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Trace element risk assessment: essentiality vs. toxicity

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Abstract

Risk assessment of essential trace elements examines high intakes resulting in toxicity and low intakes resulting in nutritional deficiencies. This paper analyzes the risk assessments carried out by several U.S. governmental and private organizations for eight essential trace elements: chromium, copper, iodine, iron, manganese, molybdenum, selenium, and zinc. The compatibility of the toxicity values with the nutritionally essential values is examined, in light of recently derived values, termed Dietary Reference Intakes, set by the U.S. Food and Nutrition Board of the Institute of Medicine. The results show that although there are differences in the values set by the different organizations, increased coordination has resulted in values that are more compatible than revealed in past evaluations.

Keywords: Risk assessment; Essential elements; Trace elements; Reference dose; Dietary reference intake; Recommended daily allowance; Estimated average requirement; Adequate intake; Tolerable upper intake level; Reference daily intake

1. Introduction

Essential trace elements are those compounds that need to be present in the human diet to maintain normal physiological functions. Risk assessment of trace elements has examined two ends of the toxicity spectrum: (1) that associated with intakes that are too high and the resulting toxicity, and (2) that associated with intakes that are too low and result in nutritional problems. The U.S. Environmental Protection Agency (EPA) has carried out risk assessments dealing with the toxicity end of the spectrum, developing Reference Doses (RfDs) for a large number of chemicals, including some essential trace elements. The World Health Organization (WHO) has set similar values for toxicity, termed Acceptable Daily Intakes (ADIs) and Provisional Maximum Tolerable Daily Intakes (PMTDIs). The U.S. Food and Nutrition Board of the Institute of Medicine has dealt with nutritional deficiency problems as well as toxicity by setting Dietary Reference Intakes (DRIs), which includes the Recommended Dietary Allowance (RDA), the Estimated Average Requirement (EAR), the Adequate Intake (AI), and the Tolerable Upper Intake Level (UL) for essential trace elements. These levels were published in 2000 and 2001, and replace the RDAs and the Estimated Safe and Adequate Daily Dietary Intakes (ESADDIs) that were set by the Food and Nutrition Board of the National Academy of Sciences in 1989. The U.S. Food and Drug Administration (FDA) has also examined the issue of nutritionally essential levels in setting Reference Daily Intakes (RDIs) for a number of essential elements.

In 1992, a workshop sponsored by the International Life Sciences Institute, the EPA, and the Agency for Toxic Substances and Disease Registry (ATSDR) examined the RfDs and RDAs for five trace essential elements (arsenic, chromium, manganese, selenium, and zinc) and compared and contrasted the methods used by toxicologists to set the RfDs with that used by nutritionists to set the RDAs. They concluded that neither the RfD nor the RDA should be assumed to be an absolute, rigid number. Instead, the workshop concluded that they both have a great deal of uncertainty surrounding them that must be taken into account, and that much of the apparent conflict between the values disappears when the scientific bases and the methods used to derive the values is examined. In addition, they

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concluded that closer coordination is needed between the nutrition and toxicology communities in setting acceptable ranges of intake for trace elements.

The purpose of this paper is to reexamine the conclusions from the 1992 workshop in light of the recent publication of the DRIs for essential trace nutrients. Eight essential elements will be examined: chromium, copper, iodine, iron, manganese, molybdenum, selenium, and zinc. This paper will present the basis for the RfDs, the RDAs or the AIs, the UIs, and the RDIs, and examine if a conflict exists between the values.

2. Toxicity risk assessments

2.1. EPA's reference dose

EPA sets RfDs, which represent an estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure to which the human population (including sensitive subpopulations) may be continually exposed over a lifetime without an appreciable risk of deleterious effects. The RfD is calculated to be protective against a critical effect, which also results in protection against other effects at higher doses. The RfD is calculated as follows: EPA reviews many human and/or animal studies and determines the highest dose level tested at which a critical adverse effect does not occur (NOAEL), or the lowest dose level at which a critical adverse effect does occur (LOAEL). Alternatively, EPA may determine the benchmark dose; i.e., the dose associated with a specified level of risk; it is determined by using a dose-response model. Uncertainty factors and an additional modifying factor may then applied to the NOAEL, LOAEL, or benchmark dose, according to the procedures presented in Table 1. The RfD is calculated in units of milligram per kilogram body weight per day (mg/kg-day) (U.S. EPA, 2002a).

The RfD is not a direct or absolute estimator of risk, but rather a reference point to gauge the potential effects. Doses at or below the RfD are not likely to be associated with any adverse health effects. However, exceedance of the RfD does not imply that an adverse health effect would necessarily occur. As the amount and frequency of exposure exceeding the RfD increases, the probability that adverse effects may be observed in the human population also increases (U.S. EPA, 2002a).

