

## Opportunity to Respond to Questions

This form provides the opportunity to respond to the questions posed in the Background Paper: Joint FAO/WHO Development of a Scientific Collaboration to Create a Framework for Risk Assessment of Nutrients and Related Substances.

Responses may be typed in to the form directly or appended as an 'attachment' to each question (use 'Upload file'). Fields with asterisks are required. Responses and your name/organization will be available for public viewing.

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### *Name/Organization*

**Title**

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**Today's Date \***

10/12/2004

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### *Question 1*

The Background Paper discusses the possibility that hazard identification and hazard characterization

have global relevance, while exposure assessment and risk characterization are relevant to populations. If such a conceptual framework for the four steps is appropriate, then scientific principles could be organized and considered along these same lines.

**Question 1a: Is the distinction between global relevance and population relevance for the four risk assessment steps a meaningful consideration for the purposes of developing an international nutrient risk assessment approach? (Please indicate why or why not)**

Yes the distinction can be meaningful but only in the sense of distinguishing between two parts of one functional whole. The GRH and PRR are just two different tools to achieve the same goal – which is defined elsewhere by WHO as ‘to maximise health’.

The following comments are made in the cautious hope that it might be possible to expand the framework for non-Nutrient risk assessment (nNRA) to include Nutrient risk assessment (NRA) as well.

The problem arises from the essentially different nature of a non-Nutrient and Nutrient with respect to human physiology and risk management.

A risk assessment framework for chemicals-in-general for the purpose of maximising health could utilise the existing GRH/PRR framework provided it incorporated three essential modifications.

- (a) add new data category/s to accommodate ‘risk due to insufficient dose’ of Nutrient;
- (b) ensure GRH informs PRR and PRR informs GRH in a continuous improvement cycle; and
- (c) interpret GRH and PRR in terms of the actual physiological processes of ‘health’ that are affected by the presence of absence of certain chemicals.

Hazards are identified from Population inputs/outcomes and the hazard is characterised in terms of Globally aggregated Population data as well as being characterised by the Physiological processes that are involved. Ongoing research should aim to develop the understanding of how chemicals interact to exacerbate or counteract the normal healthful physiology.

The Global data for each chemical (GRH and accompanying Physiological characterisation) then informs local decision-making as to the PRR. The PRR is interpreted by reference to knowledge about the quantity of risk (GRH) as well as the quality of the risk (Physiology) which enables a better understanding of the actual risk that any chemical poses as well as a mechanism by which to comprehend the interaction of different chemical combinations.

**Question 1b: If so, please provide specific suggestions about how best to further articulate and make good use of the differences in identifying the scientific principles for nutrient risk assessment.**

**GLOBALLY**

- (1) The GRH is set by aggregating Population data in terms of risk of exposure and risk of adverse health effect.
- (2) All chemicals are basically characterised according to their known and presumed physiological pathways of effect.
- (3) Research focuses on characterising the physiology of those chemicals that have been given the highest GRH classification and this should include studying how other chemicals affect the effect of those high hazard chemicals (i.e. positively; benignly; or negatively with respect to good health);
- (4) The Global set of GRH (and accompanying physiological characterisations) is continually improved (verified as to accuracy and deepened as to detail) by analysing and aggregating Population information as well as by specific research at (3).

**LOCALLY**

- (A) Populations analyse the local incidence of and exposure to specific chemicals and chemical combinations
- (B) The chemical situation is basically assessed by consulting the latest GRH data set of chemicals and their accompanying physiological characterisation and the PRR dataset is basically constructed.
- (C) Research focuses on characterising the detailed physiology of those chemical combinations that might pose greatest risk to local health (and might coincide with Global research priorities). Local research informs the Global dataset.
- (D) Investment focuses on managing the risk due to chemicals of highest local significance and this includes specific chemical-based clean-up projects as well as general education of the community regarding risk minimisation (non-Nutrients) and health maximisation (Nutrients).
- (E) The local dataset of PRR (and accompanying physiological characterisations) is continually improved by analysing the relationship between health inputs (e.g. education and clean-up) and health outputs (reduced

exposure to chemical risk and reduced incidence of ill-health).  
(F) The local dataset informs the Global dataset.

Decision-makers at the Global and the local level are interpreting the same hazard and risk data but from slightly different perspectives.

The GRH considers the relationship between [specific chemicals; their global incidence; and their effect on human physiology in general]. The PRR considers the relationship between [specific chemicals; their local incidence; and their effect on human physiology in general and in the Population in particular].

