults = 300 mg/d Children 1 – 3 yr = 100 mg/d Children 4 – 6 yr = 120 mg/d Children 7 – 10 yr = 160 mg/d Children 11 – 14 yr = 220 mg/d Children 15 – 17 yr = 260 mg/d</p>	<p><u>ULs:</u> Lifetime consumption = 800 IU (540 mg d-α-tocopherol equivalents/d) supplemental for daily vitamin E (equivalent to 9.0 mg/kg bw in a 60 kg adult).</p>	<p><u>ULs (for any form of supplementary α-tocopherol):</u> Adults \geq 19 yr = 1,000 mg/d (2,326 μmol/d) Adolescents 14 – 18 yr = 800 mg/d (1,860 μmol/d) Children 1 – 3 yr = 200 mg/d (465 μg/d) Children 4 – 8 yr = 300 mg/d (698 μmol/d) Children 9 – 13 yr = 600 mg/d (1,395 μmol/d)</p>
Intake Estimates	<p>Data presented as α-tocopherol equivalents which include all 8 naturally occurring forms.</p> <p><u>Publications including foods and supplements:</u> Means (3 studies):</p> <ul style="list-style-type: none"> • Males: 11.2 – 11.7 mg TE/d • Females: 8.6 – 11.0 mg TE/d • Household: 11 mg TE/d <p>97.5th pctl (3 studies):</p> <ul style="list-style-type: none"> • Males: 23.4 – 28.3 mg TE/d • Females: 20.4 – 38.3 mg TE/d • Household: 22 mg TE/d 	<p><u>Food:</u></p> <ul style="list-style-type: none"> • Mean = 8.5 mg/d • 97.5th pctl = 18 mg/d (1986/7 NDNS) <p><u>Supplements:</u></p> <ul style="list-style-type: none"> • Up to 670 mg/d (sales data) <p><u>Estimated maximum daily intake:</u></p> <ul style="list-style-type: none"> • 18 + 670 = 690 mg/d <p>No potential high intake groups have been identified.</p>	<p><u>Food + supplements (α-tocopherol equivalents):</u> Highest mean intake:</p> <ul style="list-style-type: none"> • Women 51 – 70 y: 45 mg/d (104.7 μmol/d) <p>Highest intake at 99th pctl:</p> <ul style="list-style-type: none"> • Women 51-70 y: 508 mg (1,181μmol/d) <p>Intake distribution is very skewed. For women 51-70 y, median is 9 mg/d (20.9 μmol/d); mean is 45 mg/d (104.7 μmol/d).</p> <p>Intakes at 99th pctl are well below the UL of 1,000 mg/d of any for of α-tocopherol.</p> <p>Vitamin E supplement use is high in the U.S. population. Supplements containing vitamin E were used by 37% of young children, 23% of men, and 29% of women in the U.S.</p>
Discussion	<p><u>Risk Characterization:</u> Current estimated intakes from food and supplements, including the 97.5th pctl, in the population are generally well below the UL. However, some users of high dose supplements may exceed the UL.</p>		<p><u>Risk Characterization:</u> The risk of adverse effects resulting from excess intake of α-tocopherol from food and supplements appears to be very low at the highest intakes noted above.</p>

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Table 6. Selenium comparison

	EU-SCF (2000)	UK-EVM (2003)	US-IOM (2000)
ULs	<p>Adults = 300 µg/d Children 1 -3 yr = 60 µg/d Children 4 - 6 yr = 90 µg/d Children 7 - 10 yr = 130 µg/d Children 11 - 14 yr = 200 µg/d Children 15 - 17 yr = 250 µg/d</p>	<p>Daily consumption over a lifetime: 0.45 mg total selenium/d</p>	<p>Persons ≥ 14 years = 400 µg/d (5.1 µmol) Children 1 - 3 yr = 90 µg/d (1.1 µmol) Children 4 - 8 yr = 150 µg/d (1.9 µmol) Children 9 - 13 yr = 280 µg/d (3.6 µmol)</p>
Intake Estimates	<p>The mean intakes of non-vegetarian adults in different studies are:</p> <ul style="list-style-type: none"> Belgium: 28-61 µg/d Denmark: 41-57 µg/d Finland: 100 - 110 µg/d France: 29-43 µg/d UK: 63 µg/d The Netherlands: 40-54 µg/d Norway: 28 -89 µg/d Spain: 79 µg/d Sweden: 24-35 µg/d. <p>The amount of selenium available in the soil for plant growth and corresponding variations in the intake of selenium by humans varies considerably among regions and countries.</p>	<p><u>Food:</u></p> <ul style="list-style-type: none"> Mean = 0.039 mg/d 97.5th pctl = 0.1 mg/d (1994 TDS) <p><u>Supplements:</u></p> <ul style="list-style-type: none"> Up to 0.3 mg/d (sales data) <p><u>Estimated maximum intake:</u></p> <ul style="list-style-type: none"> 0.1 + 0.3 = 0.4 mg/d <p>No potential high intake groups have been identified.</p>	<p><u>Food:</u></p> <ul style="list-style-type: none"> Dietary selenium intake in a high-selenium area: 68 - 724 µg/d (0.9 - 9.2 µmol). About half the subjects were consuming more than 200 µg/d. (2.5 µmol) with no evidence of selenosis. <p><u>Water:</u></p> <ul style="list-style-type: none"> Water selenium content is usually trivial compared to food selenium content. However, irrigation runoff water has been shown to contain significant amounts of selenium when the soil irrigated contains large amounts of the element. <p><u>Supplements:</u></p> <ul style="list-style-type: none"> Available in many doses but usually under 100 µg/dose (1.3 µmol). <p>The extensive food distribution system in Canada and the U.S. ensures that individuals do not eat foods that originate solely from one locality. This moderates the selenium content of diets, even in high-selenium areas</p>
Discussion	<p><u>Risk Characterization:</u> In most European countries, mean intakes are in the range of 30 - 90 µg/d</p> <p>Norway has a somewhat higher mean intake (60 µg/d) due to import of wheat rich in selenium.</p> <p>Finland has an intake of 100-110 µg/d because of selenium fertilization.</p> <p>The margin between the present mean intake, excluding supplements, in the European population and an UL (adult) of 300 µg/d would be between 2.7 to 10. The 97.5 pctl intake was 81 and 90 µg Se/d in Italy and The Netherlands, respectively, giving a margin to the UL of about 2.7.</p>	<p><u>Establishment of a SUL:</u> Assuming a maximum intake of 0.1 mg/d from food, a margin of 0.35 mg/d selenium is available for supplementation or other additional intake.</p>	<p><u>Risk characterization:</u> The risk of selenium intake above the UL for the US and Canada appears to be small. There have been no cases of selenosis in the high-selenium regions.</p> <p>Although intakes above the UL indicate an increased level of risk, these intakes - if below the LOAEL - would be unlikely to result in observable clinical disease. This is especially true in a population that could self-select for high intakes, so that people who might experience symptoms could alter their diets or move.</p>

