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Derivation of an oral toxicity reference value for nickel

Lynne T. Haber [a, *], Hudson K. Bates [b], Bruce C. Allen [c], Melissa J. Vincent [a], Adriana R. Oller [b]

[a] Department of Environmental Health, University of Cincinnati, Cincinnati OH 45267, USA
[b] NiPERA Inc., 2525 Meridian Parkway, Suite 240, Durham, NC 27713, USA
[c] Independent Consultant, 101 Corbin Hill Circle, Chapel Hill, NC 27514, USA

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ABSTRACT

Nickel (Ni) is in the earth's crust and can be found in environmental compartments such as water, soil, and air, as well as food. This paper presents an assessment of the oral nickel toxicity data in support of non-cancer health-based oral exposure limits or toxicity reference values (TRVs). This paper derives TRVs for three populations of interest: adults, toddlers, and people who have been dermally sensitized to nickel. The adult/lifetime TRV of 20 μg Ni/kg-day is based on post-implantation loss/perinatal mortality in a 2-generation reproductive study in rats. Several recent assessments by regulatory agencies have used the same study and endpoint, but the dose-response modeling conducted here was more appropriate for the study design. Toxicokinetic data from rats and humans indicate that the applied uncertainty factors are very conservative. Because the endpoint relates to fetal exposure and is not relevant to toddlers, a toddler TRV was derived based on decreased body weight in young rats; this TRV was also 20 μg Ni/kg-day. A separate TRV of 4 μg Ni/kg in addition to Ni in food was derived for protection of nickel-sensitized populations from flare-up of dermatitis, based on studies of single exposures in humans under conditions that maximize oral absorption.

1. Introduction

Nickel (Ni) is a natural element of the earth's crust and as a consequence it can be naturally found in environmental compartments such as water, soil, and air. Ni is an essential micro-nutrient for plant growth (Brown et al., 1987), and is therefore also present in a wide range of primary crops, animals and foodstuffs (De Brouwere et al., 2012). Ni is used in many industrial applications such as the manufacturing of stainless steel (e.g., for building, food and medical applications) and high Ni alloys (e.g., for plane turbine manufacturing), as well as the production of Ni-plated consumer articles, Ni-containing batteries, and Ni in electronic products. The industrial production and use of Ni as well as the burning of plant-based fuels (i.e., petroleum products) can contribute to the levels of Ni in environmental compartments. Therefore, for the human population the sources and pathways of Ni exposure are diverse.

The combination of each chemical form of nickel and each exposure route determines the overall absorption and bioavailability of Ni(II) ion. When bioavailability of Ni(II) from a particular substance or matrix is not known, the bioaccessibility of Ni(II) in

Abbreviations: ADI, Acceptable Daily Intake; AIC, Akaike Information Criterion; ATSDR, Agency for Toxic Substances and Disease Registry; AUC, area under the plasma concentration time curve; BMD, Benchmark Dose; BMDL, Benchmark Dose lower confidence limit; BMDS, Benchmark Dose Software; BMR, Benchmark response; CBD, chronic beryllium disease; ECB, European Chemicals Bureau; EFSA, European Food Safety Authority; FSCJ, Food Safety Commission of Japan; gof, goodness-of-fit; GD, gestation day; GLP, Good Laboratory Practice; IC, intra-litter correlation; IPCS, International Programme on Chemical Safety; LOAEL, Lowest Observed Adverse Effect Level; LSC, litter-specific covariate; MLE, Maximum Likelihood Estimate; MRL, Minimal Risk Level; Ni, Nickel; NOAEL, No Observed Adverse Effect Level; OECD, Organisation for Economic Co-operation and Development; OEHHA, Office of Environmental Health Hazard Assessment; OR, Odds Ratio; PM10, Particulate matter less than 10 μm in diameter; PND, postnatal day; POD, point of departure; RfC, Reference Concentration; RfD, Reference Dose; REL, Reference Exposure Level; RIVM, National Institute for Public Health and the Environment (the Netherlands); RTI, Research Triangle Institute; RVR, Rai and van Ryzin; SD, Sprague Dawley; SLI, Springborn Laboratories, Inc.; SNAS, systemic nickel allergy syndrome; SRAC, systemically reactivated allergic contact dermatitis; TD, toxicodynamic; TDI, Tolerable Daily Intake; TI, Tolerable Intake; TK, toxicokinetic; TRV, Toxicity Reference Value; UF, uncertainty factor; U.S. EPA, United States Environmental Protection Agency; WHO, World Health Organisation.

* Corresponding author. Department of Environmental Health, University of Cincinnati, College of Medicine, 160 Panzeca Way, Cincinnati OH 45267-0056, USA.
E-mail address: Lynne.Haber@uc.edu (L.T. Haber).

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synthetic fluids[1] (relative to water soluble compounds) corresponding to each route of exposure can provide an indication of the relative in vivo bioavailability. Oral toxicity studies of nickel have generally involved administration of nickel in water, either via gavage or in drinking water, conditions where the nickel is 100% bioaccessible Ni(II). This maximizes the absorption of nickel compared to nickel in food, soil or dust.