Each party deals with the same set of general components (i.e. the same general human physiology; the same general set of chemicals; the same general human health environment). But each party concerns itself with a specific combination of individual components taken from the same general set (i.e. the physiological individuals of a Population; the local combination of chemical exposure; and the general local health environment).

All parties are functionally involved in the entire process of Risk analysis (assessment; management; communication) but each one functions at a different level and draws on specific detailed aspects of the common data bank.

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## Question 2

**Hazard identification and characterization involve a number of decision points that require scientific judgment in order to derive a UL. Please provide input as to how guidelines for these judgments can be developed for the following decision points:**

### Question 2a: Criteria for the evaluation of the quality and utility of relevant scientific evidence.

The UL for Nutrients is just an interesting case of a UL for non-Nutrients. The difference comes in characterising the LL (Lower level) for Nutrients below which a risk to health can be expected to occur.

The GRH for presence of non-Nutrients should be matched by a GRH for absence of Nutrients.

Quality of scientific evidence can be assessed on whether the:

- results are consistent with the explicitly available evidence (i.e. no unsubstantiated presumptions)
- conclusions are consistent with the results and the evidence
- dose-response relationship is reliably repeatable.

The 'evidence' includes whatever is contained in a specific report as well as that which is contained in the common bank of chemical and physiological risk assessment data as noted in Q1. above.

Utility of scientific evidence depends on its:

- relevance to the individual inquiry
- capacity to be aggregated into other banks of data
- capacity to be translated into practically measurable criteria.

Please see Q.4a. for an important example of erroneous UL that has been set on the basis of very poor quality scientific evidence.

### Question 2b: Extrapolation to various age/gender groups.

Findings can be extrapolated between age/gender/other groups in the sense that all groups are just specific examples of the human physiology in general.

Nevertheless all groups need to be specifically characterised in terms of dose-response and exact physiological processes.

Research should focus on those groups that are least well characterised

#### **Question 2c: Determination and use of uncertainty factors.**

Uncertainty factors arise from the lack of any specific characterisation of any chemical or population group.

The two-framework approach in (1) aims to reduce the incidence of unknown uncertainties because all risk assessments are guided by information coming concurrently from both the chemical side and the physiological side.

The two-framework approach also provides a context of background information to support any specific decision. Each decision is made by concurrent reference to the chemically-related issues and the physiologically-related issues

#### **Question 2d: Other**

Uncertainty is minimised by treating all parties as equal partners in an ongoing process of informed decision-making based on a common bank of shared data relating to both chemicals and physiology. Physiology should not be left at the Global level (page 15) of information but must be incorporated into Population-level decisions as well.

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### **Question 3**

**The conduct of exposure assessment and risk characterization also requires sound scientific principles that can be applied to the various decision points, including but not limited to compilation and collection of intake data and decision-making for summarizing the potential for harm.**

#### **Question 3a: Please provide input on general scientific principles relevant to the process of determining exposure for a nutrient or related substance.**

Quality of scientific evidence can be assessed on whether the:

- results are consistent with the explicitly available evidence (i.e. no unsubstantiated presumptions)
- conclusions are consistent with the results and the evidence
- dose-response relationship is reliably repeatable.

Utility of scientific evidence depends on its:

- relevance to the individual inquiry
- capacity to be aggregated into other banks of data
- capacity to be translated into practically measurable criteria.

#### **Question 3b: Please provide input on general scientific principles for the characterization of the severity and the degree to which intakes exceed the UL or other aspects of risk characterization.**

The Nutrient risk question is not so much in characterising the UL as in characterising the LL.

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## Question 4

The Background Paper reflects a 'thought process' and is intended to inform a longer process for the development of a technical expert workshop. Clearly the process will benefit from additional input.

**Question 4a: Please provide comments on other general factors or considerations that could be taken into account during the process of identifying principles for nutrient risk assessment.**

Example of poor quality scientific evidence - FLUORIDE in drinking water  
(attachment)

Q 4a.

There is need for regular independent review of the data to identify gaps and anomalies.  
For example:

FLUORIDE is now classified in the WHO 'Chemical safety of drinking water' (pp.7;11;13) with Arsenic as Essential Priority for risk reduction in global terms.