2.2. WHO acceptable daily intakes

WHO collects and evaluates scientific data on a variety of chemicals and makes recommendations on safe levels of use. They have estimated ADIs for a number of chemicals. ADIs are an estimate of the amount of a substance in food or drinking water that can be ingested daily over a lifetime without appreciable risk. They are calculated using the same basic approach as EPA's RfDs; a NOAEL or LOAEL is selected from a human or animal study and an uncertainty factor is applied, using the same basic uncertainty factors as EPA (Dourson and Lu, 1995). WHO has not calculated ADIs for essential trace elements.

2.3. WHO permissible maximum tolerable daily intakes

WHO sets PMTDIs for contaminants with no cumulative properties. A PMTDI represents a permissible human exposure as a result of natural occurrence of the substance in food and drinking water. For trace essential elements, a range is expressed; the lower value representing the level of essentiality and the upper value the PMTDI (Dourson and Lu, 1995).

3. Nutritional deficiency risk assessments

3.1. Dietary reference intake

DRIs consist of a set of nutrient-based reference values, including the RDA, the EAR, the AI, and the UL. Each of these values refers to average daily nutrient intake of individuals over time. For the majority of cases, the daily amount ingested may vary substantially, without adverse health effects. Each of these values represents the quantity of a nutrient supplied by foods from a diet similar to those consumed in the U.S. and Canada (Institute of Medicine, 2001).

Table 1
Uncertainty factors used by EPA, adapted from Abernathy and Roberts (1994)

Uncertainty (UF) or modifying factor (MF)	Comments	Standard value
UF: human, intraspecies variability	Used to account for variability in the human population	3–10
UF: animal to human, interspecies variability	Used to account for differences in response between animals and humans	3–10
UF: data gaps	Used to account for the inability of any study to account for all toxic endpoints	3–10
UF: LOAEL to NOAEL	Used when a LOAEL instead of a NOAEL is used as the basis	3–10
MF	Has been used for differences in absorption rates, tolerance to a chemical, or lack of a sensitive endpoint	1–10

3.1.1. Recommended daily allowance

The RDA is the average daily dietary intake level that is sufficient to meet the nutrient requirements of nearly all (97–98%) healthy individuals in a particular life stage and gender group. The RDA is intended to be used as a goal by individuals for daily intake. It is set based on observational and experimental studies in humans published in peer-reviewed journals (Institute of Medicine, 2001).

3.1.2. Estimated average requirement

The EAR is used as the basis for setting the RDA. The EAR is the daily intake value that is estimated to meet the requirement, as defined by the specified indicator or criterion of adequacy, in half of the apparently healthy individuals in a life stage or gender group. If the standard deviation of the EAR is available and the requirement for the essential element is symmetrically distributed, the RDA is set at two standard deviations above the EAR. If there are insufficient data about variability to calculate a standard deviation, a coefficient of variation (CV) for the EAR of 10% is assumed. If a 10% CV is assumed, then twice that amount when added to the EAR is equal to the RDA. If there is insufficient evidence to set an EAR, an RDA is not set (Institute of Medicine, 2001).

3.1.3. Adequate intake

If insufficient scientific evidence is available to set an RDA, then an AI may be set. An AI is used as a goal for nutrient intake for individuals. Generally, human data are used to set AIs, but if adequate data are not available, selected animal studies may be used (Institute of Medicine, 2001).

3.1.4. Tolerable upper intake level

The UL is the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population. As intake increases above the UL, the potential for adverse effects also increases. The UL is set based upon a risk assessment model that is similar to that used by the EPA to set the RfDs: a NOAEL or a LOAEL is selected and divided by an uncertainty factor. In general, the uncertainty factors used for nutrients are typically less than the factors of 10 often applied to nonessential toxic substances (Institute of Medicine, 2001). Since the UL was developed as part of the DRIs, it has been categorized as a nutritional deficiency risk assessment value. However, the UL is actually a toxicity risk assessment value, since it is intended to protect the population from adverse health effects resulting from excess exposure to a compound.

3.2. FDA recommended daily intakes

The FDA has set RDIs for 13 vitamins and 10 trace elements. RDIs were set by selecting the highest RDA (the RDAs set by the NAS in 1989) for adults and persons 4 years of age or older (excluding pregnant and lactating women) (FDA, 1995).

4. Trace elements risk assessments

In this section, a summary of key information concerning the essentiality and toxicity of the eight trace elements are presented. The essentiality and toxicity values for the eight elements are presented in Table 2.

