Journal of Toxicology and Environmental Health, Part A
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713667303

Toxicity Due to Excess and Deficiency

Peter J. Aggett [a]
[a] Emeritus Professor of Child Health and Nutrition, Parbold, Lancashire, United Kingdom

Online publication date: 14 January 2010

To cite this Article Aggett, Peter J.(2010) 'Toxicity Due to Excess and Deficiency', Journal of Toxicology and Environmental Health, Part A, 73: 2, 175 — 180
To link to this Article: DOI: 10.1080/15287390903340443
URL: http://dx.doi.org/10.1080/15287390903340443

Journal of Toxicology and Environmental Health, Part A, 73:175–180, 2010

ISSN: 1528-7394 print / 1087-2620 online
DOI: 10.1080/15287390903340443

Taylor & Francis
Taylor & Francis Group

TOXICITY DUE TO EXCESS AND DEFICIENCY

Peter J. Aggett

Emeritus Professor of Child Health and Nutrition, Parbold, Lancashire, United Kingdom

Customary approaches to setting safe upper levels for the intake of nutrients use, as critical events, adverse health that which, when adjusted using uncertainty factors (UF), produce values that, when they are applied to population risk analysis, along with dietary reference values that have been independently derived using a different approach by nutritionists, may provide narrow and unrealistic safe ranges of dietary intake. This study describes the evolving concept of the risk assessment of nutrients in which the critical events are based on homeostatic health effects that occur at the upper extreme of the physiological range of intakes. These events can be envisaged as markers of failing adaptation to high exposures and as heralds of potential later adverse events. Such markers may be associated with smaller and more easily characterized uncertainties than those applied to the more gross toxicological architectural, functional, or reproductive health effects used in standard toxicological risk assessment. The study also outlines the potential extension of this homeostatic model to the determination of safe lower limits of intake for essential nutrients and the identification, when homeostasis fails, of thresholds for inadequate intakes that can be adjusted by using uncertainty factors (UF) to derive adequate reference intakes.

This is a concept study that addresses a need that has long been appreciated and in which interest has recently increased. The need is for a system or process whereby, for essential nutrients, assessments of intakes that are deemed to meet physiological requirements can be balanced and reconciled, using a common spine or range of objective criteria, with assessments of the higher or excess levels of intake that are associated with a risk of toxicity. The rejuvenated interest in a combined risk assessment for nutrients has been partly driven by the constant difficulties experienced by regulators who have to use differing and sometimes conflicting advice on required intakes and upper levels; it is not unknown for standard toxicological risk assessments of safe upper levels or reference doses to fall below estimates of required dietary intakes recommended by nutritionists. Consequently, in risk assessments the uncertainty factors (UF), or perhaps even the critical events (adverse health effects), are selected to avoid such anomalies. This practice, although pragmatic and done with transparent integrity, lacks a consistent standard that could be applied to all nutrients and that might also feasibly applied in the risk assessment of exposures to contaminants and additives found in or added to foods.

This discussion originates from an initiative in the International Programme on Chemical Safety (IPCS) Environmental Health Criteria program to consider "Principles and Methods for the Assessment of Risk from Essential Trace Elements" (IPCS, 2001). The presentation also draws on subsequent developments and experience in related exercises addressing nutrient risk assessment (WHO/FAO, 2006; Taylor, 2007), international harmonization on approaches for developing nutrient based dietary standards (King & Garza, 2007), and a more specific exercise exploring the strategies for modelling dose response relationships for copper (Cu) (Stern et al., 2007). Thus, many

Address correspondence to Peter J. Aggett, Emeritus Professor of Child Health and Nutrition, Littlefield, Parbold Hill, Parbold, Lancashire WN87TG, United Kingdom. E-mail: . E-mail: profpjaggett@aol.com

scientists have contributed to the concepts described herein, and I expect that they will continue to do so as these concepts are refined and tested.

The expert and task groups set up by the IPCS (2001) explored an interdisciplinary approach, involving nutritionists and toxicologists to explore and develop the concept of an acceptable range of oral intake (AROI) for essential trace elements. This is illustrated in Figure 1, which shows an AROI bracketed between, at lower intakes, the distribution of potential deficiencies, and at higher intakes the distribution of possible features of toxicity. The distributions are also summated to represent cumulative risks of deficiency and toxicity, respectively, thereby representing the concept of the "U shaped" curve of population and individual responses to low and high exposures. The AROI lies at the base of this curve, and the existing recommendations or dietary reference values and the safe upper levels of recommended intakes, or the "reference dose," would be expected to lie somewhere within that range. Traditionally the dietary reference values are the responsibility of nutritionists, and the reference dose are that of toxicologists.