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Table 7. Zinc comparison

	EU-SCF (2003)	UK-EVM (2003)	US-IOM (2001)
ULs	<p>Adults = 25 mg/d</p> <p>Children 1 – 3 yr = 7 mg/d</p> <p>Children 4 – 6 yr = 10 mg/d</p> <p>Children 7 – 10 yr = 13 mg/d</p> <p>Children 11 – 14 yr = 18 mg/d</p> <p>Children 15 – 17 yr = 22 mg/d</p>	<p>Daily consumption over a lifetime:</p> <ul style="list-style-type: none"> • 25 mg zinc/d for supplemental zinc 	<p>Adults ≥ 19 yr = 40 mg/d</p> <p>Adolescents 14 – 18 yr = 34 mg/d</p> <p>Children 1 – 3 yr = 7 mg/d</p> <p>Children 4 – 8 yr = 12 mg/d</p> <p>Children 9 – 13 yr = 23 mg/d</p>
Intake Estimates	<p><u>Publications including foods and supplements:</u></p> <p>Means (3 studies):</p> <ul style="list-style-type: none"> • Males: 10.8 – 11.4 mg/d • Females: 7.5 – 8.4 mg/d • Households: 11 mg/d <p>97.5th pctl (3 studies):</p> <ul style="list-style-type: none"> • Males: 19.0 – 23.5 mg/d • Females: 13.6 – 22.1 mg/d • Households: 19.0 mg/d <p><u>Water:</u> Concentrations of zinc in tap water may be elevated as a result of dissolution of pipes and contaminated wells may lead to high exposure. Drinking water quality standards for European countries provide a Zn content not more than 5 mg/L.</p> <p><u>Other exposures:</u> Inhalation of zinc metal or oxide fumes in industrial settings and storage of food and drink in galvanized containers.</p>	<p><u>Food:</u></p> <p>Mean = 9.8 mg/d</p> <p>97.5th pctl = 17 mg/d (from 1986/87 NDNS)</p> <p><u>Water:</u></p> <p>Up to 10 mg/d (assuming 2 L/d consumption at maximum UK concentration of 5 mg/L)</p> <p><u>Supplements:</u></p> <p>Up to 50 mg/d (sales data)</p> <p><u>Estimated maximum intake:</u></p> <p>17 + 10 + 50 = 77 mg/d</p> <p>No potential high intake groups were identified</p>	<p><u>Food:</u></p> <p>Highest 95th pctl intake:</p> <ul style="list-style-type: none"> • Adults = 25 mg/d <p><u>Supplements:</u> In 1986, approximately 17% of women and 15% of men consumed supplements that contained zinc.</p> <p><u>Intakes from Food + Supplements:</u></p> <p>Highest 95th pctl intake:</p> <ul style="list-style-type: none"> • Adult men and non-pregnant women = 25–32 mg/d. • For pregnant and lactating women, approximately 43 mg/d <hr/> <p><i>Note: Although not discussed in the IOM report, their intake estimates for zinc from food + supplements at the 95th pctl are as follows: Children 1-3 yr, 12.9 mg/d; children 4 – 8 yr, 14.2 mg/d; Boys 9 – 13 yr, 17.3 mg/d; girls 9 – 13 yr, 14.5 mg/d; and girls 14 – 18 yr, 15.5 mg/d. All of these values exceed the UL for their respective age/gender groups.</i></p>
Discussion	<p><u>Risk Characterization:</u> The available studies show that the 97.5th pctl of total zinc intakes for all age groups are close to the ULs, which, in the view of the Committee, are not a matter of concern.</p>	<p><u>Establishment of SUL:</u> Assuming a maximum intake of 17 mg/d from food, a total intake of 42 mg/d would not be expected to result in any adverse effects.</p>	<p><u>Risk Characterization:</u> The risk of adverse effects resulting from excess zinc intake from food and supplements appears to be low at the highest intakes. High intakes of zinc are due to the use of supplements, especially during lactation and pregnancy.</p>

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Table 8. Vitamin B-6 comparison

	EU-SCF (2000)	UK-EVM (2003)	US-IOM (1998)
ULs	<p>Adults = 25 mg/d Children 1 -3 yr = 5 mg/d Children 4 – 6 yr = 7 mg/d Children 7 – 10 yr = 10 mg/d Children 11 – 14 yr = 15 mg/d Children 15 – 17 yr = 20 mg/d</p>	<p>Daily consumption over a lifetime: 10 mg/d supplemental vitamin B-6 for 60 kg adult (0.17 mg/kg bw/d supplemental pyridoxine)</p>	<p><u>As pyridoxine:</u> ≥ 19 yr = 100 mg/d Adolescents 14 – 18 yr = 80 mg Children 1 – 3 yr = 30 mg/d Children 4 – 8 yr = 40 mg/d Children 9 – 13 years = 60 mg/d</p>
Intake Estimates	<p><u>Publications including foods and supplements:</u> Means (3 studies):</p> <ul style="list-style-type: none"> Men = 2.68 – 3.5 mg/d Women = 2.84 – 3.6 mg/d Households = 2.0 mg/d <p>97.5th pctl (3 studies):</p> <ul style="list-style-type: none"> Men = 5.35 – 7.6 mg/d Women = 10.46 – 30.3 mg/d Households = 3.3 mg/d <p>The Dietary and Nutritional Survey of British Adults (1990) (n>2000):</p> <ul style="list-style-type: none"> The majority of the intake by men was from food sources Supplements represented (about 50% of total intake for women > 24 y. Use of supplements by some women resulted in a skewed distribution with the highest 97.5th pctl intake = 16 mg/d in women aged 35-49 y 	<p><u>Food:</u> Mean = 2.0 mg/d 97.5th pctl = 3.9 mg/d (NDNS, 1986/7)</p> <p><u>Supplements:</u> Up to 100 mg/d</p> <p><u>Estimated maximum daily exposure:</u> 3.9 + 100 = 104 mg</p> <p>No potential high intake groups have been identified.</p>	<p><u>Food + Supplements:</u> Highest mean intake:</p> <ul style="list-style-type: none"> Pregnant females 14-55 y = 9 mg/d <p>Highest 95th pctl:</p> <ul style="list-style-type: none"> Pregnant females 14 -55 y = 21 mg/d (most of which is pyridoxine from supplements) <p>Vitamin B-6 is available over the counter in many dosages ranging up to 100 mg or more.</p>
Discussion	<p><u>Risk Characterization:</u> No safety concerns in relation to vitamin B-6 from foods.</p> <p>Intakes from foods and supplements are generally <UL. However, recent data from Ireland indicate that, while the 95th pctl intake of 18-64 y old women is 8 mg day, the intakes of 2.5% of this population group exceed the UL of 25 mg (range of intake of 30-62 mg/d) due to supplement use.</p> <p>Some supplements contain amounts per tablet/capsule that are considerably > UL.</p>	<p><u>Establishment of SUL:</u> In humans, a supplementary dose of 10 mg/d represents a clear SUL with no adverse effects being anticipated over a lifetime’s exposure. Doses of 200 mg/d or more taken for long periods are associated with reports of neuropathy in some human subjects. The effect of taking vitamin B-6 at doses between 10 and 200 mg is unclear. The risk posed by such exposure in the short term may be negligible, but the available data do not allow identification of a dose or duration of exposure above the SUL that would be of negligible risk.</p>	<p><u>Risk Characterization:</u> The risk of adverse effects from excess intake of B-6 from food and supplements appears to be very low at the highest intakes noted above.</p> <p>Increased risks are likely to result from large intakes of PN used to treat various conditions. The UL is not meant to apply to individuals who are being treated with PN under close medical supervision.</p>

