

Background Information  
IOM/FNB Workshop on Dietary Reference Intakes  
***The Development of DRIs 1994-2004: Lessons Learned & New Challenges***  
September 18-20, 2007  
Washington, DC

Information Compiled and Posted July 11, 2007

Purpose: To Provide Useful/Relevant Information for  
Workshop Participants and Attendees

Opportunity for interested parties to comment electronically through August 11, 2007:  
[www.iom.edu/driworkshop2007](http://www.iom.edu/driworkshop2007)

**DOCUMENT:**

**Risk Assessment: Is It a Relevant Organizing Structure?**

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**Date: July 2007**

# Risk Assessment: Is It a Relevant Organizing Structure?

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This paper focuses on some of the issues that may be useful to considerations of extending the risk assessment approach used for deriving reference values for tolerable upper limits (UL) to the derivation of indicators of adequacy in future revisions of the Dietary Reference Intakes (DRI). The purpose of this paper is to suggest possibilities for such an adaptation and to stimulate questions for which further discussion is needed but not to provide conclusions or specific recommendations on this topic.

## **‘Risk Assessment’ as part of ‘Risk Analysis’**

Risk assessment is the scientific arm of a triad of components making up the so-called ‘Risk Analysis’ framework. Risk analysis was developed as an organizing framework for defining the roles and responsibilities, and related interactions, among the various players involved in assessing, using, and communicating information on risks associated with exposures to potentially hazardous substances (FAO/WHO 2006). The three components of risk analysis are:

‘Risk Assessment’, the subject of this paper, is the scientific arm of the risk analysis framework. Risk assessment is conducted by qualified scientists who evaluate the available evidence and apply expert judgment where uncertainties exist to develop a scientifically sound assessment of the risks posed by exposures to hazardous substances (IOM 1998, NRC 1983, Taylor 2007).

‘Risk Management’ represents the user arm of the risk analysis triad (FAO/WHO 2006). ‘Risk managers’ are not part of the science-based risk assessment; but, as users, they identify the questions for which a risk assessment is needed and use the results of the risk assessment, along with other non-science considerations (e.g., cost, feasibility), to make practical decisions about approaches for controlling risks. Traditionally, risk managers were regulatory agencies (e.g., FDA, EPA). With the more recent application of risk assessment approaches to the setting of UL for nutrients, ‘risk managers’ would include a broad range of users: a) federal agencies that may use the UL in developing nutrient and food labeling, food standards, or food delivery programs, b) researchers who use the UL in designing and evaluating studies, c) dietitians and other health professionals who consider

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UL in conducting diet counseling of individual consumers and patients, and d) nutrition educators who provide educational materials and guidance for consumers. Thus, for nutrition applications, 'risk managers' represent a broad and diverse group of users.

'Risk Communication' is the information arm of this triad (FAO/WHO 2006). Risk messages are often difficult to formulate in ways that are accurate, clear and not misleading (NRC 1989). Successful communication occurs when it raises the level of understanding among interested parties. Media as well as agencies and health professionals are all potential sources of risk messages.

### **Risk Assessment: General Strengths and Weaknesses**

Risk assessment is a scientific undertaking having as its objective a characterization of the nature and likelihood of harm resulting from human exposure to hazardous substances. The risk assessment framework was first codified in a 1983 landmark publication by the National Research Council of the National Academy of Sciences (NRC, 1983). Modifications have evolved over time as needed improvements became apparent with use and as scientific advances provided new methodologies and more targeted research (NRC 1989, 1994, 1996).

In general, the major strengths of a well conducted risk assessment include:

- A framework for organizing and analyzing the available scientific information to address the series of decisions involved in assessing risks associated with exposures to hazardous substances.
- A systematic means of evaluating risk through the use of a set of scientific factors that are consistently considered across all risk assessments.
- An approach that emphasizes transparency through explicit documentation of the scientific evaluations, the rationale for decisions reached, the uncertainties surrounding the estimations of risk, and the public health implications of groups whose intakes exceed the reference intake.
- A framework that incorporates scientific judgment in conjunction with comprehensive reviews of the scientific evidence to address issues of public health importance when available data are limited.
- A flexible approach that, while requiring that information be organized in rather specific ways, does not require any specific scientific evaluation methods or a single fixed method of analysis.