Both disciplines apply different approaches in their assessments. Nutritionists use as an outcome clear evidence of either the elimination of a specific feature of deficiency or the presence of specific beneficial effect of intakes (Yates, 2007), whereas toxicologists apply a well-developed routine for risk assessment, which is systematically applied using compensatory uncertainty factors (WHO/FAO, 2006).

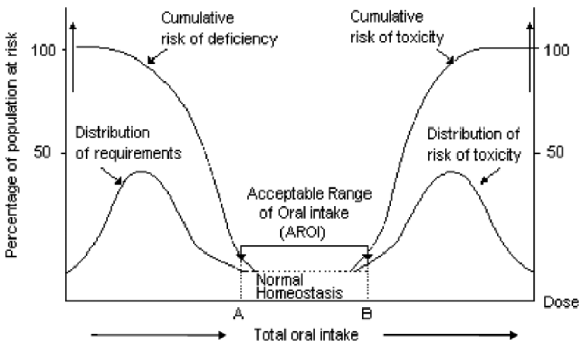

FIGURE 1. The acceptable range of oral intakes (IPCS, 2001).

The Environmental Health Criteria (EHC) expert group comprised toxicologist and nutritionists. It is personally reassuring that toxicologists and nutritionists have an appreciable mutual respect for and trust in each other, but that trust might be misplaced, especially when the disciplines are collaborating to create "risk–benefit or benefit–risk analytical scenarios." This is because one does not necessarily know the limitations of our respective databases. Collaborative and open assessment of the quality of our databases, particularly with critical appraisal of the available data on external exposures and internal burdens, demonstrates the insecurity of the basic information with which to model dose-response relationships. Similarly, appraisal of processes for the identification and characterization of critical health effects should further convince each group of the insecurity of some of the fundamental information that is used in the risk assessment, certainly of nutrients and, for that matter, other exogenous chemicals. This is because there is limited systematic information on dose-response relationships for nutrients; in the toxicological context there is no requirement for systematic acquisition of data comparable to that needed for additives, and from the nutritional perspective, data largely relate to deficiency or toxicity induced by single rather than graded exposures to particularly small or large intakes; few studies are performed at intakes at the boundaries of customary recommended intakes. Thus the databases for the risk assessment of deficiency and toxicity of nutrients lack the fundamental structure that could enable the harmonization and analysis of existing information for the formulation of key nutritional public health criteria.

Nutritionists, when they set reference values, commonly identify by various means an "average requirement" for a particular population, which, on the basis that a population's requirement is normally distributed, is assumed to be at the midpoint of the distribution. A reference range can be created around this point; it can be increased to a value that

represents the midpoint + 2 standard deviations (SD), and that is presumed to indicate the intake that would meet the needs of nearly all the population. Thus, this, in essence, accommodates interindividual variation. Decreasing the "average requirement" by 2SD provides a lower reference value at which there is presumed to be a significant risk of deficiency for some individuals (King et al., 2007; Yates, 2007). The use of UF by toxicologists is similar in principle, but is more adaptable to the major components of uncertainty and variability, and is able to use data drawn from animal models to establish "reference doses." Nutritionists have not used data from animal models directly to derive reference values.

The other important consideration in looking at the "toxicity of deficiency and excess" is the selection of the critical health effects or events that are used in the assessment of adequate and potentially toxic levels of intake. The selection of these endpoints is a difficult and potentially subjective process. Again, this is because the quality of the databases relevant to ideal critical events is poor. Thus, although the assessors have preset objective criteria, they have to use whatever information is available, and from this select endpoints that are the best characterized and that have the most complete data sets. This is another example of the paucity of the available information. It is ironic that in the regulatory context, any new chemical that is proposed to be added or used in foodstuffs needs approval based on a systematic toxicological assessment, but this does not apply to nutrients. However, of course, funding is available from manufacturers of such proposed additives to support the necessary research and compilation of regulatory data for their product, whereas nutrients have no such sponsor.