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Table 9. Copper comparison

	EU-SCF (2003)	UK-EVM (2003)	US-IOM (2001)
ULs	Adults = 5 mg/d Children 1 -3 yr = 1 mg/d Children 4 – 6 yr = 2 mg/d Children 7 – 10 yr = 3 mg/d Children 11 – 14 yr = 4 mg/d Children 15 – 17 yr = 4 mg/d	Total daily consumption over a lifetime: 0.16 mg/kg bw/d (equivalent to 10 mg/d in a 60 kg adult)	Adults ≥ 19 yr = 10 mg /d(10,000 µg/d) Adolescents 14 – 18 yr = 8,000 µg/d Children 1 – 3 yr = 1,000 µg/d Children 4 – 8 yr = 3,000 µg/d Children 9 – 13 yr = 5,000 µg/d
Intake Estimates	<u>Publications including foods and supplements:</u> Means (3 studies): <ul style="list-style-type: none"> • Males = 1.5 – 1.6 mg/d • Females = 1.2 mg/d • Households = 1.4 mg/d 97.5 th pctl (3 studies): <ul style="list-style-type: none"> • Males = 3.1 - 3.5 mg/d • Females = 2.7 - 2.8 mg/d • Households = 2.8 mg/d <u>Water:</u> Copper piping used for water distribution can add 0.1 mg/day to intakes in hard water areas but 10x this amount in acid and soft water conditions. The current EU standard is 2 mg/L for maximum concentration of Cu in drinking water. <u>Other exposures:</u> Emissions from mines, smelters and foundries, burning of coal for power generation from municipal waste incinerators.	<u>Food:</u> Mean = 1.4 mg/d 97.5 th pctl = 3.0 mg/d (NDNS, 1986,7) <u>Supplements:</u> Up to 2 mg/d (OTC 2001; sales data) <u>Drinking Water:</u> Up to 6 mg/d (assuming 2 L/d consumption and the maximum permitted water copper concentration of 3 mg/L) <u>Estimated maximum daily intake:</u> 3.0 + 2 + 6 = 11 mg/d No potential high intake groups were identified	<u>Food + supplements:</u> Highest median intakes: <ul style="list-style-type: none"> • Males 1-50 y = 1,700 µg/d • Males 51-70 y = 1,600 µg/d • Pg/lactating women = 1,600 µg/d Highest 99 th pctl: Lactating females = 4,700 µg/d Pg females and males 51-70 yr = 4,600 µg/d <u>Water:</u> Drinking water with copper at the EPA Maximum Goal would contribute 2,600 µg/d copper in adults and 1,000 µg in 1 – 4 yr old children. EPA data indicate 98% of flushed drinking water samples had copper levels < 460 µg/L. Most of the US population receives < 100-900 µg/d of copper from drinking water. Adverse health effects depend on the species of copper in the media of concern, its degree of ionization, and its bioavailability.
Discussion	<u>Risk Characterization:</u> The 97.5 th pctl of total copper intakes for all age groups are close to the ULs which, in the view of the Committee, are not a matter of concern. Additional copper intakes from drinking water may be appreciable and may need to be taken into account.	Individuals in the UK could theoretically consume in excess of 6 mg/d copper from water alone if consumed at the statutory limit. However, copper levels in UK drinking water are much lower so this level of exposure is unlikely to occur. There is no evidence that copper intakes in water in the UK present any risk to health.	<u>Risk Characterization:</u> The risk of adverse effects from excess intake of copper from food, water, and supplements appears to be very low in adults at the highest intakes. A small % of children 1 – 8 yr are likely to exceed the UL for their age group.

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Table 10. Vitamin D comparison

	EU-SCF (2002)	UK-EVM (2003)	US-IOM (2001)
ULs	<p><u>ULs:</u> Adults = 50 µg/d Children 0 – 10 yr = 25 µg/d Children 11 – 17 yr = 50 µg/d</p>	<p><u>ULs:</u> None established.</p> <p><u>Guidance Level:</u> A level of 0.025 mg/d supplementary vitamin D would not be expected to cause adverse effects in the general population. This is equivalent to 0.0004 mg/kg bw/d for a 60 kg adult.</p>	<p><u>ULs:</u> Persons ≥ 1 yr = 50 µg (2,000 IU)/d</p>
Intake Estimates	<p><u>Publications including foods and supplements:</u> Means (4 studies):</p> <ul style="list-style-type: none"> • Males = 3.7 – 11.2 µg/d • Females = 3.1 – 10.3 µg/d • Household = 3.0 µg/d <p>97.5th pctl (4 studies):</p> <ul style="list-style-type: none"> • Males = 12.7 – 37.6 µg/d • Females = 12.6 – 33.3 µg/d • Households = 8.4 µ/d <p>The main reasons for the relatively good vitamin D status in the Scandinavian countries are probably fortification of food and a higher percentage of people taking vitamin D supplements.</p>	<p><u>Food:</u> Mean = 0.003 mg/d 97.5th pctl = 0.009 mg/d (NDNS, 1986/7)</p> <p><u>Supplement:</u> Up to 0.0125 mg (manufacturer; OTC 2001)</p> <p><u>Estimated Maximum intake:</u> 0.0009 + 0.0125 = 0.022 mg/d</p> <p>No potential high intake groups have been identified.</p>	<p><u>Food:</u></p> <ul style="list-style-type: none"> • Vitamin D content of unsupplemented diets is low, averaging about 2.5 µg (100 IU)/d for women. • Diets high in fish are considerably higher in vitamin D. • Because milk is fortified to contain 10 µg (400 IU)/quart, persons with high milk intakes have relatively high vitamin D intakes. <p><u>Intakes from supplements:</u> A 1986 survey estimated that the 95th pctl of supplement intake by users of vitamin D supplements was 20 µg/d (800 IU) for men and 17.2 µg/d (686 IU) for women.</p> <p>The endogenous formation of vitamin D-3 from sunlight irradiation of skin has never been implicated in vitamin intoxication.</p>
Discussion	<p><u>Risk Characterization:</u> In Norway, the 95th pctl intake with supplements is about 1.5 x less than the UL.</p> <p>The 97.5 pctl values with supplements are 8.4, 12.7, 14.3 and 22.16 µg/d in Italy, UK, Ireland and Austria, respectively.</p> <p>These values are well below the UL.</p>	<p><u>Establishment of an SUL:</u> Due to the difficulties in assessing total vitamin D exposure, an estimate for total intake has not been provided. Such an intake, or more, might well be required under medical supervision in managing overt or occult deficiency states.</p>	<p><u>Risk Characterization:</u> For most people, vitamin D intake from food and supplements is unlikely to exceed the UL.</p> <p>However, persons who are at the upper end of the ranges for both sources of intake, particularly persons who use many supplements and those with high intakes of fish or fortified milk, may be at risk for vitamin D toxicity.</p>

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Table 11. Calcium comparison