Table 2
Summary of essentiality and toxicity data for eight essential elements[a]

Element	RDA (mg/day)	AI (ages 19–50 mg/day)	FDA RDI (mg/day)	UL > 19 yrs (mg/day)	RfD (mg/day)[b]	WHO PMTDI upper limit (mg/day)[b]
Chromium	NA	0.035 (M) 0.025 (F)	0.12	NA	105 (1.5 mg/kg-day)	NA
Copper	0.9	NA	2	10	NA	35 (0.5 mg/kg-day)
Iodine	0.15	NA	0.15	1.1	NA	1 (0.017 mg/kg-day)
Iron	8 (M and F > 51 yrs) 18 (F 19–50 yrs)	NA	18	45	NA	56 (0.8 mg/kg-day)
Manganese	NA	2.3 (M) 1.8 (F)	2	11	10 (0.14 mg/kg-day)	NA
Molybdenum	0.045	NA	0.075	2	0.35 (0.005 mg/kg-day)	NA
Selenium	0.055	NA	0.07	0.4	0.35 (0.005 mg/kg-day)	NA
Zinc	11 (M) 8 (F)	NA	15	40	21 (0.3 mg/kg-day)	NA

NA, not available.

[a] The values provided are for both males and females, unless (M) for males and (F) for females is noted.

[b] These values are calculated in mg/kg-day. They have been multiplied by 70 kg (the average body weight of an adult) in order to provide values in mg/day.

4.1. Chromium

4.1.1. Essentiality

Trivalent chromium (the form of chromium found in foods) is essential for maintaining normal glucose metabolism. Signs of chromium deficiency in humans include impaired glucose tolerance, glycosuria, fasting hyperglycemia, and elevated circulating insulin and glucagon. Severe symptoms such as nerve and brain disorders have been observed in patients on total parenteral nutrition. All of these signs and symptoms are reversible upon chromium supplementation (Anderson, 1994a). Chromium has been shown to potentiate the action of insulin (Mertz, 1969, 1993; Mertz et al., 1961), and some studies suggest that a low molecular weight chromium-binding substance my amplify insulin receptor tyrosine kinase activity in response to chromium (Davis and Vincent, 1997a,b; Vincent, 1999). An RDA has not been set for chromium. The AI for chromium for adults is 0.035 mg/day for males and 0.025 mg/day for females. These values are based on a mean chromium content of 22 well-balanced U.S. adult diets designed by nutritionists of 13.4 μg/1000 kcal, with an energy intake estimate of 1850 kcal/day for women and 2800 kcal/day for men (Institute of Medicine, 2001). The RDI for chromium is 0.12 mg/day (FDA, 1995).

4.1.2. Toxicity

The toxicity of trivalent chromium appears to be quite low. The only adverse effects noted in humans have been liver and kidney problems after ingestion of very high doses (Fristedt et al., 1965; Kaufman et al., 1970; Wasser et al., 1997; Cerulli et al., 1998; Loubieres et al., 1999). No adverse effects were noted in rats and mice ingesting 5 mg/L chromium in drinking water over their lifetimes, and no toxicity was observed in rats exposed to 100 mg/kg in the diet (IPCS, 1988). Chronic exposure to chromate dust (hexavalent chromium) has been related to an increased incidence of lung cancer; however, no human studies have shown a relationship between trivalent chromium and cancer (Anderson, 1994a).

EPA has calculated an RfD of 1.5 mg/kg-day for trivalent chromium. This was based on a study in which rats were fed up to 5% chromic oxide in the diet for 600 feedings (840 days). No effects were noted at any dose level due to the chromic oxide, resulting in a NOAEL of 1468 mg/kg-day. An uncertainty factor of 100 was applied based on inter- and intra-species variability and a modifying factor of 10 was also applied to account for database deficiencies. EPA has low confidence in the study, database, and RfD due to the lack of specific detail on the study protocol and results and the lack of an observed effect level (U.S. EPA, 2002b).

A UL has not been set for chromium and WHO has not calculated a PMTDI for the element.

4.2. Copper

4.2.1. Essentiality

Copper has been recognized as an essential element for many years, due to its presence in important proteins and enzymes. Copper-deficient animals have exhibited anemia, skeletal defects, and degeneration of the nervous system, reproductive failure, and other effects (Davis and Mertz, 1987). Under normal circumstances, dietary copper deficiency has not been observed in adults, however, it was observed in malnourished children in Peru, with symptoms including anemia, neutropenia, and bone mineralization (Cordano et al., 1964). Human and animal studies suggest a correlation between the zinc-to-copper ratio in the diet and the incidence of cardiovascular disease (Klevay, 1984). The RDA for copper is 0.9 mg/day for adults. This was based upon the results of three studies on the effects of copper intake and copper status in the body. From these studies, an EAR of 0.7 mg/day for both men and women were calculated and a CV of 15% was used. The RDI for copper is 2.0 mg/day (FDA, 1995).