- An approach that is designed to carefully take into account data uncertainties through the careful documentation and analysis of the range and types of uncertainties in the available evidence and the application of expert scientific judgment for dealing with these uncertainties.
- A framework that defines a partnership between the scientists conducting the risk assessment and the users of the risk assessment. The codification of this partnership is designed to appropriately balance the two competing demands for: a) maintenance of the scientific integrity of the risk assessment through independence of the scientific deliberations from undue sponsor and other stakeholder pressures, while b) ensuring the usefulness of the risk assessment results to sponsors and other stakeholders through discussions that clarify the information needs of the stakeholders and ensure that the results of the scientific deliberations are presented in a form that is meaningful to users.

Despite these strengths, several weaknesses or challenges remain:

- The use of risk assessment processes can not completely eliminate controversies over risk assessment decisions because of inevitable inadequacies and uncertainties in the available evidence.
- Published studies frequently lack complete information on the methodologies, interventions, and populations/test animals needed for assessing risks.
- Often, there is a general paucity of relevant evidence for a particular risk assessment.
- Frequently, scientists have diverging opinions on the merits of the underlying scientific evidence and the appropriate models, adjustments, or uncertainty factors to use in a particular risk assessment.
- With all new uses, some modifications in the terminologies, approaches and assumptions will likely be needed.

### **Risk Assessment: Aspects Unique to Nutrients**

While the risk analysis framework was originally developed for the purposes of managing potential hazards of population (sub)groups to chemicals in foods and the environment, its use has expanded to other types of hazards (e.g., microbial pathogens in foods) and more recently to potential hazards associated with consumption of excessive intakes of nutrients and related food substances. In recent years, several expert committees have adapted risk assessment approaches to derive UL for nutrients. These include expert panels convened by

the Food and Nutrition Board of the Institute of Medicine to derive UL as part of the process of developing the DRI for 45 nutrients and related substances (IOM 1998 and 2006); the Expert Group on Vitamins and Minerals convened by the UK government (EVM 2003); and the Scientific Committee on Food convened by the European Commission (SCF 2006). In 2002, a WHO expert panel proposed a risk assessment framework for analyzing an acceptable range of intake between boundaries defined by deficient and excess oral intakes of essential trace elements (IPCS 2002). Two recent panels evaluated global harmonization approaches for nutrient risk assessments (Aggett 2007; FAO/WHO 2006).

In examining the use of risk assessment for assessing risks associated with excessive nutrient intakes, these panels identified several areas which were either unique or critical to nutrients and that differed from classical risk assessments. These included:

- The dual-curve relationship for nutrient risks. Because of their essential and documented benefit, there is risk of adverse effects associated with inadequate intakes as well as with excessively high intakes of nutrients. This differs from the single-curve relationship for most substances for which risk assessments have been conducted (e.g., pesticides, microbial pathogens, food additives).
- The nature of the evidence available for evaluating nutrient risk is generally incomplete and difficult to use. Most available animal and in vitro studies were not designed to evaluate the safety of high nutrient intakes but rather were designed to evaluate beneficial effects of nutrients or to understand mechanisms of action related to classical nutrient deficiencies or to chronic disease risk reduction. These studies often failed to fully collect or report the types of information needed for risk evaluations; and they lacked the more complete dose-response data and wide range of potential adverse effects normally included in systematic safety studies for food additives and other food contaminants.
- The relatively large uncertainty factors (UF) (e.g., 100) normally used to ensure public health protection given uncertainties in the evidence for non-nutrient chemicals and microbial pathogens can not be used for nutrients. (The larger the uncertainty factor, the lower the UL). The relatively large UF used for other substances could result in UL values that fall below reference values for nutrient adequacy. Thus relatively small uncertainty factors (e.g., 0-10) are normally used in nutrient risk assessment.
- Nutrients are subject to homeostatic mechanisms that involve regulation of the absorption, excretion, and tissue redistribution and retention of nutrients to maintain optimal and safe systemic supplies for essential functions and optimal health given day to day variabilities in intakes.

Excessive intakes of a nutrient may compromise these homeostatic mechanisms resulting in an increased probability of adverse effects.

- Nutrient risk assessments are generally most meaningful if provided for the life stage groups (e.g., age/gender groups, pregnant and lactating women) that are similar to the groups used for establishing reference intakes to ensure adequacy. This differs from the accumulated lifetime exposures commonly used to express the results of risk assessments for other types of hazards. For nutrients, differences in homeostatic mechanisms and requirements for growth and development among life stage groups may influence sensitivity to nutrient toxicity.
- Different sources of nutrients and matrix effects of the foods consumed with the nutrient can affect their bioavailability or biopotency and therefore alter dose-response relationships.
- Unlike many other potential hazards, baseline diets always provide a background level of exposure to nutrients. Although RDA levels of intake are generally not considered to pose a risk for the general healthy population, the potential for excessively high intakes with the increasing availability of fortified foods and dietary supplements means that users of the DRI often need to consider safe ranges of intakes. Therefore, it is generally assumed that no decision about the potential risk of excessive intakes of a given nutrient is less preferable than an informed decision based on less than perfect data but representing a best estimate by qualified scientists.