	EU-SCF (2003)	UK-EVM (2003)	US-IOM (1997)
ULS	Adults = 2,500 mg/d	<u>ULs:</u> None provided. <u>Guidance Level:</u> <ul style="list-style-type: none"> Doses up to 1,500 mg/d supplemental calcium would not be expected to result in any adverse effect, but higher doses could result in adverse g.i. symptoms in a few people An estimate for total calcium intakes has not been made as the effect is related to calcium in supplemental doses. 	Adults ≥ 19 = 2,500 mg/d (62.5 mmol/d) Children 1 – 18 yr = 2,500 mg/d (62.5 mmol/d)
Intake Estimates	<u>Publications including supplements:</u> Means (2 studies): <ul style="list-style-type: none"> Males = 940 – 949 mg/d Females = 730 – 742 mg/d 97.5 th pctl: <ul style="list-style-type: none"> Males = 1607 – 1657 mg/d Females = 1,317 – 1,340 mg/d 	<u>Food:</u> Mean = 830 mg/d (1990 NDNS) 97.5 th pctl = 1,500 mg/d <u>Water:</u> Up to 600 mg (assuming 2 L/d consumption at 300 mg/L) <u>Supplements:</u> Up to 2,400 (3 x 800) mg/d (OTC, 2001) <u>Estimated maximum intake:</u> 1500 + 600 + 2400 = 4,500 mg/d	<u>Food:</u> Highest median intake in 1994 CSFII: <ul style="list-style-type: none"> Males 14-18 yr = 1,094 mg/d (27.4 mmol) Highest 95 th pctl intake for any age group: <ul style="list-style-type: none"> Males 14 – 18 yr with an intake of 2,039 mg/d (51 mmol/d) <u>Supplements:</u> <ul style="list-style-type: none"> Calcium supplements were used by < 8% of young children, 14% of men, and 25% of women in the US (1986). Daily dosages from supplements at the 95th pctl were relatively small for children (160 mg; 4 mmol), larger for men (624 mg; 15.6 mmol/d), and largest for women (904 mg; 22.6 mmol/d).
Discussion	<u>Risk Characterization:</u> Data from European populations indicate that the intakes of calcium from all sources in adolescents and adults can be close to the UL in a small percentage of the population, especially in those taking supplements. Although there are no data to set a numerical UL for children and adolescents, no appreciable risk has been identified even with current extreme levels of calcium intake in this age group.		<u>Risk Characterization:</u> Although the 95 th pctl of daily intake did not exceed the UL for any age group, persons with very high caloric intake, especially if intakes of dairy products are also high, may exceed the UL of 2500 mg/d. The 95 th pctl intake from foods and supplements added together for teen-age boys (1,920 + 928 mg/d), or for teenage girls (1,236 + 1,200 mg/d) are at or slightly above the UL. Users of dietary supplements tend to also have higher intakes of calcium from food than nonusers, but it is unlikely that the same person would fall at the upper end of both ranges. The prevalence of usual intakes (from foods + supplements) > UL is < 5% but recently calcium-fortified

			foods in marketplace have doubled -- important to monitor their impact on calcium intake.
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Context Paper

ANNEX 7. National model comparison: Intake assessment

Table 12. Folic acid comparison

	EC-SCF (2000)	UK-EVM (2003)	US-IOM (1998)
ULS	<p><u>ULs (as folic acid):</u> Adults = 1 mg/d Children 1 – 3 yr = 200 µg/d Children 4 – 6 yr = 300 µg/d Children 7 – 10 yr = 400 µg/d Children 11 – 14 yr = 600 µg/d Children 15 – 17 yr = 800 µg/d</p>	<p><u>ULs:</u> None provided</p> <p><u>Guidance level:</u> A supplemental dose of 1 mg/d would not be expected to cause adverse effects.</p>	<p><u>ULs (from fortified food or supplements):</u> Adults ≥ 19 yr = 1,000 µg/d Adolescents 14 – 18 yr = 800 µg/d Children 1 – 3 yr = 300 µg/d Children 4 – 8 yr = 400 µg/d Children 9 – 13 yr = 600 µg/d</p>
Intake Estimates	<p><u>Publications Used (5 studies)</u></p> <ul style="list-style-type: none"> No information as to whether supplements were included or excluded No information on dietary methodology used <p><u>Means:</u></p> <ul style="list-style-type: none"> Males = 255 -332 µg/d Females = 210 – 260 µg/d M + F = 251 – 398 µg/d <p><u>High Intake (97.5th pctl):</u></p> <ul style="list-style-type: none"> Males = 662 µg/d Females = 638 µg/d M + F = 412 – 1,795 µg/d 	<p><u>Food:</u> Mean = 0.26 mg/d (86/7 NDNS) 97.5th pctl = 0.49 mg/d</p> <p><u>Supplements:</u></p> <ul style="list-style-type: none"> Up to 0.50 mg in OTC supplements for males (OTC, 2001) Up to 0.80 mg in OTC supplements for females (sales data) <p><u>Estimated maximum intake:</u></p> <ul style="list-style-type: none"> 0.99 mg/d for males 1.29 mg/d for females <p>No potential high intake groups have been identified.</p>	<p><u>Intake Assessment – U.S.:</u> It is not possible to determine intakes of folic acid only. Survey data do not distinguish between food folate and folic acid added as a fortificant or taken as a supplement.</p> <p><u>Food</u> (included fortified ready-to-eat cereals): Highest 95th pctl.: Females 30-50 yr = 438 µg/d</p> <p><u>Food + Supplements (excluding pregnant women for whom folate supplements are prescribed):</u> Highest 95th pctl: Females 30-50 yr = 983 µg/d</p> <p><u>Intake Assessment – Canada:</u> The contribution of ready-to-eat cereals is expected to be lower because the maximum amount of folic acid that can be added to breakfast cereal is 60 µg/100g.</p> <p>It would be possible to exceed the UL of 1,000 µg/d of folic acid through the ingestion of fortified foods, supplements, or both.</p>
Discussion	<p><u>Risk Characterization:</u> 97.5th pctl. intakes for folate from dietary sources around 500 µg/d have been reported, the higher data for Austria are likely from all sources, including supplements.</p> <p>Data for the 2nd Dutch Nat'l Food Consumption Survey on supplement use indicated that 97.5th pctl and maximum intake is 400 and 800 µg, respectively.</p> <p>Regular supplements on the market usually contain 400 – 500 µg folic acid.</p> <p>In some European countries such as the UK cereals and breads are fortified with folic acid contributing 25-100 µg per serving.</p>	<p><u>Establishment of Guidance Level:</u> A general consistency of data indicates that supplementation with ≤ 1 mg/d folic acid does not mask vitamin B-12-associated anemia in the majority of patients, whereas supplementation with ≥ 5 mg/d does. The effects of doses between 1 and 5 mg/d are unclear.</p>	<p><u>Risk Characterization:</u> In the US, the intake of folate is currently higher than indicated because enriched cereal grains in the U.S. food supply, to which no folate was added previously, are now fortified with folate. The FDA estimated that the 95th pctl of folate intakes for males aged 11 to 18 years would be 950 µg of total folate at this level of fortification; this value assumes these young males would also take supplements containing 400 µg of folate. The 95th pctl for all other groups (excluding pregnant women) would be lower, and folic acid intake would be lower still.</p> <p>Using a different method of analysis, FDA estimated that those who follow the Food Guide Pyramid and consume cereal grains at the upper end of the recommended range would obtain an additional 440 µg of folate under</p>

	<p>Subjects at risk for too high folic acid supplementation are those with an undiagnosed vitamin B12 deficiency and other conditions associated with cobalamin malabsorption.</p> <p>Figures on prevalence of PA in W-Europe vary between 1.2/1000 in the UK and 1.98.</p> <p>Recent data show a high prevalence (ca 25%) of marginal cobalamin deficiency in elderly but not or hardly associated with hematological abnormalities.</p>		<p>fortification regulations. Those who eat other fortified foods (cookies, crackers) might ingest a comparable amount of folic acid.</p> <p>By either method of analysis and with the assumption of regular use of an over-the-counter supplement that contains folate (ordinarily 400 µg/dose), it is unlikely that intake of folate added to foods or as supplements would regularly exceed 1000 µg for any group.</p>
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Context Paper

