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Human biokinetic model for soluble nickel addressing inter-individual variation

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ABSTRACT

Worker-specific Biological Exposure Action Levels (BEALs) for nickel (Ni) exposure are a urinary Ni concentration that reflects a dose that can be experienced on a daily basis without adverse systemic health effects. Several health-based reference values for systemic exposure to Ni have been derived as oral daily Ni dosing levels (e.g., 2007 WHO tolerable daily intake for Ni). To support evaluation of urinary nickel biomonitoring data in workers based on such health-based criteria, new human biokinetic models for nickel (Ni) were fit jointly to data obtained for 18 adult volunteers from four newly reported human studies and to data from two previously reported studies involving a total of 14 adult volunteers. This model and associated statistical analyses characterize and predict human Ni biokinetics after ingestion of Ni doses $\leq$ 20 μg/kg bw and associated inter-individual variation in urinary Ni excretion. Using this approach, we illustrate how available health-based reference values for daily Ni exposure by the oral route developed to protect against adverse health effects can be applied to derive urinary nickel BEALs for nickel workers based on their individual characteristics (e.g., shift pattern, body weight). Such worker-specific BEALs can provide health-based reference values to evaluate measures obtained through urinary Ni biomonitoring programs to complement existing industrial hygiene air monitoring programs.

List of acronyms and parameters: ANOVA: analysis of variance; B: Ni BEAL (μg Ni in urine); BEAL: biological exposure action level; BW: body weight (kg); C_p: concentration of Ni or ^{62}Ni isotope in plasma after dosing (μg/liter); C_{po}: background concentration of Ni or ^{62}Ni in plasma (μg/liter); cdf: cumulative probability distribution function; cmf: cumulative probability mass function; C_{Pu}: cumulative percentage of orally administered soluble Ni excreted in urine (%); C_{Pum}: median value of CPu (%); CV: coefficient of variation; df: degree of freedom; F_{GI}: fraction of orally administered soluble nickel that is absorbed through the gastrointestinal tract (unitless); F_u: M_u/M_o–fraction of Ni or ^{62}Ni in urine after dosing divided by the administered Ni or ^{62}Ni dose. This fraction represents a urinary concentration that is normalized by the administered dose (unitless); GI: gastrointestinal; GM: geometric mean; GSD: geometric standard deviation; k_{ij}: rate constant for transfer between body compartments i

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and j, see Figure A1; LBM: lean body mass; M_o: administered dose of Ni or ^{62}Ni (μg/kg bw); M_u: concentration of Ni or ^{62}Ni in urine after dosing (μg/liter); NBM: Ni biokinetic model; NiPERA: Nickel Producers Environmental Research Association; $R_{p/u}$: C_p/M_u–ratio of concentration of ^{62}Ni in plasma to the concentration of ^{62}Ni in urine; R: the ratio C_{Pu}/C_{Pum} (unitless); R_n: n^{th} percentile value of R with respect to inter-individual variability (unitless); RU: rate of urinary Ni excretion; SD: standard deviation; SEM: standard error of the mean = (SD $n^{-1/2}$) for sample size n; SM: sample mean value of ln(C_{Pu})

Introduction

Although high airborne exposures to nickel (Ni) compounds by production workers have been associated with chronic respiratory effects including cancer, Ni is generally of low toxicity for exposures to consumer products or implanted medical devices, for which the primary health concern is a delayed Type IV allergic reaction in sensitive individuals (IARC 1999; McGregor et al. 2000; Jensen et al. 2003, 2006; ATSDR 2005; FIOH 2010). The World Health Organization (WHO) derived a Tolerable Daily Intake (TDI) for oral exposure of 11 μg Ni/kg of body weight (bw) per day based on a no-adverse-effect level for reproductive toxicity in a two-generation study in rats (WHO 2007). The U.S. Environmental Protection Agency developed a reference dose (RfD) of 20 μg Ni/kg bw/d based on reduced body and organ weights observed at higher doses in a two-year feeding study in rats (U.S. EPA 1986). The EFSA CONTAM panel set a TDI of 2.8 μg Ni/kg bw/d for the general population (EFSA 2015). This TDI for chronic ingestion was derived from a lower 95% confidence limit for a benchmark dose at 10% extra risk ($BMDL_{10}$) of 0.28 mg/kg bw/d for post-implantation fetal loss in rats by applying a 100-fold safety factor. The EFSA more recently updated its opinion with a TDI of 13 μg Ni/kg bw/d for chronic dietary exposure based on a revised $BMDL_{10}$ of 1.3 mg Ni/kg bw/d using the same endpoint and safety factor (EFSA 2020). Haber et al. (2017) derived a TDI value of 20 μg Ni/kg bw/d, starting with the same animal studies but using different effects for modeling (number of affected pups within each litter based on the nested data from different studies vs number of affected litters used by EFSA) and focusing on the best fitted model (instead of the one showing the lowest BMDLs). This approach resulted in a $BMDL_{05}$ of 1.8 mg/kg bw/d, which was then used to derive a rounded TDI value of 20 μg Ni/kg bw/d by applying a standard 100-fold adjustment factor (AF).