The EHC group explored how existing data could be applied to a biologically based template to assess the risk from essential trace elements; the principles involved could, however, be applied to any nutrient including energy. The group explored the spectrum of population or individual responses to a range of exposures to essential trace elements. This is illustrated in Figure 2, in which the outcomes to a range of exposures are shown as a series of curves representing the consequences of inadequacy

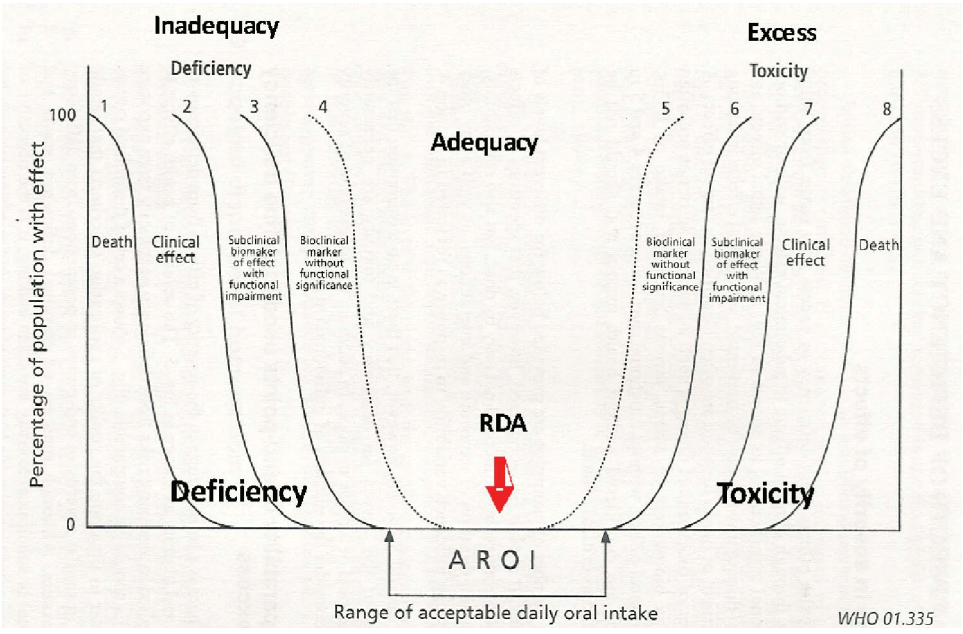

FIGURE 2. The hazard–benefit–hazard spectrum, showing the symmetry of the adaptive and pathophysiogical responses in the dose response to deficient and excessive intakes relative to requirements.

and excess. These are expressed as the range of potential effects classified as homoeostatic or adaptive phenomena, progressing sequentially through early adaptation to more ineffective adaptation marked by functional and structural disruption, through functional impairment, to gross clinical effects and death. This pathophysiological scenario is useful because it helps us to realize how far down the pathophysiological pathways the markers that are currently used to characterize deficiency or toxicity lie. The task group appreciated the difficulties in balancing and identifying "beneficial" and "adverse" events, appreciated that the value judgements inherent in using such terms are a significant barrier to providing an objective and transparent risk assessment, and discussed the use of markers from this spectrum of responses, particularly those of homeostatic adaption, as an approach to establishing an AROI and to the risk assessment of essential trace elements. The use of markers of adaptation in the AROI "biologically based approach" depends on adequate information on the metabolism of the nutrient involved. This information is the same as that on absorption, distribution, metabolism, and excretion (ADME), which is used in toxicological risk assessment.

The IPCS EHC report also recommended that the principles described for the development of AROI should be further considered and applied to nutrients in general. It recommended that all relevant disciplines should be involved in future developments, and that the report monograph should be regarded as a contribution to the ongoing process of harmonizing approaches to risk assessment. In particular, it felt that the terminology used in determining and applying the AROI approach should be more extensively harmonized and that greater emphasis should be given to risk characterization, emphasizing the strengths and weaknesses of hazard identification, dose-response, and exposure assessment components in order to increase transparency of the process, and informing future developments and research investment.