## **Steps in Risk Assessment**

The risk assessment process includes four steps (IOM 1998 and 2006; FAO/WHO 2006):

1. Hazard Identification
2. Dose-Response Assessment (sometimes called 'Hazard Characterization'),
3. Intake Assessment (sometimes called 'Exposure Assessment'), and
4. Risk Characterization.

These four steps classically provide the organizing framework for addressing the series of questions that drive the science-based decision-making process involved in evaluating risks associated with levels of exposures to hazardous substances.

These steps have been used to guide nutrient risk assessments by several expert panels (IOM 1998 and 2006; EVM 2003; SCF 2006). Recently, several

expert groups and conferences have considered the extension of risk assessment approaches to the evaluation of risks of adverse health effects associated with inadequate intakes of nutrients (EFSA 2006; IPCS 2002; IOM 2007). These groups discussed the potential benefits of concurrently using risk assessment frameworks for evaluating the risks associated with both inadequate and excessive intakes. Their proposed modifications of classical risk assessment have been described as 'risk-risk' or 'risk-benefit' assessments with 'benefit' representing the absence of risk due to inadequate intakes (Renwick 2004).

The use of these four steps in the risk assessment framework for deriving UL will be described below. Possible issues to making the approach applicable to the process of deriving indicators of nutrient adequacy<sup>2</sup> will also be discussed. Finally, examples of how use of a risk assessment framework for assessing risks associated with both inadequate and excessive intakes potentially could facilitate the identification of improvements in the DRI process will be offered.

### **Step 1 In Risk Assessment: Hazard Identification**

'Hazard identification' is defined as: "The identification of the type and nature of adverse effects that an agent has an inherent capacity to cause in an organism, system or (sub) population" (IPCS, 2004). The hazard identification step typically involves the collection, organization, evaluation, and summarization of the scientific evidence pertaining to the types and nature of several adverse effects associated with various intake levels of a given substance.

#### *Current Use of the 'Hazard Identification' Step in Deriving UL*

Using vitamin A as an example, the hazard identification step in the derivation of the UL by the FNB/IOM addressed the following questions relating to the identification of indicators of hazard for pre-formed vitamin A:

- What data are available on the adverse effects from [chronic] high intake of vitamin A?
  - bone mineral density
  - liver abnormalities
  - adverse interactions
  - other potential indicators of risk
- What data are available on the adverse effects in pregnant/lactating women (e.g., teratogenicity)
- Are there data on adverse effects that are specific for children (e.g., bulging fontanel)?

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<sup>2</sup> For purposes of simplicity, reference values for adequate intakes will be referred to as a "RDA" value throughout this paper. However, for purposes of this paper, the RDA acronym represents the full range of types of reference values used in the DRI reports, including the EAR (Estimated Average Requirement) that is used to derive the RDA values (Recommended Daily Allowance) and the AI (Adequate Intake) that is used when the data are insufficient to identify an EAR.

### Possible Use of the 'Hazard Identification' Step for Deriving the RDA

In evaluating the available evidence relative to derivation of the RDA, similar types of questions and literature reviews are part of the process, but the focus is on identifying 'indicators of adequacy' rather than 'hazards'. In considering whether or not this first step in the risk assessment process could logically be extended to evaluating adequate intakes -- or adverse effects associated with inadequate intakes -- two questions logically come to mind. First, in general, are the basic functions of this step similar for both applications? The first step in deriving a RDA is to conduct a literature review to answer questions related to the available data between intakes and various potential indicators of adequate nutrient status or reduced risk of chronic diseases. This would appear to be directly analogous to the literature review conducted for similar purposes for identifying hazards associated with excessively high intakes.

The second question relates to whether or not the terminology used for evaluating hazards associated with excessive intakes can appropriately be extended to the evaluation of adverse health effects associated with inadequate intakes. A FAO/WHO (2006) expert panel suggested that revisions to classical risk assessment terminology for nutrient applications were warranted in some cases. For example, they concluded that while the term 'hazard' applies to adverse health effects associated with excessively high nutrient intakes, it does not apply to adverse health effects associated with inadequate nutrient intakes. Their rationale for this difference is based on the definition of 'hazard' which attributes the adverse effect of the substance of interest to its 'inherent property'. Because the adverse health effects of inadequate intakes are related not to an inherent property of the nutrient but rather to its absence in the diet, the FAO/WHO panel revised the standard definition of 'hazard' for the purposes of nutrient risk assessment to clarify that the hazard was dependent on the level of intake. They revised the classical definition of 'hazard' to:

“the inherent property of a nutrient or related substance to cause adverse health effects depending upon the level of intake”.