Typically, adults contain approximately 10 mg of Ni which (baseline mass, in contrast to transiently retained excess Ni) is eliminated with a half-time of approximately 3.3 years based on an estimated net retention of about 30% of 400 μg nickel ingested/d (ICRP 1981), or ~6.6 years if daily Ni intake is closer to 200 μg (Myron et al. 1978; Clemente et al. 1980). Retained Ni is dominated by its bone-tissue burden since Ni in bone is relatively constant with age and presumably is resorbed and deposited in the mineral matrix, with non-retained Ni excreted in urine and feces (U.S. EPA 1986). Urine is the primary route of Ni excretion after absorption by humans and animals, with a typical Ni concentration of 1–4 μg/L (McNeely et al. 1972; Andersen et al. 1978; U.S. EPA 1986; Templeton et al. 1994).

More recently, several countries have set worker exposure limits for airborne nickel and compounds for protection of workers from nonmalignant and malignant

respiratory effects and dermatitis (e.g., RIVM 2014; OSHA 2017, ECHA Committee for Risk Assessment (RAC) 2018). Measurements of nickel in urine can be related to the internal dose of nickel since internally absorbed excess nickel is rapidly excreted in urine (ATSDR 2005). Biokinetic modeling of oral absorption, distribution, and excretion of nickel in urine thereby allows urinary biomonitoring data for workers to be related to an oral-TDI level of Ni exposure. To ensure that occupational limits for Ni also protect against potential reproductive or chronic toxicity based on high-dose animal studies, results of biomonitoring of urinary Ni can thus be combined with predictions from a validated adult human biokinetic model for Ni to assess whether such limits prevent oral-equivalent intake of soluble/systemically available nickel from exceeding, for example, the WHO (2007) chronic TDI of 11 μg Ni/kg bw per day. This TDI is in line with recently derived TDI values of 13 μg Ni/kg bw per day (EFSA 2020) and 20 μg Ni/kg bw per day (Haber et al. 2017).

A biokinetic model of nickel was developed by Sunderman et al. (1989) based on experimental data in human volunteers ingesting nickel sulfate in water and food. That model was recently adjusted and compared to an alternative, more complex and physiologically based biokinetic model exhibiting similar kinetics, based on a review of and predicted consistency with available human and animal data (Melo and Leggett 2017). Here we describe a new human biokinetic models for nickel (Ni) fit jointly to data obtained for 18 human subjects in a study sponsored by NiPERA, Inc. (Patriarca and Taylor 2010a, 2010b, 2011a, 2011b), and to similar data (also considered by Melo and Leggett 2017) from an earlier study by Patriarca et al. (1997) with four subjects described below, and from a study by Sunderman et al. (1989) involving six male and four female subjects. Related data by Nielsen et al. (1999), including urinary Ni excretion data on 40 female subjects, were not addressed, because this study did not report data for Ni in plasma, making it difficult to assess differences between urinary data obtained in this study vs. the others in which plasma or serum Ni data were also obtained. The resulting human biokinetic model for Ni described here incorporates a stochastic model of inter-individual heterogeneity in urinary Ni excretion fit to the data considered. Finally, we illustrate how the new model can be applied together with the WHO TDI for oral Ni exposure to develop worker-specific Biological Exposure Action Levels (BEALs) that could complement but not replace industrial hygiene air monitoring programs by enabling protective evaluation of occupational urinary Ni biomonitoring data.

Materials and methods

Experimental data

Human Ni biokinetic data

Nickel biokinetic data considered include measures reported by:

1. Sunderman et al. (1989), for Ni in serum and urine before and after 12-h-fasted adult volunteers (ages 22–55 years) drank aqueous $NiSO_4$ amounting to a Ni dose of either 50 μg/kg bw (one male), 18 μg/kg bw (two male + two female), or 12 μg/kg bw (two male + two female);

2. Patriarca et al. (1997), for stable ^{62}Ni isotope in plasma and urine of two male and two female 10–12-h-fasted adult volunteers (ages 21–30 years) obtained at eight time points up to 120 h after drinking 10 μg/kg bw administered as solution of stable 98.83%-pure ^{62}Ni isotope followed for 2.5 h by further fasting other than water and thereafter by an unrestricted diet; and
3. Patriarca and Taylor (2010a, 2010b, 2011a, 2011b), which below are referred to jointly as the Patriarca and Taylor Studies (PTS), for ^{62}Ni isotope concentrations in plasma and urine up to 72–168 h after each among 18 total adult volunteers was administered a single oral dose of either 5, 10, or 20 μg Ni/kg (in totals of six, four, and four subjects, respectively, half male and half female in each dose group) as an aqueous solution of 97.94%-pure ^{62}Ni isotope.

