Comparing the Recommended Dietary Allowance to Toxicity Values for Zn, Se, Mn, and Mb

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For essential trace elements, *e.g.*, Zn, Se, Mn, and Mb, toxicity can develop at varying levels above the required dietary intake level.

Examples will be given to show the margin of safety between nutritional requirement and toxicity.
Definition of Recommended Dietary Allowance (RDA)

The average daily dietary nutrient intake level sufficient to meet the nutrient requirement of nearly all (97-98%) healthy individuals in a particular life state and gender group.

\[
\text{RDA} = \text{EAR} + 2 \times \text{SD}_{\text{EAR}}
\]

\[
\text{EAR} = \text{Estimated Average Requirement}
\]
Definition of Estimated Average Requirement (EAR)

The EAR is the daily intake value that is estimated to meet the nutritional requirement, as defined by a specific indicator of adequacy, in one-half of the apparently healthy individuals in a life stage or gender group.
Definition of Adequate Intake (AI)

- A nutrient consumption value that is experimentally derived or is an approximation of an observed mean nutrient intake for a group of apparently healthy individuals.
- An AI is established when there is not sufficient scientific evidence to calculate an EAR.
- The AI replaces the Estimated Safe and Adequate Daily Dietary Intakes (ESADDI).
**Tolerable Upper Intake Level (UL)**

- The UL is the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects in almost all individuals in a specific life stage group.

* (An upper limit safe dietary intake level established by nutritionists)
Definition of Reference Dose (RfD) *

An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) this is likely to be without appreciable risk of deleterious effects throughout the lifespan of the individual.

* (A “safe oral exposure level” determined by toxicologists)
## Uncertainty Factors

**Default**

<table>
<thead>
<tr>
<th>UFx</th>
<th>Factor</th>
<th>Extrapolation</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>10</td>
<td>Average Human to Sensitive Human</td>
</tr>
<tr>
<td>A</td>
<td>10</td>
<td>Animal to Human</td>
</tr>
<tr>
<td>S</td>
<td>10</td>
<td>Subchronic (90 days) to Chronic Exposure</td>
</tr>
<tr>
<td>L</td>
<td>10</td>
<td>LOAEL to NOAEL</td>
</tr>
<tr>
<td>D</td>
<td>10</td>
<td>Completeness of Database</td>
</tr>
</tbody>
</table>

A value of 1, 3, or 10 is typically used in each category.
Sequence of Scientific Judgments Used in the Chemical Risk Assessment Process

* Identify the Chemical Hazard
  * Determine the Critical Study(ies)
  * Establish the Critical Adverse Effect(s)
    * Include Important Supporting Data
    * Determine the Uncertainty Factors
    * Determine the Reference Dose
Zinc Nutritional Need

- Biochemical need – for the activity of 200 metabolic enzymes
- Physiological description – Zn is needed for reproductive function & neurological development
- Recommended Dietary Allowance
  
<table>
<thead>
<tr>
<th>Gender</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>11 mg/day</td>
</tr>
<tr>
<td>Female</td>
<td>8 mg/day</td>
</tr>
</tbody>
</table>

- UL – 40 mg/day
Zinc RfD

- Critical Adverse Effect – Decrease in RBC superoxide dismutase activity in females
- NOAEL – None
- LOAEL – 60 mg/day
- Total Uncertainty Factor –3 for minimal LOAEL
- Reference Dose (RfD) – 0.3 mg/kg-day
  (21 mg/day for a 70 kg adult)
Selenium Nutritional Need

- Biochemical need – co-factor for glutathione peroxidase & other selenoenzymes
- Physiological description – needed for heart muscle development and function
- Recommended Dietary Allowance
  - Adult: 55 µg/day
  - Infant: 2.2 µg/day
  - Child (20 kg): 1 to 3 µg/day
- UL – 400 µg/day
Selenium RfD

- Critical Adverse Effect – loss of hair & nails
- NOAEL – 0.015 mg/kg-day
- LOAEL – 0.023 mg/kg-day
- Total Uncertainty Factor – 3 for sensitive subgroup
- Reference Dose (RfD) – 0.003 mg/kg-day
  
  *(210 µg/day)*
## Manganese Nutritional Need

- **Biochemical need** – an activator of hydrolases, kinases, decarboxylases, transferases & metalloenzymes
- **Signs of Deficiency** – dermatitis, low cholesterol, clotting deficiencies, reddened hair
- **Adequate Intake (AI)**
  - Female: 1.8 mg/day
  - Male: 2.1 mg/day
  - Child: 1.2 to 1.5 mg/day
- **UL**
  - Adults: 11 mg/day
  - Child: 3 mg/day
Manganese RfD