The panel defined an 'adverse health effect' as:

“a change in 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”.

Thus, the concept of an 'adverse health effect' would appear applicable to both inadequate and excessive intakes whereas the concept of 'hazard' applies only to excessively high intake levels. If a risk assessment model were to be extended to use in deriving the RDA reference values, terms such as "indicators

of adequacy and hazard” or “indicators of adverse health effects” could be considered as possible substitutes for the use of the term ‘hazard’.

Thus, for the first step in risk assessment, preservation of the organizing function of this first step combined with flexibility to make needed terminology revisions would appear to be consistent with the identified strengths of risk assessment as described above.

*Examples of how use of the first step of ‘hazard identification’ in a risk assessment framework could help in identifying possible improvements for future consideration*

If we assume that appropriate terminology will be applied to identifying indicators of adequate intake (or the converse – e.g., indicators of inadequate intakes) such that the risk assessment framework could be used for deriving indicators of both adequacy and hazard, are there ways in which using the organizing framework of the first step of risk assessment could help to identify possible improvements to future DRI processes? As noted above, the first step in the risk assessment process involves the identification of the potential adverse health effects associated with various intakes through a process of collating, evaluating, and summarizing the available scientific evidence. A basic strength of risk assessment approaches is the emphasis on transparency and documentation. A commonly expressed frustration encountered by users of past nutrient risk assessments and the DRI process has been the lack of complete documentation as to criteria used for literature searches and for evaluating the evidence. For example, a recent WHO expert panel noted that, despite access to the same scientific evidence base and the use of the same risk assessment framework, three different panels often reached different conclusions relative to setting UL for some nutrients (FAO/WHO 2006). Given the narrative style of literature review in the three reports and limited information on inclusion/exclusion and search criteria or on criteria for evaluating and weighing the available studies, it was often difficult to discern why the three panels reached differing conclusions. Because of the increasing use of systematic evidence-based approaches in other health-related activities, one possibility for improving the transparency of future scientific reviews for DRI-related efforts might be consideration of use of the so-called systematic evidence-based approaches which have been used for setting research agendas and developing clinical practice guidelines. This topic was discussed in the recent FAO/WHO report (2006). In this report, the panel concluded that the use of evidence-based review approaches would be useful in enhancing the documentation, and hence the transparency, of the identification and review of the scientific literature on a range of possible adverse health effects associated with various intake levels. However, the panel also expressed caution that if classical evidence-based review approaches were used in nutrient risk assessment, care would be needed to ensure that appropriate modifications to the types of questions guiding the evidence-based review were made because the questions that guide the derivation of nutrient reference values are different

than the types of questions that guide the processes of setting research priorities or developing clinical practice guidelines.

## **Step 2 in Risk Assessment: Dose-Response Assessment (Hazard Characterization)**

The dose-response assessment step clarifies the nature of many of the most critical decisions in the risk assessment process.

### Current Use of the 'Dose-Response Assessment' Step in Deriving UL

The current DRI process used a risk assessment approach to identify a UL for each of the nutrients for which there were sufficient data. Generally a threshold model was assumed and a UL was provided for the same life stage groups that were used for establishing RDA.

The types of questions and decisions in the dose-response assessment step of the risk assessment framework generally included:

#### Dose-Response Assessment – for each life stage group for which there are data:

- What adverse effect(s) provide the most appropriate or critical data set(s) for deriving a UL?
- At what intake level is the selected adverse effect(s) observed (e.g., identification of a LOAEL) or not observed (e.g., identification of a NOAEL)?

#### Adjustment Factors

- What differences in the bioavailability or biopotency occur among various sources of the nutrient under conditions of use?

#### Uncertainty Factors – for each selected critical end point:

- What are the sources of uncertainty in the available data?

#### Extrapolations from studied to unstudied groups

- If there are no or insufficient data for some life stage groups, what is the best approach for making extrapolations from studied to unstudied groups?

#### Other Vulnerable Groups (Special Populations)

- What special populations may experience an adverse effect lower than the UL?