ANNEX 7. National model comparison: Intake assessment

Table 13. Iodine comparison

	EU-SCF (2002)	UK-EVM (2003)	US-IOM (2001)
ULs	<p>Adults = 600 µg/d Children 1 – 3 yr = 200 µg/d Children 4 – 6 yr = 250 µg/d Children 7 – 10 yr = 300 µg/d Children 11 – 14 yr = 450 µg/d Children 15 – 17 yr = 500 µg/d</p>	<p><u>ULs:</u> None provided</p> <p><u>Guidance levels:</u> A supplemental intake of 0.5 mg/d in addition to the iodine in the diet (equivalent to 0.003 mg/kg bw in a 60 kg adult) would not be expected to have any significant adverse effects in adults.</p>	<p>Adults ≥ 19 yr = 1,100 µg/d Adolescents 14 – 18 yr = 900 µg/d Children 1 – 3 yr = 200 µg/d Children 4 – 8 yr = 300 µg/d Children 9 – 13 yr = 600 µg/d</p>
Intake Estimates	<p><u>Germany</u> -- Mean intakes of supplement users:</p> <ul style="list-style-type: none"> • Males = 124 µg I/d • Females = 102 µg I/d <p><u>Great Britain</u> -- 97.5th pctl intakes from all sources:</p> <ul style="list-style-type: none"> • Males = 434 µg/d • Females = 359 µg/d • Young children aged 1½ - 4 ½ y (high milk consumers in winter) = 247 µg/d - 309 µg/d <p>Data suggest that some pre-school children are likely to have intakes exceeding the JECFA PMTDI.</p>	<p><u>Food:</u> Mean = 0.22 mg/d (1986/7 NDNS) 97.5th pctl = 0.43 mg/d</p> <p><u>Water:</u> <0.03 mg/d (estimated intake from 2 L water containing < 0.015 g/L)</p> <p><u>Supplements:</u> Up to 0.49 mg/d (sales data)</p> <p><u>Estimated maximum intake:</u> 0.43 + 0.03 + 0.49 = 0.95 mg/d</p> <p>Children are a potential high intake group, because iodine intakes in children are higher than those in adults due to higher milk consumption.</p>	<p><u>Intake Assessment:</u></p> <ul style="list-style-type: none"> • Normal diets are unlikely to supply more than 1 mg/day. • Intake of 10 g of 0.0001% iodized salt results in an intake of 770 µg/d. • Based on the Total Diet Study, the highest intake of dietary iodine for any group at the 95th pctl was 1 mg/d, which is equivalent to the UL for adults. • The iodine intake from the diet and supplements at the 95th pctl is approximately 1.15 mg/d, which is slightly higher than the UL.
Discussion	<p><u>Risk Characterization:</u> Intakes of iodine from all sources in adults are unlikely to exceed the UL.</p> <p>In the UK where intakes are relatively high, the 97.5th pctl intake in men is 434 µg/d. In children (1 ½-4 ½ yr), iodine intakes may vary from 87-309 µg/d, mostly from milk. The UK COT considered that the intake of iodine from cow's milk is unlikely to pose a risk to health in children who are high consumers. The SCF agrees with this and notes that an UL is not a threshold of toxicity but may be exceeded for short periods without an appreciable risk to the health of the individuals concerned.</p> <p>Ingestion of iodine-rich algal products, particularly dried products, can result in dangerously excessive iodine intakes.</p>	<p><u>Establishment of Guidance Level:</u> It is possible that some consumers of foods with high levels of iodine, particularly children, may occasionally exceed this guidance level from normal dietary sources, but compensatory mechanisms exist and allay concerns for this potentially vulnerable groups.</p>	<p><u>Risk Assessment:</u> For most people, iodine intake from usual foods and supplements is unlikely to exceed the UL.</p>

ANNEX 8

2

**NATIONAL MODEL COMPARISON: SCIENTIFIC REVIEW OF DATA ON
4 VITAMIN A AND BONE DENSITY**

6 The tables are listed below and were developed by WHO staff to facilitate an
understanding as to how and in what ways three existing national/regional nutrient risk
8 assessment models are similar or differ in their considerations of scientific literature
related to vitamin A and bone density. This comparison may not be comprehensive, but
10 it may be of some interest to workshop participants.

Context Paper

ANNEX 8. National model comparison: Scientific review of data on vitamin A and bone density

Table 1. Summaries from references used, by workgroup

Reference	EU–SCF ^a (2002)	UK-EVM ^b (2003)	US-IOM ^c (2001)
Nieman C and Obbink HJK, 1954. The biochemistry and pathology of hypervitaminosis A. Vitamin Horm 12: 69 – 99.	As reviewed in Hathcock et al. 1990), Vitamin A doses (up to 13,500 µg RE per animal) have been shown to lead to bone fragility and spontaneous fractures.		
Leelaprute V et al., 1973. Hypervitaminosis A in rats. Varying responses due to different forms, doses, and routes of administration. Archives of Pathology 96, 5-9.		Gross bone lesions characterized by resorption of parts of pelvis, fibulae and scapulae with bone thinning were observed in growing female rats treated with 7500-22,500 µg RE/d vit A as palmitate or retinol for 17 days. Soft tissue calcification also occurred. Doses given either orally or by intraperitoneal injection. The latter associated with greater retinol toxicity, though not with vitamin A palmitate.	
Dhem A and Goret-Nicaise N, 1984. Effects of retinoic acid on rat bone. Fd Chem Toxic 22: 199 – 206.	Histopathological changes in animal bone following very high vitamin A doses (up to 13500 µg RE per animal) have been shown to lead to bone fragility and spontaneous fractures in rats.		
Freudenheim JL et al., 1986. Relationships between usual nutrient intake and bone-mineral content of women 35-65 years of age: Longitudinal and cross-sectional analysis. Am J Clin Nutr 44:863-876.	Measured bone mineral content in 4 year clinical trial in women receiving or not receiving calcium supplements. Highly significant effect of vitamin A at ulna only. Hard to interpret as seems due to single individual with very high intake of vitamin A (4300 µg RE) and who showed a rapid bone loss.	4 year clinical trial in 99 women aged 35-60 given either calcium supplement or placebo. Evaluated effect of usual intakes of energy and 14 nutrients on single-photon absorptiometric measures of mineral content in arm bone. There was an inverse correlation between vitamin A and rate of change in ulna bone mineral content in post-menopausal women of treatment group. In a single patient receiving a high supplemental dose (average intake 4392 µg RE/d), bone loss was very rapid with no other apparent reason.	The authors evaluated the correlation between mean 3-yr vitamin A intakes ranging from approximately 2-3 mg/d and rates of change in BMD in 82 women, 35 to 65 years of age (17 pre- and 67 postmenopausal). No consistent relationship between vitamin A intake and rate of bone mineral content. The single subject who showed rapid bone mineral loss with very high vitamin A also appeared to have consumed large amounts of other micronutrients as well, obscuring the significance of this relationship. The study also suffers from a small sample size in each of the four key groups making correlations of potential nutritional or pathological importance indeterminate.