Methods used to generate data in the first two studies were reported previously (Sunderman et al. 1989; Patriarca et al. 1997). The study and subject consenting protocol used by Patriarca and Taylor (2010a, 2010b, 2011a, 2011b), funded by NiPERA, was approved by the Royal Surrey County Hospital Research Ethics Committee. The clinical part of the study, involving isotope administration and collection and storage of all biological samples, was carried out at appropriate facilities at the Royal Surrey County Hospital. Measurements of ^{62}Ni isotope in all biological samples collected were subsequently performed at the Istituto Superiore di Sanità, using inductively coupled plasma mass spectrometry (ICP-MS). Each subject fasted for 10.5 h prior to dosing at 8:30 am, preceded by collection of basal blood and urine samples, followed by further fasting (other than water) for 6 h and then by an unrestricted diet, and thereafter by periodic collection of blood and complete urine samples (in acid-washed containers) at 10 time points up to 168 h. For the purpose of this study, measured concentrations of Ni in serum and in plasma were assumed to be equivalent, in view of their lack of significant difference and lack of correlation in repeated samples of background levels obtained *in vivo* in cattle (Luna et al. 2019).

Inter-individual variability in urinary Ni excretion

To address human inter-individual variability in urinary nickel excretion kinetics, two sets of human Ni biokinetic data were examined. Data Set 1 consists of measures obtained by PTS and by Patriarca et al. (1997). Data Set 2 consists of similar, albeit only summary, measures of urinary ^{61}Ni excretion reported by Nielsen et al. (1999), who studied 20 "control" women and 20 age-matched Ni-sensitized women, all administered the same, 12-μg/kg bw oral dose of soluble, aqueous ^{61}Ni after a 12-h fast, followed by 4 h of additional fasting. The Nielsen et al. (1999) study data included (from Table 5 of that study) consists of median, minimum, and maximum cumulative urinary ^{61}Ni excretion for each of the two study groups, measured at nine time points up to 72 h after initial exposure.

Biokinetic modeling

Average ±1 standard deviation (SD) of levels of Ni in serum and in urine estimated from Figure 2 of Sunderman et al. (1989) were compared to predictions made by the

two-compartment biokinetic model reported in that study (SM). Those data were then used to fit to a modified version (MS1) of SM in which the latter's first-order assumption for excretion from serum to urine was replaced by an alternative assumption that the first-order rate constant governing urinary Ni excretion exhibits concentration-dependent (Michaelis-Menten type) first- to zero-order saturation in relation to serum Ni concentration. The MS1-model assumption that urinary Ni excretion is saturable is consistent with the observation of bi-exponential Ni-excretion kinetics in a heavily exposed German welder (Schaller et al. 2007), and with expectations that Ni excretion is reduced as elevated Ni concentrations in plasma decline to near-normal background levels, and that excretion approaches zero if plasma Ni concentrations fall below normal background levels. The MS1 model also adds a "slow tissues" exchange compartment that predicts a 10.39-mg Ni body burden for a reference 70-kg adult (U.S. EPA 1986; ICRP 1994). Background Ni intake absorbed from the diet was adjusted to predict the baseline serum Ni concentration (C_{po}) of 0.32 µg/L at time zero reported by Sunderman et al. (1989). Exponential gastrointestinal (GI) absorption of soluble Ni was assumed at the rate estimated by Sunderman et al. (1989).

Nielsen et al. (1999) measured ^{61}Ni in urine, but not in plasma, in a total of 40 women administered 12 µg/kg bw ^{61}Ni after fasting for 12 h. This study also applied additional protocols involving different periods of time of nickel dosing in water before and/or after which food was consumed; these other protocols are not directly comparable to those employed by Sunderman et al. (1989), Patriarca et al. (1997), and PTS. Because unreported plasma levels from the study by Nielsen et al. (1999) would be required to compare results from that study meaningfully to analogous data reported for both urine and plasma by Sunderman et al. (1989), Patriarca et al. (1997), and PTS, Nielsen et al. (1999) study data were not used for the present analysis involved in biokinetic model development and validation.

Mathematical details of the Sunderman et al. (1989) and MS1 biokinetic models considered are further described in Appendix 1. Model parameter values reported, assumed, or estimated for these models are listed in Table A1 in Appendix 1.