Regulatory and guidance agencies throughout the world set non-cancer health-based oral exposure limits or toxicity reference values (TRVs). Although there are some variations in the specifics of the methods, these limits are generally designed based on a specific problem formulation (e.g., consideration of a specific exposure duration and population), with the goal of protecting the population of interest from adverse effects. TRVs for the general population are generally intended to protect the exposed population of interest, including sensitive subpopulations. Although TRVs are most commonly derived for chronic exposure scenarios, it is often useful to have TRVs for other durations and populations, such as for addressing intermittent exposures (Haber et al., 2016). The resulting TRVs can then be used to derive regulatory standards protecting the population of interest, such as levels of nickel in drinking water, metal migration from food contact material, etc.

When deriving an oral TRV for nickel, several key questions need to be considered. First among these are the problem formulation:

- What is the purpose of deriving the TRV?
- What is exposure scenario(s) of interest (duration, route, etc.)?
- Who are the target populations or receptor populations (e.g., toddlers, adults)?

General questions for development of any oral TRV include:

- What are the most sensitive systemic effects of concern after oral exposure (i.e., key studies, critical effects and associated points of departure)?
- What uncertainty factors should be used to develop the TRV?
- What are the main sources of uncertainty and how do they affect the calculated value?

When deriving an oral TRV for nickel, additional questions arise because nickel is prevalent in food, and because of the substantial differences in bioavailability of nickel from different matrices (e.g., food, water, soil), and in the presence of a full versus fasted stomach:

- Do point of departure values include all sources of exposure (e.g., do they include food)?
- Should bioavailability of Ni(II) be considered in either the development of the TRV or in its application in a risk characterization? Will the TRV be defined as an absorbed dose or as an external exposure? Should media-specific TRVs be developed?

This paper aims to address the questions posed above with the goal of deriving appropriate and relevant TRVs for nickel. For this assessment, the purpose of the TRV is to identify safe oral intake levels after exposure to Ni from food, water and soil, as these are the main sources of Ni exposure (section 3.1). Exposure from food and drinking water are of interest for the entire population. In addition, ingestion of soil by young children is of particular interest, since this group is identified as being the population with the highest oral intake of soil on a per kg body weight basis. Toxicokinetics related to acute exposures to nickel (e.g., from the first drink of water in the morning on an empty stomach) as well as long-term exposures in rats and humans are considered in section 3.2. The toxicity database for nickel is discussed in section 3.3. The populations of interest include adults, children, and people who have been dermally sensitized to nickel. The development of a chronic TRV for the adult population, an acute TRV for nickel hypersensitive populations, and a TRV for young children are described in section 3.4, 3.5, and 3.6, respectively. Uncertainty in the calculations and how this was addressed in our derivations are explained in section 4, together with consideration of how medium-specific estimates of bioavailability could be used to compare exposures to the TRVs.

2. Methods

2.1. General approach to TRV derivation

The general methods for deriving TRVs are well documented in a variety of publications (e.g., IPCS, 1994; 1999; Meek et al., 1994; US EPA, 2002). In brief, the process begins with a problem formulation, identifying the purpose for deriving the TRV, as well as the exposure scenario (e.g., duration(s) and route(s)) and potential exposed population. A literature search is then conducted to identify relevant studies. The studies are reviewed to characterize the effects caused by the chemical under the exposure conditions of interest. As part of the hazard characterization, the relevance to humans of effects seen in animal studies is considered (Cohen et al., 2003; Seed et al., 2005), as well as factors that may result in specific sensitive populations. This allows one to identify the most sensitive endpoint(s) for the scenarios of interest. In particular, the goal is to identify the critical effect, defined by US EPA (2011) as “the first adverse effect, or its known precursor, that occurs to the most sensitive species as the dose rate of an agent increases.” A point of departure (POD) is then identified, typically a No Observed Adverse Effect Level (NOAEL), Lowest Observed Adverse Effect Level (LOAEL), or a benchmark dose (BMD). The approach for low-dose extrapolation depends on the mode of action. For effects that do not result from interaction with DNA, a subthreshold dose is calculated by applying uncertainty factors to the POD (IPCS, 1994; 1999; Meek et al., 1994; US EPA, 2012). There are some differences across agencies in the specifics of uncertainty factor (UF) application, but all organisations include UFs for human variability, extrapolation from experimental animals to humans, and various database deficiencies, such as not having a NOAEL. For this assessment, the methods of IPCS (1994. 1999) were used.

There are a number of recent authoritative reviews for nickel (US EPA, 1991; Health Canada, 1996a; 1996b; RIVM, 2001; ATSDR, 2005; WHO, 2007; OEHHA, 2012; FSCJ, 2012; EFSA, 2015). Therefore, the literature search was conducted only for studies published since 2014, relying on the authoritative reviews to ensure that the literature on nickel toxicity has been adequately captured. The remainder of the steps in the risk assessment process were followed, as described in the previous paragraph.

2.2. Benchmark dose modeling methods

2.2.1. General methods

All BMD modeling was done using extra risk. Extra risk at dose d (ER(d)) is defined as

[1] The bioaccessible concentration of Ni(II) ion is defined as the fraction of the material (food, soil, plated item) that can be released as soluble ion in a particular solution (e.g., synthetic fluids relevant to each route of exposure). The bioaccessibility of Ni from a Ni-containing substance provides a high end estimate of its in vivo bioavailability (i.e., not all bioaccessible Ni gets absorbed).