Continues

^a Scientific Committee on Food/European Food Safety Authority, EC

^b Expert Group on Vitamins and Minerals, UK

^c Institute of Medicine, USA

Reference	EU-SCF ^a (2002)	UK-EVM ^b (2003)	US-IOM ^c (2001)
<p>Frankel TL et al. 1986. Hypervitaminosis A and calcium-regulating hormones in the rat. J Nutr 116: 578-87.</p>		<p>Single oral dose of 82,000 µg RE/kg bw given to adult rats had no biologically active parathyroid hormone concentrations. Secretions of bioactive PTH not altered by incubation of rat thyroparathyroid complexes with retinol <i>in vitro</i>. 3 wk old rats given 15,000 µg RE 3 times a wk for 6 wk had higher osteoclast numbers and lower osteoid than in controls. Serum bioactive PTH was not detectable and serum 25-hydroxyvitamin D was significantly lower than in controls. At 7500 µg RE 3 times a wk for 3 wk, serum bioactive PTH was suppressed to undetectable levels but no effect on serum 25-hydroxyvitamin D. Serum calcium and 25-hydroxyvitamin D were lower in vitamin D intoxicated rats which were also given 7500 µg RE 3 times a week. Authors suggested that skeletal changes caused by high levels of vit A were independent of the effects on PTH but could be caused by changes in vit D metabolites. However these pathological changes could be modified by secondary changes in calcium metabolism and in the metabolism of calcium-regulated hormones.</p>	
<p>Hough S et al. 1988. Effects of hypervitaminosis A on the bone and mineral metabolism of the rat. Endocrinology 122:2933-9.</p>		<p>Young rats (100 g) treated with 3000 or 7500 µg RE/d retinyl palmitate for 21 days by stomach tube. Tibial histomorphometry revealed increased bone resorption (increased osteoclast size and number) and reduced bone formation. There was a paucity of trabecular surfaces covered with osteoid. Spontaneous limb fractures and increased skeletal turnover (as measured by serum alkaline phosphatase and urinary hydroxyproline excretion) were also observed in high dose group. Serum calcium and magnesium levels were unremarkable but serum phosphorus levels were significantly elevated in the control animals. Circulating levels of potent bone resorbers, PTH, 1,25-dihydroxyvitamin D and 25-OH vitamin D were comparable suggesting that vitamin A was having a direct effect on bone.</p>	
<p>Biesalski HK, 1989. Comparative assessment of the toxicology of vitamin A and retinoids in man. Toxicology 57: 117-161.</p>	<p>Several isolated cases of skeletal problems in children with severe hypervitaminosis A have been reported and were reviewed in this article. Bone symptoms involve a decrease in density, osteoporotic changes and cortical thickening of the long tubular bones,</p>		

Reference	EU-SCF ^a (2002)	UK-EVM ^b (2003)	US-IOM ^c (2001)
	leading to retarded growth.		
Sowers MF and Wallace RB, 1990. Retinal, supplemental vitamin A and bone status. J Clin Epidemiol 43: 693-699.	No relationship between vitamin A intake or serum retinol concentrations and radial bone mass or fracture history in 246 postmenopausal women.	Vit A intake, serum retinol, radial bone mass and fracture history evaluated in 246 postmenopausal women. More than 36% used a vitamin A supplement, with 8% using a supplement containing >2000 µg RE/d. No relationship between radial bone mass and fracture history and vitamin A or serum retinol. No statistically significant relationship between serum retinol and bone mass after adjusting for factors associated with bone mass such as age, when population was stratified by supplement use. When serum retinol was divided into tertiles, no relationship with bone mass when adjusted on age, muscle area, and use of thiazide anti-hypertensives. Study had inadequate power to test an association between bone mass and vitamin A intakes > 2000 ug RE/day. 36% of the population were aged <60 y and were likely to be heterogeneous w/r to estrogen depletion bone loss; the site where bone mass was measured (central radius) is considered less responsive to change.	
Scheven BA and Hamilton NJ, 1990. Retinoic acid and 1,25-dihydroxyvitamin D3 stimulate osteoclast formation by different mechanisms. Bone 11, 53-59.	Retinoic acid stimulates osteoclast formation and bone resorption.		
Hathcock J et al. 1990. Evaluation of vitamin A toxicity. AJCN 52: 183-202.	Histopathological changes in animal bone following high vitamin A doses (up to 13,500 µg RE per animal) were reviewed.		
Johnell O et al. 1992. The apparent incidence of hip fractures in Europe: A study of national register sources. Osteoporosis Internat. 2: 298-302.		MEDOS study group – found that hip fracture rates varied across Europe being 11- and 7-fold higher for women and men in N. Europe than in S. Europe particularly in Sweden and Norway. The difference in European rates was sufficiently marked that fracture rates were higher in Swedish men than in Swiss or English women. The difference in incidence was higher between countries than between sexes suggesting that an important genetic or environmental factor was involved. Known risk factors were not thought to explain the finding.	

Reference	EU-SCF ^a (2002)	UK-EVM ^b (2003)	US-IOM ^c (2001)
Melton LJ. 1995. Epidemiology of fractures. In: Osteoporosis: Etiology, Diagnosis, and management. 2 nd Ed. Lippincot-Raven.		Hip fracture rates were higher in Scandinavia than in comparable populations in N. America. When dietary patterns in Europe were compared in different European towns, retinol intakes were 6-fold higher in Scandinavia compared to S. Europe.	
Kindmark A et al., 1995. Inhibitory effects of 9-cis and all-trans retinoic acid on 1,25(OH) ₂ vitamin D ₃ -induced bone resorption. Calcif Tissue Int 57, 242-244.	Retinoic acid stimulates osteoclast formation and bone resorption.		
Houtkooper LB et al., 1995. Nutrients, body composition and exercise are related to change in bone mineral density in premenopausal women. J Nutr 125: 1229-1237.	Measured annual rates of change in bone density in 66 premenopausal women taking calcium supplements. They had a slight loss of bone during 18 months of study (within measurement error of techniques involved). At one of measured sites was an indication that high intakes of vitamin A were associated with less loss of bone.	Relationships among nutrient intakes and rates of change in bone mineral density measured in 66 premenopausal women taking calcium supplements. Nutrients were not significant variables in regression models predicting bone mineral density slopes at any femur site, but retinol intake was associated with decreased bone mineral density.	Longitudinal study of 66 women (28-39 y) showed vitamin A intake significantly associated with increased annual rate of change in total body BMD. The mean rate of change in total body BMD over the 18 month study was negative although several sites (lumbar spine, trochanter, and Ward's triangle) showed small positive slopes. The estimated mean intake of preformed vitamin A from diet was 1220±472 (SD) µg/d. The estimated vitamin A intake from provitamin A carotenoids was 595±352 (SD) µg/d. Multivariable regression models showed the slopes for vitamin A and carotene were both positive with r ² values of approx 0.3. While the positive association between vit. A and carotene intake and change in BMD may not be causal, the data provide evidence that vitamin A does not adversely affect premenopausal bone health within this range of intake.
Lapadula G et al., 1995. Early ultrastructural changes of auricular cartilage and synovial membrane in experimental vitamin A induced osteoarthritis. J. Rheumatol 22: 1913-1921.	Bone lesions (histopathological changes in animal bone) leading to bone fragility and spontaneous fractures have been described in the rabbit following intra-articular injection of 30,000 µg RE of retinyl palmitate.		
Theiler R et al. 1995. Can Vitamin A (retinol) and synthetic retinoids influence bone metabolism? Three case reports. Challenges Modern	A brief report by the authors suggested that chronic vitamin A intoxication in adults might be related to osteoarthritis.		