4.2.2. Toxicity

Very high levels of copper can cause acute toxicity. Human deaths have been known to occur from deliberate ingestion of large quantities of copper sulfate. In general, an oral dose of about 200 mg/kg-day is considered fatal in humans. Wilson's disease is an autosomal recessive condition characterized by a deficiency of the copper-protein ceruloplasmin. Individuals with Wilson's disease cannot adequately metabolize and eliminate copper, and progressive accumulation of copper in the brain, kidneys, and liver may occur if they do not control their intake of copper (IPCS, 1982). Abdominal pain, cramps, nausea, diarrhea, and vomiting have been seen from the consumption of beverages containing high levels of copper. However, no adverse gastrointestinal effects were reported in U.S. adults who consumed water containing approximately 8.5–8.8 mg/L copper for over 20 years beginning in childhood. Liver damage has been seen in individuals with Wilson's disease and other diseases of copper metabolism. However, studies have shown that, in addition to high levels of copper, genetic factors are required for liver damage to result from high levels of intake of copper (Joshi et al., 1987; Kishore and Prasad, 1993; Pandit and Bhave, 1996; Tanner, 1998).

EPA has not calculated an RfD for copper. The Institute of Medicine has set a UL for copper of 10 mg/day based on a critical endpoint of liver damage. A NOAEL of 10 mg/day was selected based on the results of a 12 week, double-blind study in which 10 mg of copper as copper gluconate capsules was ingested daily by seven adults and liver function tests were normal. An uncertainty factor of 1 was applied because of a large

database indicating no adverse effects from daily consumption of 10–12 mg/day of copper in foods and the fact that liver damage is rarely seen in human populations with normal copper metabolism (Institute of Medicine, 2001). WHO has set a PMTDI of 35 mg/day, based on the fact that copper does not appear to be a cumulative toxic hazard in humans, except for those individuals with Wilson's disease (IPCS, 1982).

4.3. Iodine

4.3.1. Essentiality

Iodine is an integral part of the thyroid hormones thyroxine and triiodothyronine, and is an essential element for all animal species, including humans (Hetzel and Maberly, 1986). Deficiency can lead to a number of diseases, ranging from enlargement of the thyroid to severe cretinism with mental retardation (NAS, 1989). An expert group of the Pan American Health Organization considered excretion of more than 0.05 mg of iodine per gram of creatinine as adequate for normal function, excretion of 0.025–0.05 mg/g as associated with increased risk of hypothyroidism, and excretion of less than 0.025 mg/g as indicative of serious risk for endemic creatinism (Querido et al., 1974). Since dietary iodine is well absorbed, a minimum level of 0.05–0.075 mg/day was determined to be necessary to maintain the higher level of iodine excretion in a population (NAS, 1989). The RDA for iodine is 0.15 mg/day based on an EAR of 0.095 mg/day calculated from studies of thyroidal radioiodine accumulation, and a CV of 40%. The RDI is also 0.15 mg/day (FDA, 1995).

4.3.2. Toxicity

Toxicity from excess iodine results in goiter, hypothyroidism, or hyperthyroidism in humans (Institute of Medicine, 2001). Acute toxicity of iodine to animals has resulted in death at levels of 200–500 mg/kg-day, while levels of iodine greater than 10 mg/day, due to the intake of iodine-containing drugs or the result of accidental poisoning, were toxic to some humans. Forty-eight individuals were reported to have adverse effects, including goiter, hypothyroidism, and sensitivity reactions, from iodine levels less than or equal to 10 mg/day (IPCS, 1988). One study reported that long-term intakes greater than 18 mg/day increased the risk of goiter (Wolff, 1969), and other studies have reported that high iodine intake is associated with an increased risk of thyroid papillary cancer in humans (Franceschi, 1998; Lind et al., 1998). EPA has not set an RfD for iodine. A UL of 1.1 mg/day was set based upon thyroid dysfunction as a critical endpoint. A LOAEL of 1.7 mg/day was selected based on two studies that reported elevated thyroid stimulating hormone (TSH) concentrations in men receiving iodine supplements. An uncertainty factor of 1.5 was applied to the LOAEL to derive a NOAEL of 1–1.2 mg/day. A further uncertainty factor was not applied to the NOAEL since there is little uncertainty about the ranges of iodine intake likely to induce elevated TSH concentrations (Institute of Medicine, 2001). WHO has set a PMTDI for iodine of 1 mg/day. This was based on the observation that an iodine intake of 1 mg/day or less is probably safe for the majority of the population, but may cause adverse effects for some individuals, e.g., people with thyroid disorders or those that are particularly sensitive to iodine (IPCS, 1988).