Data analysis

Model development

Univariate parameter estimations were each performed by inverse-variance weighted chi-square minimization, with variances for each measurement estimated as the square of the standard error (SE) of each model-specific predicted value of Ni or ^{62}Ni in serum/plasma or urine at the times at which samples were obtained in each study. Multivariate optimization was performed by visual inspection of the fit obtained when a corresponding approximate chi-square test of goodness of fit was either clearly acceptable, or was clearly impossible to obtain using the fitted model. Each test was performed with the indicated degrees of freedom (df) assuming approximate normality of estimated error associated with each model prediction, where df values were set equal to the number of data points fit minus the total number of estimated model parameters, and normality was tested where feasible by Shapiro-Wilk test (Royston 1992). Where indicated, adjusted p-values (p_{adj}) used were obtained by applying Hommel's procedure

(Wright 1992) to raw p-values obtained from independent tests applied to multiple data sets. Because individual data on Ni in serum and in urine were not reported by Sunderman et al. (1989), plots of group mean and standard deviation data in Figure 2 of that study were used to estimate that SE values in that study were all approximately 50% of each corresponding predicted concentration.

Inter-individual variability characterization

Cumulative percentage Ni measured in urine (denoted C_{Pu}) was characterized in terms of inter-individual variability based on the following approaches used to analyze Data Sets 1 and 2 described above (*Experimental Data*). From Data Set 1, combined C_{Pu} measures were transformed to corresponding measures of relative deviation on a log-transformed scale, that is, as corresponding absolute deviations $\Delta\ln(C_{Pu})$ of each $\ln(C_{Pu})$ value from the sample mean value of $\ln(C_{Pu})$ (denoted SM), where ln denotes natural logarithm. Thus, for each C_{Pu} measure, a corresponding relative deviation was defined as $\Delta\ln C_{Pu} = \ln(C_{Pu}) - SM$, which characterizes (on a natural log scale) the magnitude of the ratio R of observed C_{Pu} to its estimated median value. To assess the independence of subject-specific sets of $\Delta\ln C_{Pu}$ values, within-subject correlation of $\Delta\ln C_{Pu}$ values obtained at each of various time points with that measured at time 120 h (the latest time point common to all subject-specific data sets) was assessed by Pearson product-moment correlation analyses. In view of significant intra-subject correlation between $\Delta\ln C_{Pu}$ value pairs (see Results), only $\Delta\ln C_{Pu}$ values obtained at 120 h were used to characterize inter-subject variability exhibited in Data Set 1. Normality of this restricted set of $\Delta\ln C_{Pu}$ deviations at 120 h was assessed by Shapiro-Wilk test (Royston 1992), and a suspected outlier from a complementary set of data consistent with normality was assessed by 2-tail t-test (Kendall and Stuart 1979). For 120-h $\Delta\ln C_{Pu}$ deviations, Bartlett's test and one-way analysis of variance (1-way ANOVA) (Snedecor and Cochran 1989) were used to test variance and means homogeneity across dose groups, and multiple continuous/categorical linear regression was applied to the data from all dose groups to test for potential univariate associations using subject-specific sex, age, and ratio of total to lean body mass (LBM), with or without dose, as joint linear predictors of ln C_{Pu}. For this purpose, sex-specific LBM was calculated (as LBM_1) by the method of Hume (1966) for subjects of age $\geq$ 30, for both sexes (as LBM_2) by the method of Otte et al. (2000) for subjects of age $\leq$ 22, and for subjects for whom 22 < age < 30 by linear interpolation as $LBM = p\ LBM_1 + (1–p)LBM_2$, where $p = (30–Age)/8$.

Analyses of information from Data Set 2 indicated that each set of 20 ratios R of C_{Pu} relative to its median value (denoted C_{Pum}), collected at each time point, were determined to be asymmetrically distributed (see Results). A skewed distributional form was therefore used to characterize ratios $R_{lo} = C_{Pum}/\mathrm{Min}(C_{Pu})$ and the ratios $R_{hi} = \mathrm{Max}(C_{Pu})/C_{Pum}$ separately for the 20 control subjects and for the 20 Ni-sensitized subjects, as follows. In view of relatively small observed magnitudes of inter-individual variation in values of R_{lo} and in values of R_{hi} (see Results), arithmetic mean values of each of these ratios, respectively denoted R_{loHat} and R_{hiHat}, were used to characterize corresponding magnitudes of inter-individual variation in C_{Pu}. The R_{loHat} (and R_{hiHat}) estimates for control vs. Ni-sensitized women from Nielsen et al. (1999) were compared by Welch's t-test (Kendall and Stuart 1979), in view of significantly ($p \leq 0.05$) different