- Critical Adverse Effect – neurological disturbances including tremors & dystonia
- NOAEL – 0.14 mg/kg-day
- LOAEL – Not definitively established
- Total Uncertainty Factor - 1
- Reference Dose (RfD) – 0.14 mg/kg-day
  (9.8 mg/day)
Molybdenum Nutritional Need

- Biochemical need – co-factor for sulfite oxidase, xanthine oxidase & aldehyde oxidase
- Signs of Deficiency – impaired neurological function
- Recommended Dietary Allowance
  - Adults 45 µg/day
  - Child (20 kg) 34 µg/day
- UL – 2000 µg/day
Molybdenum RfD

- Critical Adverse Effect – increased uric acid levels in serum of humans
- NOAEL – none
- LOAEL – 0.14 mg/kg-day
- Uncertainty Factor – 30 (3 \( UF_H \), 10 \( UF_L \))
- Reference Dose (RfD) – 0.005 mg/kg-day
  \((350 \mu g/day)\)
### Comparison of RDAs, RfDs and ULs for Zn, Se, Mn, and Mb

<table>
<thead>
<tr>
<th>ELEMENT</th>
<th>RDA (mg/day)</th>
<th>RfD (µg/day)</th>
<th>UL (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zn</td>
<td>11</td>
<td>15</td>
<td>40</td>
</tr>
<tr>
<td>Se</td>
<td>55</td>
<td>210</td>
<td>400</td>
</tr>
<tr>
<td>Mn</td>
<td>2.3</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Mb</td>
<td>45</td>
<td>350</td>
<td>2000</td>
</tr>
</tbody>
</table>

**Note:** The units for Zn, Mn, and Mb are mg/day, while Se is given in µg/day.
## Ratio of Nutritional Need to Toxicity

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Ratio to RfD</th>
<th>Ratio to UL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zn</td>
<td>1.3 Fold</td>
<td>4 Fold</td>
</tr>
<tr>
<td>Se</td>
<td>4 Fold</td>
<td>8 Fold</td>
</tr>
<tr>
<td>Mn</td>
<td>5 Fold</td>
<td>5 Fold</td>
</tr>
<tr>
<td>Mb</td>
<td>8 Fold</td>
<td>40 Fold</td>
</tr>
</tbody>
</table>
## Ratio of Nutritional Need to Toxicity for Zinc in Various Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>RDA (mg/kg)</th>
<th>Ratio RfD/RDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant</td>
<td>0.85</td>
<td>0.35</td>
</tr>
<tr>
<td>Toddler</td>
<td>0.33</td>
<td>0.91</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>0.22</td>
<td>1.36</td>
</tr>
<tr>
<td>Lactation</td>
<td>0.24</td>
<td>1.14</td>
</tr>
<tr>
<td>Adult Male</td>
<td>0.16</td>
<td>1.35</td>
</tr>
<tr>
<td>Adult Female</td>
<td>0.16</td>
<td>1.35</td>
</tr>
</tbody>
</table>
Ratio of Nutritional Need to Toxicity for Zn in Various Groups

mg/kg

Infant  Child  Lactation  Pregnancy

RDA
RFD
UL
Note

- **Risk Characterizations** are usually written for toxicity assessments and are usually written for individual compounds.

- Since the nutritional databases are quite similar for these trace elements but the toxicity data are variable, nutrition data will be discussed as a group and toxicity data will be discussed as a separate group.
The nutritional databases are quite strong since human data is available for varying age groups as well as pregnancy & lactation. The process of quantifying daily requirements for adults is straightforward, however, extrapolation was sometimes used for other age groups. Few assumptions were made regarding the nutritional data.
Risk Characterization
(Toxicity)

- Although human toxicity data are used for each of the elements, not all age and gender groups have been fully evaluated.
- The procedures for determining Uncertainty Factors have not been applied uniformly and is not consistent with the process used for xenobiotics.
Summary

- The nutritional need to toxicity ratios for these trace elements range from 1.3 to 40.
- When subgroups such as infants, children and pregnant mothers are included there is a wide range of RDAs and for the ratio to toxicity values and there is even greater variation.
- The RfD methodology, as currently used, needs to be modified for establishing quantitative toxicity values for essential nutrients.
Recommendations

- A separate methodology for risk assessment of essential nutrients is needed so that accurate values are established for all subgroups.
- One adjustment to the methodology would be to use Modifying Factors that may be less than one.
- More information pertaining to human subgroups including children is needed.
Key References

Disclaimer

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