The text of 'Chemical safety' emphasises the hazard that Arsenic and Fluoride both pose to human health and the general hazard of chemicals consumed at low doses over prolonged periods of time

Yet in setting the Health Based Guideline Values (pp 63 etc) the document allocates a very low Value to Arsenic (10 micrograms per litre water; p. 63) and a relatively high Value to Fluoride (1.5 milligrams per litre water or 1.5ppm; p.70).

This discrepancy is not supported by any actual evidence in 'Chemical Safety' but refers (as does this draft 'Nutrient risk assessment' project) to related documents such as WHO 'Guidelines for drinking water standards' and NAP 'Dietary Reference Intakes for Calcium, Phosphorous, Magnesium, Vitamin D, and Fluoride' (1997).

However an examination of those documents does not reveal any scientifically credible evidence to support the idea that Fluoride is safe to consume at 1.5ppm.

On the other hand there is considerable published research reporting on the lack of Fluoride data.

For instance the pre-eminent 'Review of water fluoridation' by UK York University (McDonagh 2000) surveyed all relevant epidemiological research that had been conducted in the world between 1944 and 1999. It concluded that while water fluoridation might (i) reduce tooth decay in some people it might also (ii) cause adverse health and dental effects in others.

In 2002 the UK Medical Research Council (MRC UK 2002: 41-44) followed up the findings of the York Review by investigating priority areas for research and found the urgent need to:

1. Assess the different bio-availability of naturally-occurring against artificial fluorides such as silicofluorides and their rates of bio-accumulation;
2. Estimate lifetime intakes of fluoride and trends in fluoride exposure by individual groups;
3. Estimate the intake and effects of fluoride on children;
4. Further assess the impact of fluoridation on tooth decay including damage by fluorosis;
5. Monitor rates of dental fluorosis and its effect on the individual's self-image;
6. Assess the effect of fluoridation on social inequalities;
7. Undertake an updated analysis of 'other health' effects.

These findings are supported by the 1993 report of the US National Research Council which found 'inconsistencies in the fluoride toxicity data base and gaps in knowledge' warranting further research in 'fluoride intake and dental fluorosis as well as on bone strength and fractures and

carcinogenicity' (NRC US 1993:11).

These studies have still not been done.

On the other hand there is a considerable body of evidence showing that Fluoride may not be safe to consume at around 1.5ppm.

The following information is provided to illustrate the range of available evidence and has been sourced from Diesendorf M 2003, 'A kick in the teeth for scientific debate' Australasian Science vol. 24, no. 8, pp.35-37, September. .

- Clinically significant cases of skeletal fluorosis have been reported in at least nine papers from five countries when natural Fluoride concentrations are below 4 ppm and mostly below 2.5 ppm (3).

- On comparing hip fracture rates between fluoridated and unfluoridated communities there have now been 19 studies, and 11 of them show a higher rate of hip fractures in fluoridated communities (7). In particular, a recent epidemiological study, which examined the aged in six naturally fluoridated Chinese villages, hip fracture rates doubled at 1.5 ppm, and tripled at 4.3 ppm, when compared to the fracture rates at 1 ppm fluoride (8). This finding again suggests a very small (if any) safety margin for such a serious outcome. In Mexico, a linear correlation between the severity of dental fluorosis and the incidence of bone fractures in children has been observed (9).

- It is well known to biochemists that fluoride is highly active biologically, forming a strong hydrogen bond with the groups found in proteins and nucleic acids (10). In vitro experiments demonstrate that fluoride inhibits enzymes, and induces chromosome aberrations (11) and genetic mutations (12).

- Professor Anna Strunecka of Charles University in the Czech Republic has shown in laboratory experiments that fluoride in the presence of aluminum disrupts G-proteins (13). G-proteins take part in a wide variety of biological signaling systems, helping to control almost all important life processes.

- Animal experiments reveal that fluoride increases the uptake of aluminum into the brain at 1 ppm in the drinking water (14). Dr NJ Chinoy from Gujarat University, India, has found that higher doses of fluoride cause reproductive problems (15). Dr Z. Machoy, from the Pomeranian Academy of Medicine, Poland, points out that AIF3 activates several guanine nucleotides, mimicking the actions of some neurotransmitters and hormones. His group has performed computer modeling of how AIF3 attacks the biologically important GDP nucleotide (16).