variances in the group-specific values tested as assessed by 2-tail F-test. Measures log(R) were assumed to be distributed as a "bi-normal" distribution specified by $\sim$N(0, [σ/k if $R \leq 1$, otherwise k*s]), where $\sigma = \log(R_g)/z_{20}$ in which R_g = the geometric mean (GM) value of R_{loHat} and R_{hiHat} (calculated separately for the 20 control subjects and for the Ni-sensitized subjects, where, as shown in Results, it was observed that $R_{loHat} > R_{hiHat}$ for both subject groups), z_{20} is the expected normal score (1.8675) of the largest of 20 random samples of a random N(0,1) variable (Royston 1982); k = the (by definition, equal) value of each of the ratios R_{loHat}/R_g and R_g/R_{hiHat}, and N(0,σ) denotes a normally distributed random variable with mean and SD equal to 0 and σ, respectively. Related results-dependent methods applied are described in Results.

All numerical and statistical calculations were conducted using *Mathematica*® 8.0–10.0 software (Wolfram Research 2013). Error bars shown in data plots denote ±1 standard error of the mean (SEM) of the measured values. Calculated p-values $<10^{-10}$ are listed as $\sim$0.

Illustrative BEAL derivation

The following approach was used to illustrate how the urinary Ni biokinetics/variability model developed can be combined with the WHO TDI for oral Ni intake to derive urinary Ni BEALs for orally exposed Ni workers. The new Ni biokinetics model was first numerically evaluated iteratively conditional on each of two illustrative work schedules, assuming an oral exposure of either 0 or 11 µg Ni/kg bw. The two work schedules considered were: an 8-hr/d 5-d/week work schedule (denoted "M–F 8-hr shift"), and a 12-hr/d alternating work schedule (denoted "2,2,3 12-hr shift") with 2-days-on/2-days-off/3-days-on followed by 2-days-off/2-days-on/3-days-off. Urine was assumed to be collected from a participating worker only once, at the end of day 4 (Thursday) in the M–F schedule, or at the end of the second day of a week containing a 3-days-on period of the 2,2,3 schedule. Under each scenario, a spot sample of urinary Ni accumulated over a specified duration $T_{accum} = T_{collect} - T_{lag} - T_{void}$ is assumed to be collected at time $T_{collect}$, subsequent to the time T_{void} at which urine was last voided during a current work shift, where lag of, say, $T_{lag} = 0.2$ hr might typically occur between sample void and $T_{collect}$. To examine the effect of assumed Ni-intake exposure pattern each day under each work week scenario, occupational intake of oral Ni was always assumed to occur in either of two patterns: (1) as a 6-min pulse at the start of each work day, or (2) as a constant intake rate over each entire work day. Under these assumptions, net urinary Ni outputs above predicted background output for a reference 70-kg adult under each or the two work-week schedules and two daily Ni-intake patterns considered were calculated only after a number of simulated work weeks sufficient for each corresponding pattern of cumulative modeled urinary Ni over time to have attained virtual dynamic equilibrium.

Results

Human biokinetic model

The combined sets of PTS and Patriarca et al. (1997) data available for modeling include 18 subjects in total, for whom data were extracted pertaining to post-dosing

^{62}Ni isotope concentration in plasma and ^{62}Ni isotope excreted in urine at various time points extending out to 72–168 h. The combined data on 18 subjects include approximately 186 measures of ^{62}Ni excreted in urine (M_u) and approximately 258 measures of ^{62}Ni concentration (C_p) in plasma for three different administered oral doses (5, 10, 20 μg/kg bw). In contrast, the earlier study by Sunderman et al. (1989) did not involve dosing with ^{62}Ni, but rather involved measurement of total Ni concentration, including from background exposure.

Consistent with results reported in previous studies (Sunderman et al. 1989; Patriarca et al. 1997), the PTS data exhibit considerable variation in individual levels of nickel in plasma and urine, some of which may be associated with differences in GI absorption, excretion of nickel in bile and enterohepatic circulation, or dosing based on total body mass versus lean body mass. Although Patriarca et al. (1997) estimated GI absorption based on ^{62}Ni in feces, fecal data may be complicated by biliary excretion.

Serum Ni levels measured by Sunderman et al. (1989) in subjects dosed orally with 12, 18, or 50 μg/kg bw soluble Ni after a 12-h fast were compared to predicted levels of Ni in serum from the model presented in that study (dashed curves in Figure 1, top panel). The close correlations originally reported by Sunderman et al. (1989) between predicted and observed serum and urine levels reported in Figures 4 and 5 of that study are somewhat at odds with larger deviations of predicted levels from corresponding mean measures in serum and urine in the present reassessment (Figure 1). In particular, predicted serum levels for the high-dose group clearly overestimate three of the measures obtained at early time points. The discrepancies may reflect the fact that estimates listed in Table 1 of Sunderman et al. (1989) could represent means (±1 SD) of individual-specific parameters that appear to have been estimated by fitting their model to nine individual data sets, rather than estimates obtained by fitting their model to average values of the dose- and time-specific measurements they made. Individual-level data and parameter estimates were not reported in that study, nor were predictions of their model plotted in relation to their reported measures of Ni in serum and urine. The Sunderman et al. model provides an acceptable overall fit to the combined reported mean serum Ni data involving five estimated parameters ($\chi^2 = 14.5$, df = 19, $p = 0.75$). Similarly, corresponding predictions of the cumulative percentage of applied Ni dose excreted in urine are clearly consistent with the variability associated with the reported urine data (Figure 1, bottom panel).