4.4. Iron

4.4.1. Essentiality

Iron is an essential element for humans. It is a constituent of hemoglobin, myoglobin and a number of enzymes, and as much as 30% of the body iron is found in storage forms such as ferritin and hemosiderin, in the spleen, liver, and bone marrow, and a small amount is associated with the blood transport protein transferrin. Iron deficiency results in anemia, which ranges from a fall in plasma ferritin with no functional impairment to severe iron deficiency characterized by small red blood cells with low hemoglobin concentrations (NAS, 1989). The Institute of Medicine calculated an RDA for iron of 8 mg/day for men and women over age 51, based on modeling the components of iron requirements, estimating the requirement for absorbed iron at the fiftieth percentile, and using an upper limit of 18% iron absorption. The RDA for iron for women ages 19–50 was calculated to be 18 mg/day, based on factorial modeling considering basal and menstrual losses (Institute of Medicine, 2001). The RDI is also 18 mg/day (FDA, 1995).

4.4.2. Toxicity

Acute toxicity resulting from the accidental ingestion of large doses of iron has been reported. Death has occurred from the oral ingestion of iron sulfate at doses ranging from 40 to 1600 mg/kg (Hoppe et al., 1955; NRC, 1979), with accidental iron overdoses being the most common cause of poisoning deaths in children under 6 years of age in the U.S. (FDA, 1997). Iron toxicity is characterized by vomiting and diarrhea, with subsequent effects on the cardiovascular and central nervous systems, kidney, liver, and blood (Anderson, 1994b). A genetic disease known as hereditary hemochromatosis is characterized by the long, slow accumulation of iron in tissues, without evidence of excessive iron intake (Bacon et al., 1999). Iron overload has also been reported in people with certain types of anemia, in particular when there are abnormalities in hemoglobin synthesis (Bothwell and Finch, 1968).

EPA has not calculated an RfD for iron. The Institute of Medicine has calculated a UL for iron, based on gastrointestinal effects seen after intake of iron supple-

ments in a Swedish study. A LOAEL of 70 mg/day was used, based upon 60 mg/day from the iron supplements and 10 mg/day from the estimated mean iron intake from food for women in six European countries. The LOAEL was divided by an uncertainty factor of 1.5, resulting in a UL of 45 mg/day (Institute of Medicine, 2001). WHO has calculated a PMTDI of 56 mg/day for iron from all sources except from iron oxides used as coloring agents, supplemental iron taken during pregnancy or lactation, and supplemental iron for specific clinical requirements. This was based on the observation that normal individuals have taken supplements of 50 mg/day ferrous iron for long periods of time without any adverse effects (IPCS, 1983).

4.5. Manganese

4.5.1. Essentiality

Manganese has been shown to be essential in every animal species studied. Deficiency signs include poor reproductive performance, growth retardation, congenital malformations in offspring, abnormal function of bone and cartilage, and impaired glucose tolerance (Hurley and Keen, 1987). There are two enzymes known to contain manganese; pyruvate carboxylase and superoxide dismutase (NAS, 1989). There has been one recorded case of a possible manganese deficiency in humans: a man in a vitamin K deficiency study who was fed a purified diet from which manganese was inadvertently omitted. The man developed a scaly, transient dermatitis, hypocholesterolemia, depressed vitamin K-dependent clotting factors, and a slight reddening of the hair. It was concluded that the inadvertent omission of manganese created a manganese-deficient-diet containing only 0.34 mg/day manganese (Keen et al., 1994). An RDA has not been calculated for manganese. An AI of 2.3 mg/day for males and 1.8 mg/day for females was set based on the FDA's Total Diet Study (1991–1997) that showed a median manganese intake for men of 2.1–2.3 mg/day, and for women of 1.6–1.8 mg/day. Because overt symptoms of manganese deficiency are not apparent in North America, these data were determined to be appropriate to set the AI. The highest intake values were used, since dietary intake assessment methods tend to underestimate the actual intake of foods (Institute of Medicine, 2001). The RDI is 2 mg/day (FDA, 1995).

4.5.2. Toxicity

Manganese is quite toxic via inhalation at high doses. Toxicity to humans is manifested by a psychologic and neurologic disorder, termed manganism, which closely resembles Parkinson's disease. Both manganism and Parkinson's disease involve alterations of neurotransmitter systems, and are irreversible processes (Keen et al., 1994). Two studies have reported toxicity from ingestion of drinking water containing high levels of manganese. In one study, 25 individuals in Japan consumed manganese-containing well water. Health effects included lethargy, tremor, and mental disturbances; the concentration of manganese was estimated to be at least 28 mg/L (Kawamura et al., 1941). In another study, neurologic symptoms were reported in individuals who consumed drinking water with manganese levels of 1.8–2.3 mg/L in Greece (Kondakis et al., 1989). In animals, the toxicity of ingested manganese is low and toxicity has been observed only after concentrations greater that 1.0 mg/g diet (Hurley and Keen, 1987).