As shown above, the first decision is selection of the critical adverse effect that will form the basis of the UL and a description of the dose-response relationship for this critical adverse effect among life stage groups for which there are sufficient data. The second type of decision is whether or not some adjustment to the dose response relationship is warranted. The most common type of adjustment derives from the need to account for differences in the bioavailability or biopotency among various sources of the nutrient of interest. The third type of decision relates to the need to account for uncertainties in the available

evidence. The derivation of nutrient UL is dependent on the available evidence – most of which was not done for the purpose of setting a UL. There is generally a paucity of evidence, available evidence may not be directly relevant, and ethical considerations frequently preclude the design and conduct of human intervention studies designed to document adverse effects. Therefore, intake levels associated with adverse effects must either be generalized from animal studies or obtained from human studies that often lack key information needed for risk assessments because they were not designed for this purpose. For these reasons, there is always uncertainty about the nature of the relationship between high nutrient intakes and adverse health effects. Therefore, levels of intake below those associated with adverse health effects, or at the lowest level of intake associated with adverse health effects, were often divided by an uncertainty factor to derive a UL intake level that is lower than that observed in available studies. The derivation of an appropriate UF requires the integration of information from available studies and scientific judgment. Its use adds a measure of public health protection to data that by their very nature have inherent uncertainties.

Although the decision-making process described above is applied to all life stage groups for which there is sufficient evidence, commonly there will be several groups for which no data or insufficient data are available (e.g., children, pregnant and lactating women). In these cases, a UL is often extrapolated from studied to unstudied groups. Thus another decision in this step in the risk assessment process relates to how best to extrapolate from studied to unstudied life stage groups for which DRI are provided.

Finally, although UL are generally not set for groups outside the target population (e.g., general healthy population), there may be special groups for which the general UL would be inappropriate because of disease conditions and/or medication use. Although a separate UL will not generally be provided for these individuals, a description of appropriate deviations from the established UL for these groups is often provided.

#### Possible Use of the “Dose-Response Assessment” Step for Deriving a RDA

To a large degree, the types and sequence of the decisions identified above for deriving a UL are similar to those followed in establishing a RDA. Therefore, the organizing framework in step 2 of the risk assessment process in which the various types of decisions leading to the derivation of the UL reference value are clearly identified would appear to be similar to the derivation of reference values for adequate intakes. A possible exception might be the use of uncertainty factors to lower the UL beyond intakes associated with, or below, adverse health effects. In general, uncertainty factors have not been used in deriving RDA values, although there are some exceptions (e.g., an adjustment was made to the AI for vitamin D to cover individuals with no or limited sun exposures) (IOM 1997). To some degree, this difference may relate to the nature of the available evidence for adverse health effects associated with inadequacies vs. excessive

intakes. However, there also are uncertainties in the assessments of risk for both inadequacy and toxicity. Therefore, in the context of risk assessment as an organizing framework, the key issue would seem to be the need to adequately describe and decide how best to deal with the types of uncertainties in the available evidence regardless of whether the assessment was focused on inadequacy or toxicity. Because the risk assessment framework does not specify methodologies, the approaches for accounting for uncertainties could differ between the two types of assessment. In both cases, it is reasonable to assume that assessment and documentation of the uncertainties associated with reference values are needed. Thus the organizing need for addressing and describing uncertainties is likely common to both types of assessment; but variations in the methodologies for dealing with uncertainties in the two assessments could be flexible so as to be appropriate for each case

*Examples of how use of the second step of 'dose-response assessment' in risk assessment framework could help in identifying possible improvements for future consideration*

By subdividing the second step of risk assessment (i.e., the dose-response assessment step) into its component parts, transparency and the systematic nature of the process are enhanced. Moreover, if both the evaluation of adequate and safe levels of intake systematically followed a similar organizing framework around the decisions being made, greater coordination between these two types of decisions could be facilitated. This would not only be likely to benefit users, but could also identify potential inconsistencies between the decision-making relative to inadequate and excessive intakes before final conclusions are reached by the risk assessment panel.

For example, for individual components in this second step of the risk assessment, the following types of issues may warrant further discussion:

Selection of critical data set: Differences in the nature of the endpoints (e.g., severity of effect) selected for deriving the RDA vs. the UL have created difficulties for some applications where there is not wide separation between the intake levels of these two reference values; therefore, public health implications of not achieving an adequate intake or of exceeding a UL can become challenging issues for users. An approach for categorizing indicators of adverse effects ranging from biochemical changes without adverse health effects through to irreversible pathological changes in the functioning of an organism has been proposed as a basis for more directly comparing the public health implications of potential adverse effects associated with adequate and excessive intakes (FAO/WHO 2006, Renwick 2004).

