

Essentiality and toxicity of selenium with respect to recommended dietary allowances and reference doses¹

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Selenium is a nutrient with multiple metabolic fates determined in part by dosage level. Thus it can be associated with impaired performance at both extremes of intake. Low selenium intake can result in dysfunction characterized by clinical signs in “deficiency” syndromes, whereas excessive selenium intake can alter function, usually in different ways that are characterized by other signs of toxicity (1). Two constructs have been developed in the United States for considering the health implications of extremes in selenium exposure, the recommended dietary allowance (RDA), derived by a committee of the Food and Nutrition Board of the National Research Council, and the reference dose (RfD), derived by the Reference Dose Working Group of the United States Environmental Protection Agency (EPA). These constructs were reviewed and critiqued in March 1992 at a workshop on risk assessment of trace elements, held in Herndon, Virginia, under the sponsorship of the EPA and the International Life Sciences Institute/Risk Science Institute. The following analysis will be presented in detail in the proceedings of that workshop.

Recommended daily allowance for selenium

An RDA was established only recently for selenium (RDA_{Se}) (2). The scientific rationale for the RDA_{Se} , as reviewed by Levander (3), is based upon the results of the study by Yang et al (4), which showed young men of very low selenium status to respond to daily dietary supplements of selenium given as L-selenomethionine (SeMET) with increases in their plasma activities of selenium-dependent glutathione peroxidase (SeGSHpx). With the use of the selenium value that Yang et al (4) reported to support maximal SeGSHpx activities, $40 \mu\text{g} \cdot \text{d}^{-1}$, and a presumed coefficient of variation of 15% [thus an upward adjustment by a factor of 1.3 (ie, 2 SD) to accommo-

date the selenium needs of 97.5% of the population], the RDA_{Se} was calculated as $RDA_{Se} = [(40 \mu\text{g} \text{ selenium} \cdot \text{d}^{-1})/60 \text{ kg body weight}] \cdot 1.3 = 0.87 \mu\text{g} \text{ selenium} \cdot \text{kg body weight}^{-1} \cdot \text{d}^{-1}$. With adjustments for average body weights of “typical” Americans (men 79 kg, women 63 kg), the value becomes about 70 and 55 $\mu\text{g} \cdot \text{d}^{-1}$ for men and women, respectively.

The explicit assumptions in deriving the RDA_{Se} are that 30 $\mu\text{g} \cdot \text{d}^{-1}$ of supplemental selenium supported maximal plasma SeGSHpx activity in the study of Yang et al (4), that a “background” intake of 10 $\mu\text{g} \cdot \text{d}^{-1}$ occurred in that study, that intraindividual selenium needs to show a coefficient of variation of 15%, that the young Chinese men in that study weighed 60 kg, and that Americans weigh about 79 kg (men) and 63 kg (women). In addition, other assumptions are implicit to the derivation of the RDA_{Se} , for example, that the bioavailability of selenium in the experimental supplement (SeMET) is equivalent to that of the “background” (ie, dietary) selenium in the Yang et al (4) study, that selenium needs vary linearly with body weight and are independent of gender, age and other variables, and that the maximal SeGSHpx activity is optimal physiologically. Each of these assumptions is open to some debate. In particular, the assumption that maximal SeGSHpx activity is optimal is difficult to defend. It is possible that less than maximal SeGSHpx activities (eg, 80%) may be physiologically adequate, particularly in individuals with adequate vitamin E.

Thus the derivation of the RDA_{Se} involved several assumptions made largely on the basis of judgment. The value so derived, therefore, must be considered subject to error according to the accuracy of the assumptions. With an alternative set of assumptions and the same basic data, it can be fairly argued that the RDA_{Se} could be as much as one-third lower than its current value. It should be noted that the putative anticarcinogenic activities of selenium compounds (5) were not considered in the derivation of the RDA_{Se} due to the specificity implied in the definition of the RDA as a nutrient level adequate to meet “all known nutritional needs.”

Reference dose for selenium

An RfD has also been established for selenium (RfD_{Se}) (6). The rationale for its derivation has been described by Abernathy et al (7). The critical study

¹ Extended abstract: full report to be published in S Olin, ed. *Risk Assessment of Essential Elements: Proceedings of a conference on risk assessment of essential elements, Herndon, Virginia*. In press.