EPA has calculated an RfD of 0.14 mg/kg-day for manganese. This was based on a NOAEL of 10 mg/day for chronic consumption of manganese in the diet from a composite of data from several studies and an uncertainty factor of 1. EPA has stated that there are significant concerns about possible adverse neurological effects at doses not far from the range of essentiality. Because of this concern, EPA recommended that a modifying factor of 3 be applied when assessing risk from manganese in drinking water or soil. EPA has medium confidence in the study, the database, and the RfD. This was based on the fact that there is no single study used to derive the RfD for manganese and no quantitative information is available to indicate toxic levels of manganese in the diet. In addition, EPA stated that numerous factors, such as dietary constituents, alcohol consumption, anemia, liver function, and general nutritional status can significantly influence an individual's manganese status (U.S. EPA, 2002c). The Institute of Medicine calculated a UL of 11 mg/day based on a study indicating that people who ate a Western-style diet and vegetarian diets may have intakes as high as 10.9 mg/day of manganese. Since no adverse effects have been noted, 11 mg/day was selected as a NOAEL from food, and an uncertainty factor of 1 was applied due to the lack of evidence of human toxicity from doses less than this level of manganese (Institute of Medicine, 2001). WHO has not calculated a PMTDI for manganese.

4.6. Molybdenum

4.6.1. Essentiality

Molybdenum is considered to be an essential element due to its role in several enzymes, such as aldehyde oxidase, xanthine oxidase, and sulfite oxidase (Rajagopalan, 1988). Molybdenum deficiency has not been documented in humans, except for one case in which a patient on long-term total parenteral nutrition developed symptoms including amino acid intolerance and irritability (Abumrad et al., 1981). Treatment with 0.3 mg/day ammonium molydate (equivalent to about 0.163 mg molybdenum) resulted in clinical improvement. Molybdenum deficiency has been seen in goats when they were fed a diet containing less than

0.00007 mg molybdenum per gram of diet. Symptoms included reduced weight gain, decreased food consumption, and impaired reproduction (Anke et al., 1985). An RDA of 0.045 mg/day was set based upon an EAR of 0.034 mg/day and a CV of 15%; these values were from controlled studies in which specific amounts of molybdenum were consumed (Institute of Medicine, 2001). The RDI for molybdenum is 0.075 mg/day (FDA, 1995).

4.6.2. Toxicity

Molybdenum toxicity was observed in humans in the U.S.S.R., where an excessive dietary intake of 10–15 mg/day was associated with an increased incidence of a goutlike syndrome, with elevated blood levels of molybdenum, uric acid, and xanthine oxidase (Koval'skiy and Yarovaya, 1966). However, there were methodological problems with these studies, including possible analytical difficulties in the assessment of blood and urinary copper levels, and the very small size of the control group compared to the group exposed to molybdenum (Institute of Medicine, 2001). Kidney failure was observed in rats after exposure to molybdenum at 80 mg/kg-day, but not at 40 mg/kg-day. There is also evidence of diuresis and proteinuria after animals ingested high doses of molybdenum (Bompart et al., 1990).

EPA has set an RfD of 0.005 mg/kg-day for molybdenum, based on a LOAEL of 0.14 mg/kg-day from a study in the U.S.S.R. This study showed that this level of molybdenum could result in serum uric acid levels elevated above the average range of the adult population. An uncertainty factor of 30 was applied for protection of sensitive human populations and for the use of a LOAEL rather than a NOAEL. EPA has medium confidence in the study, database, and RfD based on the fact that the study only examined gross physical effects of the disease and only some blood chemistry parameters (U.S. EPA, 2002d). A UL of 2 mg/day was calculated based upon a study showing adverse reproductive effects in female rats. A NOAEL of 0.9 mg/kg-day was selected, with an uncertainty factor of 10, based on the extrapolation of animal data to humans, and an additional uncertainty factor of 3, for intraspecies variation, yielding a total uncertainty factor of 30 (Institute of Medicine, 2001). WHO has not calculated a PMTDI for molybdenum.

4.7. Selenium

4.7.1. Essentiality

Selenium is essential due to its association with proteins, known as selenoproteins (Stadtman, 1991). Fourteen selenoproteins have been identified to date in animals, with several selenoproteins defending against oxidative stress (Flohe, 1988), others regulating thyroid hormone metabolism (Berry and Larsen, 1992), and additional selenoproteins regulating the redox status of vitamin C and other molecules (May et al., 1998). In 1979, Chinese scientists reported an association between low selenium status and Keshan disease, a cardiomyopathy that primarily affects young children and women of child-bearing age (Keshan Disease Research Group, 1979). However, newer research suggests that this disease appears to be triggered by an additional stress, such as a chemical exposure or an infection (Ge et al., 1983). In animals, many diseases are caused by simultaneous deficiencies of selenium and Vitamin E, and they can be prevented or cured by supplementation with either nutrient alone (NRC, 1983).