Reference	EU-SCF ^a (2002)	UK-EVM ^b (2003)	US-IOM ^c (2001)
Med 7: 393-397.			
Saneshige S et al., 1995. Retinoic acid directly stimulates osteoclastic bone resorption and gene expression of cathepsin K/OC-2. <i>Biochem J</i> 309: 721-724.	May have mechanistic explanation related to a possible effect of retinoic acid in regulating expression of genes since both osteoblasts and osteoclasts express RARs and RXRs..		
Melhus H et al., 1998. Excessive dietary vitamin A is associated with reduced bone mineral density and increased risk for hip fracture. <i>Ann Intern Med</i> 129: 770-778.	<p>Nested case control for 247 women with a hip fracture and 873 controls of Swedish women in a mammography study cohort showed dose dependent association between dietary intake of pre-formed retinol and higher risk of hip fracture. Both uni- and multi-variate analysis showed a significant 1.5 – to 1.6-fold ↑ in risk per mg retinol consumed daily. An associated cohort study indicated that similar intakes of retinol reduced bone density. The risk for hip fracture is doubled for retinol intake greater than 1500 µg RE/d as compared to intakes less than 480 µg RE/d. Based on univariate analysis, the RR at intakes of 500 – 1000 µg/d, 1000 – 1500 µg/d, and >1500 µg/d, compared with intakes <500 µg/d, were 0.93, 1.27, and 1.95, respectively. The intake was from dietary sources and it is possible that the effects may have arisen from unrecognized confounding; however, the mechanistic data on the actions of retinoic acid on bone metabolism are consistent with the reported relationship.</p> <p>This study indicates an ↑ risk of bone fracture over an intake range similar to that normally consumed from food or supplements.</p>	<p>Data from two studies: a randomly selected cross-sectional study involving 175 women (28-74 yr) and a nested case-control study involving 247 women (40-60 yr) who had first hip fracture 2-64 months after enrollment and 873 age-matched controls from a mammography study cohort. No reported use of vitamin A supplements. Intake of pre-formed retinol was negatively associated with bone mineral density. For intake >1500 µg RE/d compared with less than 500 µg/d, bone mineral density was reduced by 10% at femoral neck, 14% at lumbar spine and 6% for total body. Risk for hip fracture was doubled. For every 1000 µg ↑ in daily intake, risk of hip fracture ↑ by 68%. Smoking was a confounder. Possibility of information bias resulting from questioning case-patients after hip fracture. Data on thyroid hormone therapy and family history of osteoporosis were not available. Could not rule out confounding influences of an unidentified dietary factor; high degree of random error in assessment of retinol intake might lead to underestimation of true risk of hip-fracture.</p>	<p>Cross sectional (175 women) and nested case control (247 cases and 873 controls) studies in women suggest a dose-dependent increase in risk of hip fracture with increasing increments of vitamin A. Chronic intake of 1.5 mg/d of preformed vitamin A associated with osteoporosis and increased risk of hip fracture. A cross-sectional multivariate regression analysis in 175 Swedish women 28 to 74 y of age showed a consistent loss in BMD at four sites and in total BMD with increased preformed vitamin A intake. Numerous nutritional and non-nutritional exposures were assessed allowing substantial control of potential confounders. With use of stratified estimates of retinol intake in regression analysis, BMD increased with each 0.5 mg/d increment in intake above a reference intake of less than 0.5 mg/d until intakes exceeded 1.5 mg/d. Above this level, mean BMD decreased markedly at each site. It is not clear whether the findings are equally applicable to pre- and postmenopausal women.</p> <p>The second part was a nested case control study on the risk factors for hip fracture. Cases were mostly postmenopausal women with first hip fracture within 2-64 months after entry into the large cohort study, or 5 to 67 months after mid-point of the recalled dietary assessment. Four matched control subjects were selected for each case. Logistic regression showed a dose-dependent increase in risk of hip fracture with each 0.5 mg/d increment in reported retinol intake above 0.5 mg/d baseline. Odds ratio was 2.05 at intakes >1.5 mg/d.</p>

Reference	EU-SCF ^a (2002)	UK-EVM ^b (2003)	US-IOM ^c (2001)
Cohen-Tanugi A and Forest N, 1998. Retinoic acid suppresses the osteogenic differentiation capacity of murine osteoblast-like 3/A/1D-1M cell cultures. Differentiation 63: 115-123.	Retinoic acid inhibits osteoblast differentiation.		
Cruz JA et al. 1999. Intake of vitamins and minerals. Eur J Clin Nutr 45(3):121-138.		When dietary patterns in Europe were compared in different European towns, retinol intakes were 6 fold higher in Scandinavia compared to Southern Europe.	
Rohde CM et al., 1999. Vitamin A antagonizes the action of vitamin D in rats. JNutr 129:2246-2250.	Molecular interaction of A and D could be responsible for antagonism of vitamin A towards action of vitamin D in rats.		Chronic excessive vitamin A intake has been shown to lead to bone mineral loss in animals making such a consequence in humans biologically plausible.
Binkley N and Krueger D. 2000. Hypervitaminosis A and bone. Nutr Rev 58: 138-144.	Data suggest that excessive vitamin A may increase bone resorption and decrease bone formation		
Ballew C et al. 2001. High serum retinyl esters are not associated with reduced bone mineral density in the Third NHANES1988-1994. J Bone Mineral Res 16: 2306-2312.	No association between serum retinyl esters and reduced bone density in UK's 1988-94 National Health and Nutrition Survey although serum retinyl esters reflect recent intake and are not a good indicator of vitamin A status.	Association between fasting serum levels of retinyl esters and bone mineral density was studied in 5790 non-pregnant participants ≥ 20 y. Using multiple regressions, there were no significant associations between fasting serum retinyl esters and BMD as assessed at the femoral neck, trochanter, intertrochanter and total hip.	<i>(Availability at time of report???)</i>
Johansson S and Melhus H, 2001. Vitamin A antagonizes calcium response to vitamin D in man. J Bone Mineral Res 16: 1899-1905.	Data from a trial in 9 healthy volunteers receiving 8250 μ g RE vitamin A or 2 μ g of 1,25(OH) ₂ D ₃ vitamin D, or both, indicated that retinyl palmitate antagonizes rapid calcium response to physiological levels of vitamin D.		<i>(Availability at time of report???)</i>
Kawahara TN et al., 2002. Short-term vitamin A supplementation does not affect bone turnover in men. J Nutrit 132: 1169-1172.	No changes in serum markers of skeletal turnover in 40 males given 7.6 mg vitamin A retinyl palmitate daily for 6 weeks. These measures were considered by authors to be sensitive markers of bone turnover. Could not determine whether long-term vitamin A supplementation might have adverse skeletal effects.		<i>(Availability at time of report???)</i>
Feskanich D et al., 2002.	Nurses' Health study in the U.S. reported increased	Nurses Health Study – related high vit. A intake from	<i>(Availability at time of report???)</i>

Reference	EU-SCF ^a (2002)	UK-EVM ^b (2003)	US-IOM ^c (2001)
<p>Vitamin A intake and hip fractures among postmenopausal women. JAMA 287: 47-54.</p>	<p>risk of hip fractures in >72000 women studied for 18 years that was attributable to total retinol intake but not to β-carotene. Significant elevated RR in quintiles with intakes >3000 and >2000 $\mu\text{g RE/d}$ (1.48 and 1.89) compared to lowest quintiles. Multivariate analyses reveal highly significant trends for total intakes of vitamin A and food + supplement but not for food only.</p> <p>Data divided into quintiles for total vitamin A and for retinol intake. Significant trends apparent between RR and intakes from food and supplements of total vitamin A and retinol. A significant \uparrow for the 2 highest quintiles compared with the lowest. Trend analysis for retinol from food and supplements compared with food only indicates an important contribution from supplements and this would be less likely to be affected by dietary confounding than the Melhus et al. study.</p>	<p>food and supplements and hip fracture for >72,000 post-menopausal women aged 34-77 y from 1980-1998. 603 hip fractures occurred after low or moderate trauma. After controlling for confounding factors, women in highest quintile of vitamin A intake ($\geq 3000 \mu\text{g RE/d}$) had a significantly elevated relative risk for hip fractures compared to women in lowest quintile of intake ($< 1250 \mu\text{g RE/d}$) (RR 1.48). Intake risk primarily attributable to retinol. Association of retinol with hip fracture was reduced in women taking postmenopausal estrogens. β-carotene did not contribute to fracture risk. Women currently taking vitamin A supplements had \uparrow 40% risk of hip fracture (N.S.) compared to those not taking supplements. Among women not taking supplements, retinol from food was significantly associated with fracture risk. Long term intake of diet high in retinol may promote the development of osteoporotic hip fractures in women. (Study cohort primarily white women).</p>	
<p>Promislow et al. 2002. (REF info not GIVEN).</p>		<p>570 women and 388 men, 55 – 92 yr. Dietary intake by questionnaire for 4 yr. Four years later measured BMD and bone loss measures. Retinol intake was associated with decreased BMD and increased bone loss at intakes $> 840 \mu\text{g RE/d}$ even after adjustment for possible confounders. Supplemental retinol use also associated with decreased BMD and increased bone loss.</p>	<p><i>(Availability at time of report???)</i></p>