The MS1 model was fit to measures of Ni in serum reported by Sunderman et al. (1989) by (visually) optimizing two estimated parameters (F_{GI} {gastrointestinal absorption fraction} and k_{23} {rate constant for transfer of Ni from tissue to bone}) after conditioning on the values of four of the five parameters estimated by Sunderman et al. (see Appendix 1). One of the estimated parameters, F_{GI}, had been estimated to be 0.27 by Sunderman et al. (1989). The MS1 model estimate of this parameter ($F_{GI} = 0.30$) was slightly larger than that associated with the two-compartment model of Sunderman et al. (1989), reflecting additional loss to the Bone compartment that is included in the MS1 model but not in the Sunderman et al. model. The resulting MS1 model fit to the Sunderman et al. data on Ni in serum is statistically consistent with those data ($\chi^2 = 15.3$, df = 22, $p = 0.85$). Corresponding MS1 model predictions of the cumulative percentage of applied Ni dose excreted in urine, made without optimizing the model in

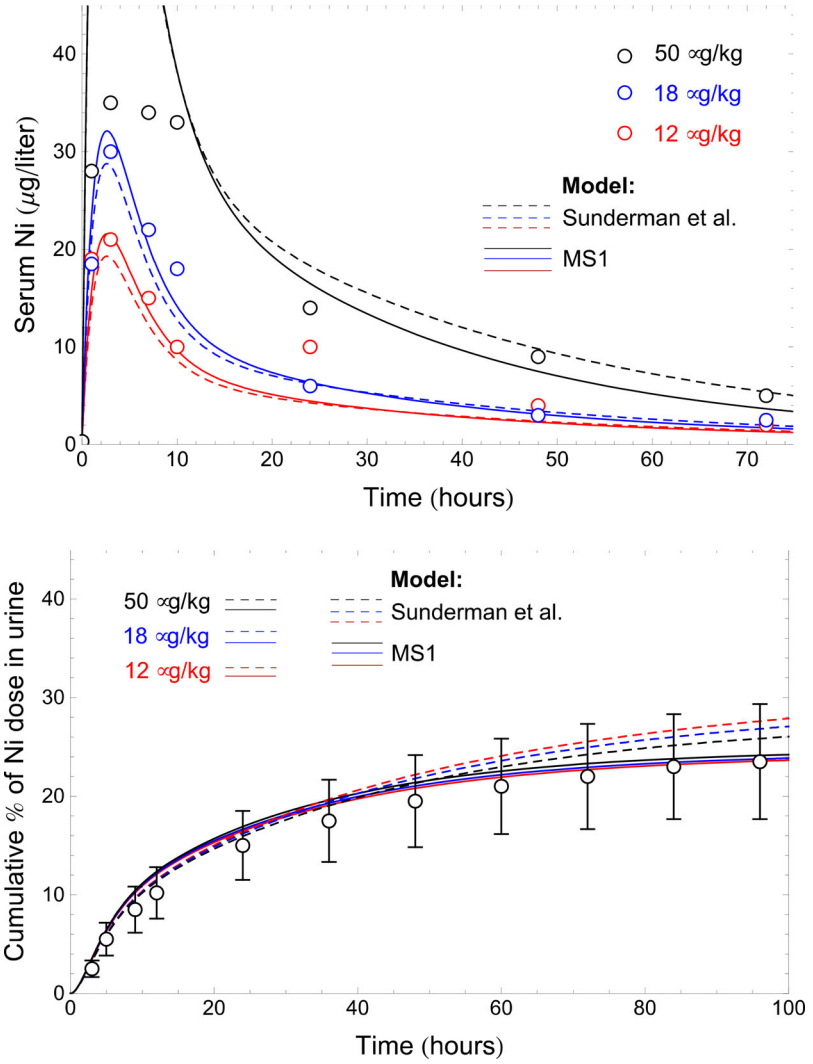

Figure 1. Average levels of Ni in serum (top panel, open points) and cumulative percentage of administered Ni excreted in urine (bottom panel; open points) vs. time after different ingested doses of soluble Ni in water measured in human volunteers by Sunderman et al. (1989). Error bars = ±1 SEM. Data are compared to predictions by the two-compartment biokinetic model proposed by Sunderman et al. (1989) and by the MS1 model. Plotted urine data were averaged by Sunderman et al. (1989) over all three dose groups.