The RDA for selenium was calculated based upon the results of two studies of selenium supplementation. The first study was in China; the results indicated that a daily intake of selenium of 0.041 mg/day from the diet plus 0.030 mg/day from supplements resulted in a plateau being reached in the activity of plasma glutathione peroxidase. An EAR of 0.052 mg/day, after adjusting the weight for North American males was calculated. The second study was in New Zealand, and consisted of 52 adults who were given selenium supplements for 20 weeks, with an EAR of 0.038 mg/day. The average of these studies, 0.045 mg/day was chosen as the EAR for selenium. The RDA was set by assuming a CV of 10% because information was not available on the standard deviation of the requirement for selenium. Therefore, the RDA was calculated to be 0.055 mg/day (Institute of Medicine, 2000). The RDI for selenium is 0.07 mg/day (FDA, 1995).

4.7.2. Toxicity

Chronic toxicity of selenium in humans results in a condition termed selenosis, characterized by hair and nail loss and brittleness, gastrointestinal problems, skin rash, garlic breath odor, and nervous system abnormalities (Yang et al., 1983). In China, it was reported that selenosis occurred with increased frequency in people who consumed selenium at levels above 0.85 mg/day (Yang and Zhou, 1994). Selenosis was also reported in the United States in 13 people who ingested dietary supplements containing 27.3 mg of selenium per tablet (Helzlsouer et al., 1985). In another study in China, approximately 5 mg/day of selenium from foods resulted in fingernail changes and hair loss. It was also reported that a person who consumed 1 mg of selenium daily as sodium selenite for more than 2 years had symptoms of selenosis (Yang et al., 1983).

EPA has set an RfD of 0.005 mg/kg-day. This was based on an epidemiological study of 400 individuals in China. Selenosis was observed in 5 out of 349 adults, with blood selenium concentrations in this group ranging from 1.054 to 1.854 mg/L, with a mean of 1.346 mg/L Clinical signs observed included garlic odor of the

breath, thickened and brittle nails, hair and nail loss, lowered hemoglobin levels, mottled teeth, skin lesions, and central nervous system abnormalities. EPA correlated the whole blood selenium level at which clinical selenosis occurred (1.35 mg/L) with 1.262 mg/day of selenium intake. The next lowest blood selenium level, which did not show signs of selenosis, was 1.0 mg/L, corresponding to 0.853 mg/day selenium intake. EPA used 0.85 mg/day selenium as the NOAEL and 1.26 mg/day as the LOAEL. An uncertainty factor of 3 was applied to the NOAEL to account for sensitive individuals. EPA has medium confidence in the study on which the RfD was based since this was an epidemiological study with a sizable population with sensitive subpopulations, but there were several possible interactions that were not fully accounted for; high confidence in the data base because many animal studies and epidemiologic studies support the principal study; and therefore high confidence in the RfD (U.S. EPA, 2002e). The Institute of Medicine has set a UL of 0.4 mg/day for selenium based on the same study as was used by the EPA to set the RfD. The same NOAEL, 0.80 mg/day, (rounded from the EPA value of 0.85), was used, with an uncertainty factor of 2 applied to protect sensitive individuals. Since the toxic effect is not severe, but may not be readily reversible, an uncertainty factor of 2 was deemed appropriate (Institute of Medicine, 2000). WHO has not set a PMTDI for selenium.

4.8. Zinc

4.8.1. Essentiality

Zinc is a component of a wide variety of enzymes, including the ribonucleic polymerases, alcohol dehydrogenase, carbonic anhydrase, and alkaline phosphatase (Institute of Medicine, 2001). Signs of zinc deficiency in humans include loss of appetite, growth retardation, skin changes, and immunological abnormalities. Studies in animals have shown that zinc deficiency during pregnancy may lead to developmental disorders in the offspring (Hurley and Baley, 1982).

The RDA for zinc was set based upon several studies that investigated the minimal quantity of absorbed zinc that is adequate to replace endogenous losses of zinc. Based upon these studies, an EAR of 9.4 mg/day for males and 6.8 mg/day for females were calculated. A CV of 10% was applied, resulting in an RDA of 11 mg/day for males and 8 mg/day for females (Institute of Medicine, 2001). The RDI for zinc is 15 mg/day (FDA, 1995).

4.8.2. Toxicity

Gastrointestinal irritation and vomiting have been observed following the ingestion of 2 g or more of zinc sulfate (Prasad, 1976). Impairment of the copper status of volunteers by dietary intakes of 18.5 mg/day (Festa et al., 1985) or 25 mg/day (Fischer et al., 1984) has also been observed. Intake of 300 mg/day of zinc sulfate for 6 weeks resulted in some functional impairment of the immune system (Chandra, 1984). Studies have investigated the effects of zinc supplementation on the high-density lipoprotein (HDL) levels of adult males. One study reported that zinc supplementation was found to lower HDL levels in healthy men (Hooper et al., 1980), although in another study, HDL levels returned to normal 11 weeks after supplementation ended (Pennington et al., 1989).