If a risk assessment organizing framework was used for deriving reference values for both adequacy and toxicity, consistency in handling issues of bioavailability and biopotency could be enhanced. For example, although

the use of vitamin A and folate equivalents has relevance to both inadequate and excessively high intakes and places them on a common scale, for other nutrients such as iron, vitamin B6 and vitamin B12, the algorithms used to adjust the RDAs are based on bioavailabilities from mixed diets (Yetley 2007). The relevance of these values to persons/groups having relatively high intakes from supplements, particularly if not consumed with meals, is therefore unclear.

If a risk assessment organizing framework was used for deriving reference values for both adequacy and toxicity, consistency in extrapolation procedures, or the need to document justifications for differences, could be facilitated. For example, the extrapolation from adults to children for deriving RDAs was commonly based on the so-called metabolic body weight ( $[\text{kg body wgt}]^{0.75}$ ) while reference body weights were more commonly used for deriving UL (IOM 2001). Whether or not the metabolic body weight conversion or the reference body weight conversion was used can make a significant difference in the resulting reference value (FAO/WHO 2006). If this decision step is clearly identified as a subcomponent of the risk assessment framework and the same framework is used for assessing both inadequacies and toxicities, inconsistencies in the two approaches likely would become apparent during the panel's deliberations. As appropriate, differences in the two types of assessment could be identified and the panel could determine how best to deal with these inconsistencies (i.e., through documentation of the need for differences or through modifications to minimize differences).

Controversy has evolved over the required assumption of a threshold effect for intakes associated with increased adverse health effects because of inadequacies or excessive intakes. While the threshold model for deriving RDA or UL values was applicable for a number of nutrients, it did not work for nutrients such as saturated and trans fat or the energy-yielding macronutrients. The question can then be asked whether or not other models might be considered for those cases where a threshold effect is not relevant? If other models were adopted for these exceptions, what criteria could guide their use so that they were only used when necessary? By concurrently using a risk assessment framework for derivations of reference values for both adequate and excessive intakes, the ability to find appropriate solutions for model challenges may be enhanced.

### **Step 3 in Risk Assessment: Intake Assessment (Exposure Assessment)**

The third step in the risk assessment model is intake assessment. The purpose of this step is to provide estimates of the intakes of the nutrient of interest for the life stage groups for which DRI reference values are provided. Classically, this

information is used in the final step of the risk assessment model (i.e., risk characterization step) to identify the prevalence of persons with intakes exceeding the UL.

#### Current Use of the 'Intake Assessment' Step in Deriving UL

The DRI reports included Appendices with intake estimates from several surveys. Intakes were generally reported as distributions for the life stage groups for which DRI are reported. When data were available, intakes were reported for foods and supplements separately and as total intakes from all sources. In some cases and where relevant, intakes from water were also included in the estimates of total intake. A brief summary of selected percentile intakes (e.g., median, 95<sup>th</sup> pctl) was included in the individual nutrient reports for some of the various life stage groups for which DRI were established. Where available, distributions of clinical and biochemical indicators of nutritional status were also provided in the appendices and briefly described in the nutrient chapters.

#### Possible Use for the 'Intake Assessment' Step in Deriving the RDA

The current DRI reports generally also assessed intakes from foods, supplements and total diets in the section of the reports focused on derivation of the RDA. The relevance and similarity of intake assessments for assessing both inadequate and excessive intakes is self evident.

#### Examples of how use of the third step of 'intake assessment' in a risk assessment framework could help in identifying improvements for future consideration

A separate section that focuses on intake assessments could provide an opportunity for critically examining the quality and relevance of the intake assessments. Since the same database and analyses are generally used to estimate intakes at both the low and high ends of the distribution curves, a combined intake assessment for evaluating both adequacy and toxicity seems logical. One frustration commonly expressed by users in the current DRI reports has been the very limited intake information included in the individual nutrient chapters. For example, Table C-26 (IOM 2001, pg 640-641) provides intake distributions for zinc for all life-stage groups for which DRI are reported. However, the zinc chapter does not flag the fact that young children have very high intake levels, or that overlaps in RDA and UL intakes occur among some life stage groups, even though the data to identify this potential concern is available in the appendix tables. A limited discussion of the fact that intakes of some groups are high is included elsewhere in the report (pg. 572-575) but this information is not integrated into the zinc chapter. Thus inclusion of a more focused and comprehensive intake assessments relative to the prevalences of both inadequate and excessive intakes in the specific nutrient chapters could enhance usefulness of the reports.