any additional way with respect to these urine data, are clearly consistent with the variability associated with the reported urine data (Figure 1, bottom panel). MS1 model predictions appear to represent the trend in the urinary excretion data (which had been averaged by Sunderman et al. over all three dose groups) and in serum slightly better than those of the Sunderman et al. model prior to ∼40 h post-exposure. More specific predictions made by the MS1 model as functions of administered Ni dose, conditional on an assumed background rate of dietary Ni absorption (see Appendix 1), are shown in Figure 2.

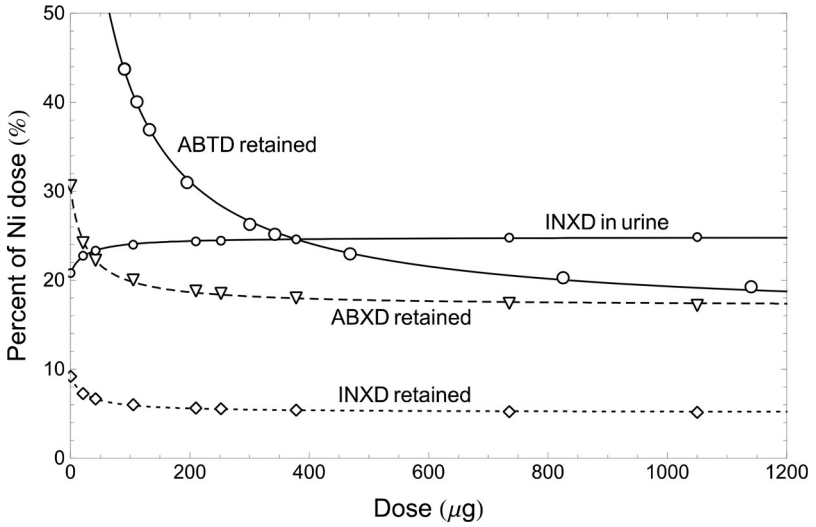

Figure 2. MS1 model predictions of various outputs as a percentage of ingested Ni dose in water after a 12-h fast by a 70-kg reference adult, assuming concurrent daily Ni ingestion resulting in dietary Ni being absorbed at a rate of 2.167 μg/d. ABTD = absorbed total dose (including background daily ingestion), ABXD = absorbed ingested experimental dose (excluding daily ingestion), INXD = ingested experimental dose (excluding daily ingestion). The percent of INXD in urine can also be expressed as (100%)F_u (fraction of oral dose in urine). All doses were calculated using the MS1 model, evaluated over a simulated post-experimental-dose follow-up period of 1000 h. Each relationship was evaluated at the points indicated, and corresponding (virtually perfect) hyperbolic fits were estimated from these points.

Patriarca et al. (1997) measured ^{62}Ni in samples of plasma and urine obtained for four subjects administered 10 μg/kg bw of soluble ^{62}Ni after a 12-h fast. All of the nine time-specific data sets with >3 measures were approximately normally distributed ($p \geq 0.10$). Predictions made by the MS1 model, as optimized to the serum Ni data of Sunderman et al. (1989), were compared directly to the corresponding data reported by Patriarca et al. (1997), without any optimization to those data or to corresponding data reported on cumulative ^{62}Ni excretion (Figure 3). Remarkably, these non-optimized MS1 model predictions provide a good fit to the plasma data from the Patriarca et al. (1997) study ($\chi^2 = 16.0$, df = 13, $p = 0.25$). A good fit was also obtained to corresponding data on cumulative percent of administered ^{62}Ni dose excreted in urine ($\chi^2 = 5.33$, df = 8, $p = 0.72$), although the model predictions appear to overestimate the urine data systematically by a relatively small magnitude (Figure 3).

Of 45 time-specific PTS data sets available, all but one were found by separate Shapiro-Wilk tests to be approximately normally distributed ($p \geq 0.086$), and the combined set of 45 test results are consistent with approximately normally distributed data ($p_{adj} \geq 0.29$). Predictions made by the MS1 model, as optimized to the serum Ni data of Sunderman et al. (1989), were compared directly to the corresponding PTS data on plasma ^{62}Ni, without any optimization to those data or to corresponding data reported on cumulative ^{62}Ni excretion. The non-optimized MS1 model predictions in this case failed to provide a good fit, substantially overestimating the PTS data plasma ^{62}Ni levels in all three dose groups ($\chi^2 \geq 33.9$, df = 14, $p < 0.0025$, for all three comparisons).