EPA has set an RfD of 0.3 mg/kg-day for zinc. This was based on a clinical study that investigated the effects of oral zinc supplements on copper and iron balance. A LOAEL of 1 mg/kg-day was determined as the level that caused a 47% decrease in erythrocyte superoxide dismutase concentration in adult females after 10 weeks of zinc exposure. An uncertainty factor of 3 was applied, based on a LOAEL from a moderate-duration study of sensitive humans, considering that zinc is an essential nutrient. EPA has medium confidence in the studies on which the RfD was based since they are well-conducted clinical studies with many biochemical parameters, but only a few humans were tested; medium confidence in the overall database since the studies were all of short duration; and medium confidence in the RfD (U.S. EPA, 2002f). A UL of 40 mg/day was set based upon a LOAEL of 60 mg/day from a study that investigated altered copper balance from ingestion of zinc gluconate for 10 weeks. An uncertainty factor of 1.5 was used to account for sensitive humans and for extrapolation from a LOAEL to a NOAEL. A higher uncertainty factor was not used because reduced copper levels are uncommon in humans. WHO has not set a PMTDI for zinc.

5. Discussion

There are four compounds with both RfDs and ULs: manganese, molybdenum, selenium, and zinc. The RfD and UL for manganese are similar (10 and 11 mg/day, respectively), as are the values for selenium (0.35 and 0.4 mg/day, respectively). However, the UL for molybdenum (2 mg/day) is approximately six times greater than the RfD for the same compound (0.35 mg/day), while the UL for zinc (40 mg/day) is twice the RfD (21 mg/day). Since both the RfD and UL represent the upper level at which there are not likely to be adverse health effects in a population, these values would be expected to be in the same range. The reason for the differences between the RfD and the UL appears to be primarily a difference in uncertainty factors. In the calculations of the RfD, historically animal studies have been used as the basis, with uncertainty factors set based on multiples of 10, with little precedent for using uncertainty factors less than 3. However, in the calculation

of the ULs, human studies are primarily being used with smaller uncertainty factors routinely applied.

None of the elements have RDAs or AIs in the same range as the RfDs. In the past, RDAs were often set at similar levels to the RfDs. Olin (1998) documented three major reasons why this occurred: (1) the uncertainty in the data results in both the RfD and the RDA being set more conservatively; with the RDA being set at higher dietary intakes and the RfD being set at lower intakes, (2) the RfD is usually set based on animal data, while the RDA is based primarily on human data. Thus, in the RfD calculations, a 10-fold uncertainty factor for interhuman variability is almost always applied, and other uncertainty and modifying factors also may be applied. However, the RDA calculation typically applies only a factor of 1.3 to the estimated population mean requirement, and (3) the RfD is intended to cover sensitive subpopulations, while the RDA is estimated to satisfy the nutritional needs of 97.5% of the healthy U.S. population.

PMTDIs have been calculated by WHO for three of the eight essential elements: copper (35 mg/day), iodine (1 mg/day), and iron (56 mg/day). For iodine and iron, the PMTDIs are in a similar range to the ULs: iodine has a UL of 1.1 mg/day and iron has a UL of 45 mg/day. However, the UL for copper is 10 mg/day, one-third the value of the PMTDI. The reason for this difference appears to be due to the fact that the copper UL was developed examining all the human data on liver effects after chronic exposure to copper, selecting a NOAEL of 10 mg/day. The PMTDI was not set using the same database, and appears to be set based upon a higher NOAEL.

The RDIs were set based upon the RDAs developed by the NAS in 1989, and thus it is not surprising that these values differ from the current RDAs. Although most of the values are in the same general range, the copper RDI (2 mg/day) is twice the level of the copper RDA (0.9 mg/day), and the RDI for zinc (15 mg/day) is almost twice the RDA for zinc for females (8 mg/day).

6. Conclusions

The conclusions of the 1992 workshop on the risk assessment of trace essential elements was that closer coordination is needed between the nutrition and toxicology communities in setting acceptable ranges of intake for trace elements. It appears that a good attempt has been made at meeting this goal in setting the DRIs by the Institute of Medicine. The ULs have been set based on the same method as used by the EPA to set the RfDs. The differences in these values seem to be due to the uncertainty factors applied, and the data sets investigated. Many of the RfDs were set years ago and need to be updated based upon the newer data that has since become available and was used to set the DRIs. In addition, the fact that the RfD is intended to protect sensitive subpopulations, while the RDAs and the ULs are intended to protect 97–98% of the population, also results in differences in the values. This difference appears to be manifested in the uncertainty factors applied, since EPA often applies an additional uncertainty factor of 10 to account for sensitive subpopulations.

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