By having a separate section on intake assessments, it provides an opportunity for the panels to assess and document potential biases and uncertainties in the

available intake data. The usefulness of this type of assessment is underscored by recent reports of under-reporting for calories and protein from commonly used dietary intake methodologies in surveys and observational studies (Subar et al. 2003). Since calories deliver nutrients (except those from supplements), calorie under-reporting can result in under-reporting of other nutrients although there is currently little or no data to permit quantitative adjustments for nutrients other than calories and protein. Another source of underestimation of intakes can occur when food composition tables use label information as surrogates for analyzed values, particularly for fortified foods and dietary supplements (Whittaker et al. 2001). Given current regulations in the US, label values represent the lower tail of the actual values, thus underestimating actual levels in foods and supplements (Yetley 2007). Other sources of bias in the composition values may also occur. For example, we now know that until recently the analytical methods used to measure the folate content of foods underestimated the actual content (Rader et al. 1998). It is interesting to note that the nutrition monitoring reports convened a number of years ago by the Life Sciences Research Organization provided an extensive summary and evaluation of the quality of the data used in estimating nutrient intakes from national nutrition monitoring databases (LSRO 1995). A more extensive documentation of potential uncertainties and biases in the intake estimates could enhance the usefulness of the DRI reports.

Clinical and biochemical measures of nutritional status are also useful in this step of the risk assessment paradigm. Where data were available, distributions of values from the NHANES were provided in appendices to the DRI reports. As with the food intake assessments above, however, a discussion of potential sources of error and bias would be useful. Examples of how changes in analytical methodologies can affect interpretation of population-based prevalence estimates and time trends have been reported (Pfeiffer et al, in press; Picciano et al. 2007; LSRO 1995). Also, because the intake estimates often appear to give very different estimates of prevalences of inadequacy and excessive intakes than do clinical and biochemical measures of nutritional status, a discussion of the differences in these two types of measures of status and interpretive guidance has the potential for enhancing the usability of the DRI reports significantly.

Finally, by identifying and assessing potential sources of uncertainty and bias in intake estimates and measures of nutritional status, this information could also be informative for the expert panel activities in the hazard identification and dose-response assessment steps – in evaluating the potential for biases in published data used in evaluating dose-response relationships, in comparing results across studies, or in combining data from several studies to generate a composite dose-response curve.

#### **Step 4 in Risk Assessment: Risk Characterization**

The final step in the risk assessment model is the risk characterization step. From a user perspective, it is perhaps the most important step; but in practice, it is a step that has not always been well developed. Its importance was highlighted in a 1996 IOM report (IOM 1996). This step does not recommend a course of action for addressing potential public health risks as that is the responsibility of the risk manager (i.e., users). Rather this step provides an assessment of the nature of the public health consequences of exceeding the UL. Information is also frequently provided on vulnerable groups for whom the UL may not be appropriate.

#### *Current Use of the 'Risk Characterization' Step in Deriving UL*

There is considerable variability in the completeness of current risk characterization sections. For example, the risk characterization section in the zinc chapter does not discuss the fact that the intake distributions provided in the appendices showed that a relatively high prevalence of young children had intakes that exceeded their UL. The public health implications of these excessively high intakes were also not discussed.

#### *Possible Use of the 'Risk Characterization' Step for Deriving the RDA*

Although a risk characterization step was not included in the sections of the reports that addressed issues related to the derivation of the RDA, it is likely that a comprehensive analysis and characterization of the potential public health implications of current intakes relative to the prevalence of inadequate intakes and nutritional status would be valuable to users of the DRI.

#### *Examples of how use of the 'risk characterization' step in a risk assessment framework could help in identifying improvements for future consideration*

A major advantage of applying a risk characterization approach to both the RDA and UL decision-making process is that the public health implications of nutrients that either fail to meet a RDA-related reference level or exceed the UL reference level could be considered together. For nutrients where there is a narrow range between the RDA and the UL, a comprehensive and concurrent analysis of the public health implications of current intakes could enhance the ability of users to apply these reference values to situations where they must deal with the competing pressures of achieving adequate intakes for low consumers while not exceeding safe intakes for high consumers. For other nutrients (e.g., folate) where data are available for both intakes and clinical/biochemical measures of status, a rigorous analysis in this section could provide guidance for users who need to understand the public health implications of frequently observed inconsistencies between prevalence estimates based on intake estimates versus measures of status.