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upon which the RfD_{Se} was based is that conducted by Yang et al (8, 9) (ie, the same research group that produced the critical study upon which the RDA_{Se} was based). According to the conclusion that no adverse effects were observed among individuals with blood selenium concentrations as great as $1 \text{ mg} \cdot \text{l}^{-1}$ (ie, 1000 ppb), the regression of the blood selenium concentration (Y) and dietary selenium intake (X) calculated by Yang et al (9) ($\log Y = 0.767 \log X - 2.248$) yielded a no-observed adverse-effect level (NOAEL) of intake of $0.853 \text{ mg} \cdot \text{d}^{-1}$. This NOAEL was adjusted according to the mean body weight of the subjects in the Yang et al study (9) and by an uncertainty factor of 3 to derive the RfD_{Se} as $RfD_{Se} = (0.853 \text{ mg selenium} \cdot \text{d}^{-1}) / (55 \text{ kg body weight} \cdot 3) = 0.005 \text{ mg selenium} \cdot \text{kg body weight}^{-1} \cdot \text{d}^{-1}$. With the aforementioned reference body weights, this RfD_{Se} value projects NOAEL values of $395 \mu\text{g} \cdot \text{d}^{-1}$ and $315 \mu\text{g} \cdot \text{d}^{-1}$ for American men and women, respectively. These levels are within known selenium intakes of apparently healthy populations.

The explicit assumptions upon which the RfD_{Se} is based have been reviewed (6, 7). They are that the NOAEL could be based on a blood selenium concentration of $1 \text{ mg} \cdot \text{l}^{-1}$, that blood selenium (Y) is related to dietary selenium intake (X) according to the function: $\log Y = 0.767 \log X - 2.248$, that subjects of the Yang et al study (9) had a mean body weight of 55 kg, and that an uncertainty factor of 3 is appropriate. In addition to these explicit assumptions, the derivation of the RfD_{Se} would appear to involve certain implicit assumptions, for example, that the findings of Yang et al (9) are generalizable, that the NOAEL varies linearly with body weight, and that no other variables affect the toxic potential of selenium. Again, these assumptions are open to some debate.

The derivation of the RfD_{Se} reveals, like that of the RDA_{Se} , a set of assumptions made largely on judgment. Therefore, alternative judgments concerning some of these assumptions can yield RfD_{Se} values that differ from the one presented. For example, if one were to assume that an American population is likely to consume more biologically available zinc, more total protein, and more methionine (all of which have been shown to reduce selenosis in animals) than the rural Chinese subjects of the Yang et al study (9), then one can also expect a different relationship between the blood selenium concentration and dietary selenium intake. Such a population may tolerate greater intakes of the element before developing hazardous tissue levels of it; such effects might increase the NOAEL by as much as 25%. Therefore, it would appear that available information would support an RfD_{Se} of $0.0075 \text{ mg} \cdot \text{kg body weight}^{-1} \cdot \text{d}^{-1}$ (with the use of an uncertainty factor of 3). Such an estimate would project selenium intakes of $600 \mu\text{g} \cdot \text{d}^{-1}$ for men and $475 \mu\text{g} \cdot \text{d}^{-1}$ for women, both of which are consistent with the observations of Longnecker et al (10).

Apparent selenium intakes of Americans, with reference to the recommended daily allowance and the reference dose

Estimates of the dietary selenium intakes of healthy Americans have varied from barely above the RDA_{Se} in relatively low-selenium parts of the country (eg, northeast, southeastern seaboard, Pacific northwest) to above $200 \mu\text{g} \cdot \text{d}^{-1}$ in relatively high-selenium areas (eg, the Dakotas). Except for populations in high-selenium areas, estimates have not exceeded the current RfD_{Se} ; in fact, the most recent estimates put typical selenium intakes within the ranges delineated by the RDA_{Se} on the low side and the RfD_{Se} on the high side (ie, 70–395 and 55–315 $\mu\text{g} \cdot \text{d}^{-1}$ for the 79-kg man and 63-kg woman, respectively).

The selenium intakes of some individuals appear to differ appreciably from the "typical" ones. Indeed, some Americans appear to have daily selenium intakes that are not far above the RDA_{Se} . For example, Welsh et al (11) found that 17% of 132 self-selected diets of free-living Maryland residents provided a selenium intake of no more than $50 \mu\text{g} \cdot \text{d}^{-1}$. On the basis of plasma selenium concentrations, Combs & Clark (12) estimated that as much as 15% of their study population, most of which resided in the eastern Carolinas, Georgia and Florida, have daily selenium intakes of less than about $60 \mu\text{g} \cdot \text{d}^{-1}$. Other individuals appear to have selenium intakes greater than the RfD_{Se} ; Longnecker et al (10) found that adults residing in western South Dakota and eastern Wyoming had chronic daily selenium intakes as great as $724 \mu\text{g}$ without any adverse effects. Thus it seems that the current RfD_{Se} , while certainly protective of health, is unnecessarily conservative. It may be appropriate to employ alternative assumptions to derive an RfD_{Se} estimate that is consistent with practical experience.

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