Concept Paper

ANNEX 8. Summary of the workgroups' scientific review of data on vitamin A and bone density

Table 2. Conclusions, risk characterization, and recommendations concerning vitamin A and bone density, by workgroup

Basis of Comparison	EU–SCF^a (2002)	UK-EVM^b (2003)	US-IOM^c (2001)
Conclusions: scientific evidence	<p>Risk for hip fracture in Swedish women (Melhus 1998) is doubled for retinol intake > 1500 ug RE/day. Mechanistic data on actions of retinoic acid on bone metabolism are consistent with this. Similar dose response relationship reported by Feskanich from a large cohort in US studied over a period of 18 years. Both major epidemiologic studies indicate an increased risk of bone fracture over an intake range similar to that normally consumed from food and supplements.</p> <p>The lowest doses reported to produce adverse effects on bone density/fracture are 1500 µg RE/d. (Trend analyses do not show a threshold).</p>	<p>Recent epidemiological data have indicated that post-menopausal women with long-term high intakes of vitamin A have an increased risk of hip-bone fracture. Other supporting epidemiological data have indicated that this effect may occur in men as well as in women. These findings are supported by animal data, which have indicated that retinol has a direct effect on bone, possibly via interaction with D and an effect on parathyroid hormone and therefore calcium metabolism.</p>	<p>Four studies provide interpretable evidence relating changes in BMD and risk of hip fracture with variation in dietary intake of preformed A (Freudenheim et al., 1986; Hautkooper et al., 1995; two studies from Melhus et al., 1998). The studies are distinguished by their well described study designs and populations, adequate dietary intake estimates, and accurate methods for measuring BMD at multiple sites.</p> <p>The findings from these studies are provocative but conflicting and therefore are not useful for setting a UL for vitamin A.</p>
Conclusions: upper limits (as related to adverse bone effects)	<p>Determining an upper level for preformed vitamin A is difficult, because any proposal has to take into account the narrow margin between the population reference intake and the intakes associated with adverse effects. The findings on bone density and the risk of fracture were reported at lower daily intakes than other adverse effects. However, it was considered that the currently available data did not provide sufficient evidence of causality, and were not appropriate for establishing a tolerable upper level.</p>	<p>It is not possible to establish a SUL for vitamin A. Two threads of evidence regarding potential adverse effects of vitamin A: teratogenicity and risk of bone fracture. These suggest different levels of intake at which adverse effects may occur. Both of these ranges appear to overlap with dietary intakes of vitamin A.</p>	<p>Bone changes were not used as endpoint because of the conflicting findings and the lack of other data confirming the findings of Melhus et al. (1998).</p>

Continues

^a Scientific Committee on Food/European Food Safety Authority, EC

^b Expert Group on Vitamins and Minerals, UK

^c Institute of Medicine, USA

Basis of Comparison	EU–SCF^a (2002)	UK-EVM^b (2003)	US-IOM^c (2001)
Risk characterization	<p>Because the TUL may not adequately address the possible risk of bone fracture in particularly vulnerable groups, it would be advisable for postmenopausal women, who are at greatest risk of osteoporosis and fracture, to restrict their intake to 1500 µg RE/d.</p> <p>Because the current intakes may exceed the TUL, careful consideration should be given to the appropriateness of the enrichment of human foods with vitamin A, and to the potential effects on human exposure of the addition of vitamin A to animal feed.</p>	<p>In studies of long-term dietary intake, vitamin A has been associated with decreased bone density and increased risk of hip fracture. This finding is supported by investigations in laboratory animals in which vitamin A has been reported to affect calcium metabolism as well as to have a direct effect on bone. Other supportive epidemiological data suggest that the effect may also occur in men since fracture risk is increased in both males and females in Scandinavian countries, where retinol intake is also higher than in Southern Europe.</p> <p>The risk of hip fracture is a continuous graded response associated with exposure levels that include average dietary intakes. It is not possible to identify an intake that is without some degree of risk. However, the available data indicate that total intakes greater than 1500 µg RE/d may be inappropriate. This corresponds to 25 µg RE/kg bw/d in a 60 kg adult.</p> <p>Data on retinol intakes from food and supplements suggest that high level consumers of liver and liver products and/or supplements may exceed intakes at which adverse effects have been reported in the literature. It should also be noted that dietary supplements may contain 20-100% more vitamin A than is stated on the label, due to the practice of using ‘overages’ within the food supplements industry to ensure that the product contains no less than the stated content of the vitamin throughout its shelf life. This may be particularly important given that the effect on fracture risk appears to be a graded response, with the risk of fracture increasing with increased intake.</p>	
Recommendations	<p>The possible link between bone density, the risk of fracture and vitamin A intake should be reviewed when further data become available.</p> <p>Ideally, resolution of the issue of bone mineral density and the risk of fracture should be studied by a prospective study, in which the effects of age on the risk, and also of confounding variables are taken into account in the study design. It is recognized that such a study would require a very large population and prolonged treatment and follow up.</p>		<p>More research is needed to clarify whether chronic vitamin A intake, at levels that characterize upper-usual intake ranges for many American and European populations, may lead to loss in BMD and consequent increased risk of hip fracture in certain population groups, particularly among pre- and postmenopausal women.</p>

ANNEX 9

2

COMMENTS TO NOVEMBER 2004 BACKGROUND PAPER

4

In November 2004, FAO/WHO made available a background paper that requested
comment on the development of a scientific collaboration to create a framework for risk
assessment of nutrients and related substances. In response to the questions asked in the
background paper, comments from 16 individuals/organizations were received. These
comments have been made available to workshop participants so that they may take them
into account. They are also posted on the public FAO/WHO website with the
background paper (http://www.who.int/ipcs/highlights/nutrientproject_april05/en/).

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In summary, the commenters identified their affiliations as government (4), industry (4),
academic (2), professional association (1), non-profit organization (4), and consumer (1).
The nature of the comments was broad with some supporting the work by offering
specific suggestions as to how scientific issues may be addressed, for example, a
suggested focus on dose-response relationships, refinement of nomenclature, and the
possibility that different nutrient forms should be viewed as different nutrients. Others
expressed the need for caution in moving from a model derived for non-nutrients to one
for nutrients and related substances or the concern that principles for hazardous chemicals
cannot be applied to nutrients. A number of comments focused on terminology and its
importance both in considering nutrition-related paradigms and in choice of wording and
inclusiveness of definition. The definition of 'hazard' or harm or risk was highlighted by
several as potentially problematic. The comment from the professional association
suggested that a difficult task for workshop participants would be developing a
quantitative metric that can include and weigh the different aspects of concern that go
into establishing risk.. One commenter specified factors that in the judgment of the
commenter had been omitted from consideration by the background paper, for example,
the body's demand for nutrients according to its momentary health status. One comment
included editing revisions for the background paper for the purposes of improving scope,
focus and precision. While there are no plans to revise or reissue the background paper,

2 this input can be considered by workshop participants should they choose to incorporate any text or concepts from the background paper (or related context paper) into the final report.