Finally, by consistently applying the risk characterization step to both the assessment of adequacy and toxicity, approaches suggested by Renwick et al. (2004) for deriving and directly comparing intake-incidence curves for risks associated with both adequacy and toxicity may be considered. Illustration of

this approach (i.e., the “Full Probability Approach”) was provided in Table 14-1 for inadequate intakes of iron (IOM 2001, pg 571). This approach has been suggested as providing an enhanced basis, as compared with current cut-point approaches, for identifying intakes that will maximize the likelihood of adequate intakes while minimizing the risk of adverse effects from excessive intakes (Renwick et al. 2004). If intake-incidence curves were included, this step could discuss the public health implications with use of the traditional cut-point reference values as well as the public health implications with use of intake-incidence curves – thus providing users with maximum flexibility to decide which level of adequacy and which approach works best for their particular application.

### **Risk Assessment and Risk Management: What Interactions Are Needed?**

This paper began by describing the different roles of risk managers (i.e., the broad range of ‘users’ of the risk assessments) and the risk assessors (i.e., the scientists) but also emphasizing the need for appropriate interactions to ensure the usefulness of the risk assessment report while preserving the independence and integrity of the scientific risk assessment process itself. What then are appropriate points and types of interactions between these two groups? These interactions typically come at two different points in time – at the beginning of the risk assessment process to ensure that the risk assessors understand the risk managers’ needs for the risk assessment. And, at the end of the risk assessment process to enhance the likelihood that the results of the risk assessment will be presented in a manner that is most meaningful and helpful to those persons and groups who will be using the results of the risk assessment for a wide range of applications.

The first interaction period is commonly called ‘problem formulation’. For the DRI, there are a broad range of potential uses and users. The nature of the nutrient risk manager questions for UL has been described in the FAO/WHO (2006) report. Similar needs would be expected for the RDA.

Generally, there are two types of information that risk managers need to address. First, is there a need for action? Secondly, if so, what information is needed to decide how best to develop a program, policy, counseling advice, or educational program to ensure a safe and adequate intake level by population groups, clients, research participants, and consumers?

Possible examples of the types of problem formulation issues that could be posed for the DRI process include:

- Provide intake reference values for adequate and tolerable upper limits
- Provide reference values for groups but also provide guidance for applying these values to individuals

- Provide reference values for the healthy general population but also provide guidance for applying these values to members of the general population who are at increased risk of chronic diseases
- Express reference values using traditional cut-points but also provide information on intake-incidence curves (probability curves) when data permit.
- Provide reference values for individual nutrients but also provide guidance for potential nutrient-nutrient interactions that need to be considered.
- Provide reference values for individual nutrients but also provide guidance for incorporating these values into a total diet context.
- Describe special vulnerable groups for whom the DRI are not appropriate or may need to be adjusted.

The second type of interaction between risk managers and risk assessors can occur towards the end of the risk assessment process. The purpose of this interaction is not to provide a forum for risk managers to challenge the scientific assessment, but rather to ensure that the analysis and documentation of the risk assessment are presented in ways that will enhance the usability of the report by the wide range of users of DRI reference values. Conversely, the purpose of this interaction is not to provide risk assessors an opportunity to tell risk managers how to make policy or program decisions. The mixing of science and policy by risk assessors runs the risk of undermining the integrity of the scientific reviews. If government agencies or other groups need advice on how best to implement a policy or program that uses the DRI, they can convene advisory panels independent of the risk assessment process. While this latter type of advisory committee is common, it is different from the science-based risk assessment process. A policy-based advisory committee is generally composed of a mixture of scientists and other stakeholders and is specifically charged with addressing the appropriate use of a science-derived assessment in policy applications. On the other hand, a risk assessment committee is composed of qualified scientists and conflicts of interest and undue stakeholder pressures are minimized. This does not mean that the risk assessment scientific panels can not solicit information from stakeholders that may be of use in their scientific assessments but it does provide a mechanism for maintaining the independence and integrity of the scientific process itself.

## **Summary and Conclusions**

This paper discussed the characteristics of risk assessment in general and described how it was applied to the derivation of UL reference values during the recently completed DRI process. A major goal of the paper is to describe the strength of risk assessment as an organizing framework while also noting that its use provides for flexibility in methodologies and terminologies as appropriate in specific applications. The paper suggests some ways in which the organizing

framework components could be extended to derivation of the reference values for adequate intakes. Some suggestions for modifications in terminologies and methodologies if this were to be done are made. Finally, the paper suggests some issues that, if the organizing framework of risk assessment were to be applied to the derivation of reference values for both adequacy and toxicity, could help to identify ways to 'tweak' future DRI initiatives so as to enhance the usability of the reports for the broad range of program, policy, counseling and educational applications for which the DRI reference values are used. Hopefully, all of these points, as well as others not identified in this paper, will stimulate further discussions as to the usefulness of a risk assessment framework in future DRI reviews.

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