- Research on aged human cadavers by Dr Jennifer Luke at University of Surrey has shown that fluoride concentrates in the pineal gland (17). Furthermore, in animal studies, she showed that this concentration is associated with the earlier onset of puberty. As a mechanism she makes the hypothesis that the increased fluoride concentration leads to the reduced production of melatonin (because fluoride is known to inhibit the enzymes needed to produce it) and that this in turn leads to an accelerated sexual maturation. This work dovetails with studies which have shown that girls in the US – one of the world's most heavily fluoridated countries – are reaching puberty earlier and earlier.

- Standard toxicological practices allow a 100 fold margin for potentially toxic chemicals. As adverse effects have been demonstrated at just 1ppm fluoride in water then a 100 fold margin implies a safe upper limit of 10micrograms per litre (i.e. equivalent to the HBGV for Arsenic).

1. e.g. Diesendorf M 1986, 'The mystery of declining tooth decay', Nature 322: 125-129; Diesendorf M, Colquhoun J, Spittle BJ, Everingham DN, Clutterbuck FW 1997, New evidence on fluoridation. Australian & New Zealand J. Public Health 21:187-190; Diesendorf M 1995, 'How science can illuminate ethical debates: a case study on water fluoridation', Fluoride 28(2): 87-104.

2. McDonagh M, et al. 2000, A Systematic Review of Public Water Fluoridation. ("The York Review"), NHS Center for Reviews and Dissemination, University of York, September.

3. e.g. Singh A, Jolly SS & Bansal BC, 1961, Skeletal fluorosis and its neurological complications, *Lancet* 1:197-2000; Jolly SS, Prasad S, Sharma R & Chander R, 1973, Endemic fluorosis in Punjab. I. skeletal aspect, *Fluoride* 6:4-18; Siddiqui AH, 1970, Neurological complications of skeletal fluorosis with special reference to lesions in the cervical region, *Fluoride* 3:91-96.
4. Diesendorf M, 1990, The health hazards of fluoridation: a re-examination, *International Clinical Nutrition Review* 10(2):304-321.
5. Diesendorf M & Diesendorf A 1997, Suppression by medical journals of a warning about overdosing formula-fed infants with fluoride, *Accountability in Research* 5:225-237.
6. Riggs BL, et al., 1990, Effect of fluoride treatment on the fracture rates in postmenopausal women with osteoporosis, *New England Journal of Medicine* 322:802-809.
7. See references listed in <http://www.SLweb.org/fluoride-bone.html>
8. Li Y, et al. 2001, Effect of long-term exposure to fluoride in drinking water on risks of bone fractures. *Journal of Bone and Mineral Research* 16(5):932-9.
9. Alarcon-Herrera MT, et al. 2001, Well water fluoride, dental fluorosis, bone fractures in the Guadiana Valley of Mexico. *Fluoride* 34(2): 139-149.
10. Emsley J, et al. 1981, An unexpectedly strong hydrogen bond: Ab initio calculations and spectroscopic studies of amide-fluoride systems. *Journal of the American Chemical Society* 103: 24-28.
11. Suzuki N, Tsutsui T. 1989, [Dependence of lethality and incidence of chromosome aberrations induced by treatment of synchronized human diploid fibroblasts with sodium fluoride on different periods of the cell cycle]. [Article in Japanese] *Shigaku*. 77(2):436-47.
12. Caspary WJ, et al. 1987, Mutagenic activity of fluorides in mouse lymphoma cells. *Mutation Research* 187(3):165-80.
13. Strunecka A & Patocka J, 1999, Pharmacological and toxicological effects of aluminofluoride complexes, *Fluoride* 32:230-242.
14. Varner JA, et al. 1998, Chronic administration of aluminum-fluoride and sodium-fluoride to rats in drinking water: Alterations in neuronal and cerebrovascular integrity, *Brain Research* 784: 284-298.
15. Chinoy, NJ, Narayana MV 1994, In vitro fluoride toxicity in human spermatozoa. *Reproductive Toxicology* 8(2):155-9.
16. Machoy Z 2002, Interactions between guanosine diphosphate (GDP) and aluminum fluoride (AlF<sub>3</sub>) (conference abstract), *Fluoride* 35:244-5.
17. Luke J 2001, Fluoride deposition in the aged human pineal gland, *Caries Research* 35:125-128.
18. Brunelle, JA & Carlos JP, 1990, Recent trends in dental caries in U.S. children and the effect of water fluoridation, *Journal of Dental Research* 69 (special edition): 723-727.

**Question 4b: Please provide other comments on the content of the Background Paper.**

Thank you for the opportunity to comment on this proposed project.