An initial strategy to reconcile the nutritional and toxicological ends of the dose-response spectrum has been to bring together existing approaches under the concept of "risk–benefit" analysis. However, "risk" and "benefit" are not philosophically balanced concepts and are not antonyms. Risk already includes the likelihood that an already specified hazard will actually produce harm to an individual or population. Benefits are, like hazards, more related to a critical event. A hazard of deficiency would equate to a hazard of toxicity or excess. Thus, analyzing the dose-response spectrum in terms of the adaptive phenomena that underpin the AROI approach would enable a "hazard–benefit–hazard" analysis, or perhaps a better term would be a "deficiency risk–excess risk" analysis, which although cumbersome is more representative of what this combined risk assessment process entails than is "risk–benefit" analysis. Furthermore, such a more descriptive title would better frame the approach to the assessment, alert assessors to the underpinning concepts, and would offer the opportunity to focus developments in assessment on events characterized by markers of the adaptive responses.

Recently, a joint FAO/ WHO Technical Workshop on Nutrient Risk Assessment was convened (WHO/FAO, 2006). This worked on a model for establishing upper levels of intake for nutrients and related substances. It started by critically evaluating the toxicological risk assessment approach, its application to nutrients, and its potential rigor and transparency. In turn, the workshop agreed that the qualities of this approach could enable it to accommodate, in the risk assessment of high intakes of nutrients, markers based on pathophysiologically earlier critical events or adverse health events than those customarily used in risk assessment.

The Technical Workshop used the spectrum of "adverse health effects used in hazard characterisation" (Table 1) as described by Renwick et al. (2004). This also enables one to appreciate that most adverse health effects currently used in risk characterization lie at stages 5, 6, or 7. The workshop agreed that a biologically based model could be based on phenomena that occur either at lower exposures or

TABLE 1. Range of Adverse Health Effects That Could Be Used in Hazard Characterization (Renwick et al., 2004)

1. Biochemical changes within homeostatic range and no adverse sequelae.
2. Biochemical changes outside the homeostatic range without known sequelae.
3. Biochemical changes outside the homeostatic range: a marker of potential adverse effects due to excess.
4. Clinical symptoms indicative of a minor but reversible change.
5. Clinical symptoms of significant but reversible effects.
6. Clinical signs indicative of significant reversible organ damage.
7. Clinical signs indicative of irreversible organ damage.

after exposures of shorter duration, i.e., at stages 3 or 4. These events could be identified by validated biomarkers that are predictive of the more serious sequelae that would occur at higher doses or with more prolonged exposures. It is arguable that this approach would enhance toxicological risk assessment by enabling the use of events that are pathophysiologically closer and more specific to the exposure. Even so, such markers would need to be identified and validated.

The Joint FAO/WHO Technical Workshop on Nutrient Risk Assessment defined a hazard as "the inherent property of a nutrient or related substance to produce adverse health effects depending upon the level of intake" (WHO/FAO, 2007). This definition would lend itself to low exposures to nutrients as well as to high doses, and as a corollary it is conceivable that a similar use of markers of critical events could be used in hazard identification and characterization of phenomena occurring with reduced exposure and intake, i.e., a deficiency risk assessment (Figure 3). Nonetheless, there are several issues relating to the use of markers of adverse health events that occur with diminishing exposures or intakes. These will be familiar to toxicologists, namely, uncertainty about the critical event, the identity of the critical event, and acquiring the appropriate data not only to reduce the uncertainty but also to define the variability to further enable the application of UF. Even so, one would expect that the uncertainty involved with the use of a biologically based model would be more definable and therefore smaller than that involved in the traditional risk assessment.

This supposition, however, has not really been substantiated, and however sound and logical the biologically based model may be, a lot of the necessary information is still not yet available to allow the creation of a single

