UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OFFICE OF
THE ADMINISTRATOR

March 15, 1991

Honorable William K. Reilly
Administrator
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

Subject: Science Advisory Board's review of a Proposed Revision to The Reference Dose (RfD) for Nickel

Dear Mr. Reilly:

The Metals Subcommittee of the Science Advisory Board met in Bethesda, Maryland, on August 6-7 to consider a revision of the RfD for nickel, based on reproductive toxicity and dermatotoxicity data. A roster of the Subcommittee members and citations for the references in the text are attached.

The current RfD for nickel, 20 µg/kg body weight daily, is based on a chronic feeding study, in rats, by Ambrose et al (1976). Alternative bases for calculating a RfD can be extracted from reproductive and fertility data in rodents, or dermal toxicity data in humans. We wish to point out some of the limitations of using the Ambrose data, to review other relevant studies, and to propose an alternative basis for setting the RfD for nickel.

Reproductive toxicity studies have been performed by Schroeder and Mitchener (1971), Ambrose et al (1976), the Research Triangle Institute (1987), and Smith et al (1989). All of the studies present interpretive problems. For example: the adequacy of the statistical analyses, unexplained anomalies in dose-response functions, unreplicated findings from one breeding to another, and confounding introduced by reduced fluid (and, concurrently, reduced food) intake.

A significant proportion of the population, predominantly females who are sensitized, exhibit a dermatitis in response to nickel ingestion (Kaaber et al, 1978). Even some individuals without dermatological complaints may respond to challenges with nickel (Burrows, et al, 1981; Gawkrodger, et al, 1986; Jordan, et al, 1979; and Nielsen, in press). Because it is preferable to use human data (when available) as the basis for human exposure standards, these studies (cited above) would ordinarily be an attractive option upon which to base an RfD. Unfortunately, however, the Subcommittee found considerable uncertainty in the results from these challenge studies due to experimental design problems, including a lack of control subjects and appropriate double-blind precautions. Therefore, these studies cannot be used as a basis for an RfD.

The Office of Drinking Water proposed a new RfD, derived either from reproductive studies (yielding an RfD of 1.0 μg/kg/day), or an RfD derived from dermal toxicity research (yielding an RfD of 2.0 μg/kg/day). The Subcommittee recommends against adopting either of these options. First, it is not persuaded by the empirical data. Second, these values are less than the amounts consumed in typical diets (see below), distorting their translation into regulatory standards. Third, a compilation of the most cogent of the alternatives to the Ambrose et al data (RTI, 1987, and Smith, et al, in press) fails to yield an RfD substantially different from the current one.

The problems noted above provide further arguments to support the Environmental Health Committee's recommendation (as expressed in the earlier Executive Committee Letter Report to you "Comments on The Use of Uncertainty and Modifying Factors in Establishing Reference Dose Levels," EPA-SAB-EC-005) that the Agency elect options other than effects levels to develop its RfD computations. For example, a member of the Subcommittee performed a preliminary analysis of the study by Ambrose et al (1976), in which weight gain provided the index of adverse effects, solely to illustrate another approach. Relying on a linear model to regress organ weight against log dose, this analysis indicated that a 10% relative increase in heart weight among female rats was associated with a diet concentration of 450 μg/kg/day of nickel sulfate. An uncertainty factor (UF) of 100 would yield an RfD of 4.5 μg/kg/day. The lower bound of the 10% estimate cannot be calculated accurately because the full data set was not provided in Ambrose et al (op cit). EPA has assumed a No Observed Adverse Effects Level (NOAEL) of 5000 μg/kg; the dose-related increase in heart (and reduction in liver) weight, as indicated by the experimental data, is obscured by relying on a NOAEL. Although the 10% change in heart weight was merely chosen as an illustrative index, it does not fit everyone's definition of an insignificant biological change. The data published by Ambrose et al, however, are too sparse to support more elaborate statistical modeling (such as those based on alternative transformations) than that used in the simple linear regression described above.

For future studies sponsored by EPA, either of nickel or of other potential toxicants delivered in the diet or drinking water, the Subcommittee recommends that preliminary experiments be conducted to determine the attenuation of food or water intake resulting from taste aversion. Cory-Slechta and Weiss (1981; Neurootoxicology 2:711-721) reported that remarkably low concentrations of cadmium were detectable by, and aversive to, rats. The Subcommittee also urges that confirmation of absorption be assessed by tissue analyses and other means; simple calculations of ingested dose are unlikely to reflect homeostatic processes that govern tissue uptake and distribution or the marked influence of diet composition.

Assuming that the current RfD of 20 μg/kg/day is valid within the limitations noted above, what bearing might it have for computations such as drinking water standards? Estimates of nickel in the diet give an upper limit of about 600 μg/day, or about 10 μg/kg body weight (Since females seem far more susceptible to nickel-induced dermal toxicity, a 60 kg, rather than a 70 kg average body weight, is adopted). This value is 50% of the RfD. If drinking water is assumed as the source of the other 50%, sharp differences in bioavailability of nickel between food and water must be confronted. If roughly 1% of dietary nickel is absorbed, the biological dose is actually about 6 μg/day. About 25% of the nickel in drinking water, after an overnight fast, is absorbed according to Sunderman et al (1989). If water intake is calculated as 2 liters daily, its bioavailable nickel should not exceed a total of about 6 μg, for a limiting concentration, or Maximum Contaminant Level Goal (MCLG), of 12 μg/liter (12 ppb).

The conventional MCLG calculation, based on the assumption that 20% of the dietary contribution would come from drinking water, yields a different figure. The Drinking Water Equivalent Level (DWEL) for nickel, based on a RfD of 20 μg/kg/day is computed as follows:

$$\text{DWEL} = \frac{\text{RfD } (\mu g/kg) * 60 \text{ (kg)}}{2 \text{ (liters water/day)} * 25 \text{ (absorption factor)}}$$

$$= 20*60/50 = 24 \ \mu g/l.$$

$$\text{MCLG} = 24*0.2 = 4.8 \ \mu g/l.$$

An absorption factor of 40, based on the precise values published by Sunderman et al (1989) would yield a slightly different MCLG OF 3.0 μg/l, using the conventional partitioning of 20% to water intake. These prevailing calculations, as noted, are distorted by the failure to make use of all of the information about dietary nickel and its absorption that is now available and that led the Subcommittee to recommend a MCLG of 12 μg/l. Because these figures are based on adults whose sources of exposure other than ingestion are trivial, a final recommendation should take account of several additional issues: air contamination can be a significant source of nickel at some sites where nickel is mined or processed; infants and small children may have significantly higher dietary exposures to nickel due to higher absorption rate of nickel by infants and higher intakes of calories per kilogram of body weight per day by infants and children than was assumed for adults used in the calculation. Such variables should also be considered explicitly in MCLG's for other substances.

We appreciate the opportunity to review this issue, and look forward to your response regarding selection of the appropriate MCLG and RfD for nickel.

Raymond C. Loehr

Dr. Raymond Loehr, Chairman
Science Advisory Board

Arthur C. Upton

Dr. Arthur Upton, Chairman
Environmental Health Committee

Bernard Weiss

Dr. Bernard Weiss, Chairman
Metals Subcommittee

ATTACHMENTS