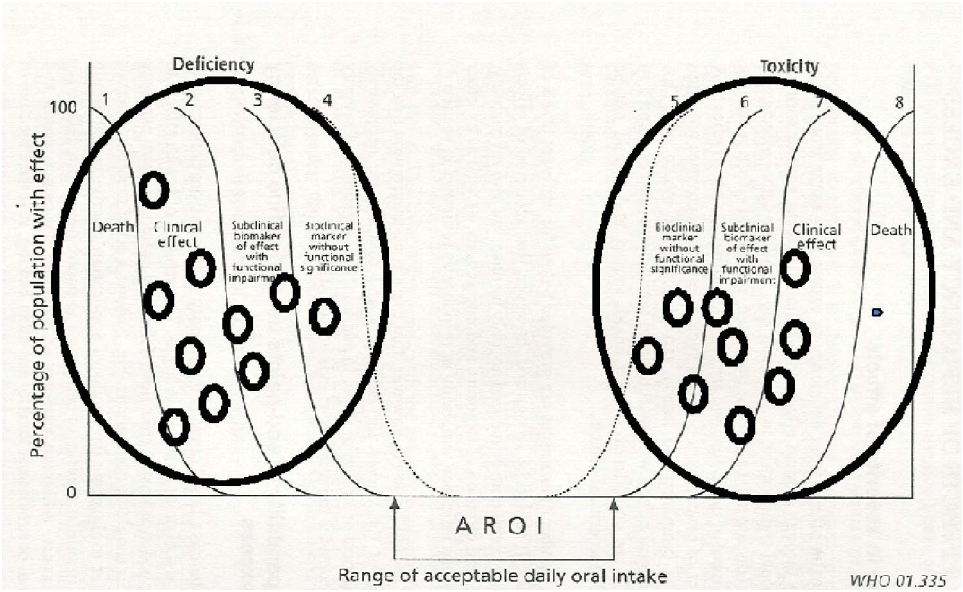

FIGURE 3. The hazard–benefit–hazard responses to inadequate and excess exposures; the smaller circles represent a potential or hypothetical cascade of adverse health effects (IPCS, 2002).

dose-response continuum for nutrients, or, for its use to set upper levels of intake. It is possible that recognition of this approach might generate interest in funding or creating appropriate strategies to construct such databases, but in the first instance it is probably important to explore the feasibility of using existing data for such approaches. A project on modeling dose-response relationships for Cu was undertaken in an extensive critical evaluation of the literature and concluded that, for the moment, the information available on Cu is not sufficient to support the full development of a biologically based dose-response model (Stern et al., 2007). The current understanding of the mechanisms involved in Cu homeostasis is actually quite extensive, but little of it is related to specific exposures to Cu.

The use of markers of adaption and the biologically based model in the risk assessment of nutrients complements the current interest in evidence-based toxicology, and its use in the derivation of appropriate markers either directly from an understanding of kinetic (ADME) or dynamic phenomena, or by back-extrapolation along the pathophysiological pathway from a particular critical event to a related preceding phenomenon. The commonalities of the basic principles and of the technical and informatics expertise might allow the commonality of the responses in the dose-response model to be defined in terms of proteomic or metabolomic markers.

REFERENCES

IPCS Working Group. 2002. *Principles and methods for the assessment of risk from essential trace elements. Environmental Health Criteria 228*. Geneva: WHO.

King, J. C., and Garza, C., eds. 2007. International harmonization of approaches for developing nutrient-based dietary standards. *Food Nutr. Bull.* 28(suppl.): S1–S153.

King, J. C., Vorster, H. H., and Tome, D. G. 2007. Nutrient intake values (NIVs): A recommended terminology and framework for the derivation of values. *Food Nutr. Bull*. 28(suppl.):S16–26.

Renwick, A. G., Flynn, A., Fletcher, R. J., Muller, D. J., Tuitjelaars, S., and Verhagen, H. 2004. Risk benefit analysis of micronutrients. *Food Chem. Toxicol*. 42:1903–1922.

Stern, B. R., Solioz, M., Krewski, D, Aggett, P., Aw, T. C., Baker, S., Crump, K., Dourson, M., Haber, L., Hertzberg, R., Keen, C., Meek, B., Rudenko, L., Schoeny, R., Slob, W., and Starr, T. 2007. Copper and human health: Biochemistry, genetics, and strategies for modeling dose-response relationships. *J. Toxicol. Environ. Health B* 10:157–222.

Taylor, C. L. 2007. Highlights of 'A model for establishing upper levels of intake for nutrients and related substances: Report of a Joint FAO/WHO technical workshop on nutrient risk assessment, May 2–6, 2005'. *Nutr Rev.* 65:31–38.

World Health Organization, and Food and Agricultural Organization. 2006. *A model for establishing upper levels of intake for nutrients and related substances. Report of a joint FAO/WHO technical workshop on nutrient risk assessment*. Geneva: WHO/FAO.

Yates, A. A. 2007. Using criteria to establish nutrient intake values (NIVs). *Food Nutr. Bull.* 28(suppl.):S38–S50.