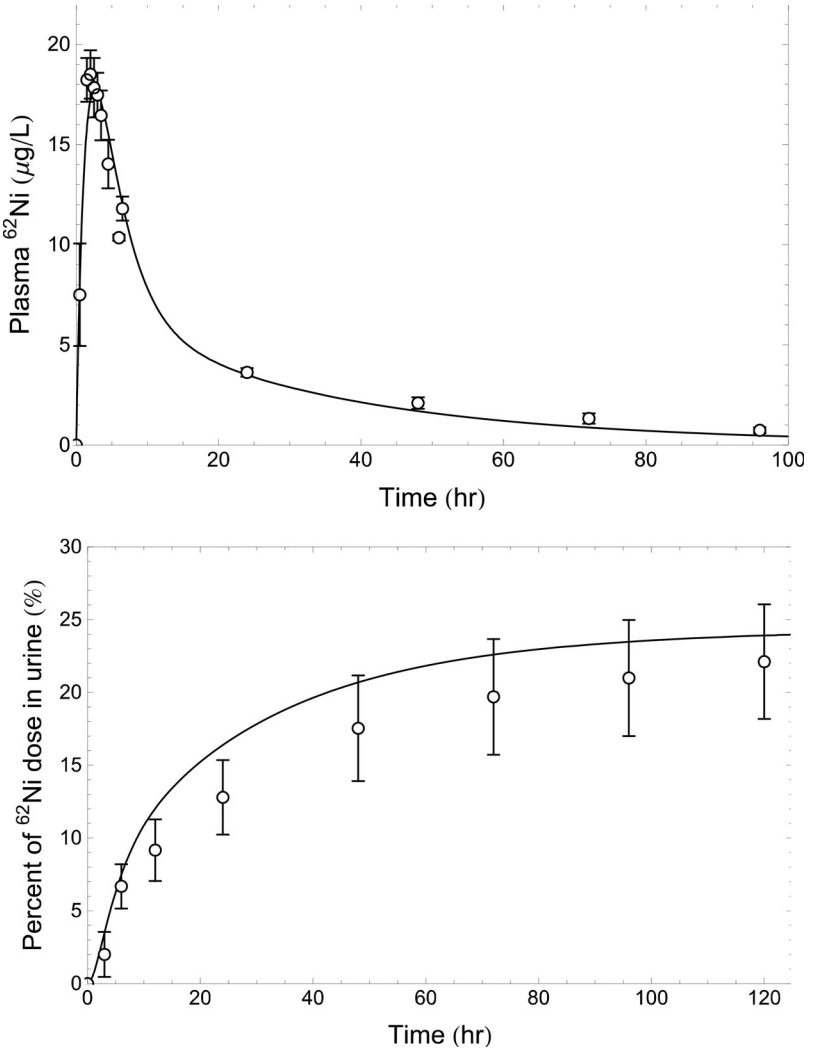

Figure 3. Mean measures (open points) of ^{62}Ni in samples of plasma and urine obtained by Patriarca et al. (1997) for four subjects administered 10 µg/kg bw of soluble ^{62}Ni after a 12-h fast. Error bars denote ±1 SEM. The plotted data on ^{62}Ni in plasma and urine are compared to corresponding predictions of the MS1 model (curves). The MS1 model was optimized only to serum Ni data of Sunderman et al. (1989), and was not further optimized to fit the ^{62}Ni data plotted.

However, after adjusting for reported baseline ^{62}Ni concentrations in serum (as discussed below), and after adjusting one outlying (relatively small) measured SD value (as discussed below), excellent MS1 model fits were obtained to all three sets of plasma data after values of the parameter F_{GI} were reduced to alternative values $F_{GI} = 0.105$, 0.11, and 0.19, for the 5-, 10-, and 20-µg/kg bw dose groups, respectively ($\chi^2 \leq 4.2$, df $= 14$, $p \geq 0.99$, for all three comparisons; see Figure 4). In relation to dose D (in µg Ni per kg bw), these estimated values of F_{GI} are predicted (virtually exactly) by the relationship

$$F_{GI} = 0.104 + 0.146/[1 - \exp(6.6663 - 3.5132D)] \quad (1)$$

The good fit of the MS1 model to the Patriarca et al. (1997) data, but not to PTS data without substantially adjusting F_{GI} values, is due primarily to differences between respective plasma concentrations after dosing at 10 μg/kg bw, peak values of which both occurred at ~2 h after dosing but with clearly different mean values ($p = 00085$, by 2-tail t-test).

Baseline plasma Ni concentration predicted by the MS1 model was assumed to be 0.32 μg/L as reported in Sunderman et al. (1989) (see above, and Appendix 1), so the corresponding baseline ^{62}Ni concentration was assumed to be the product of 0.32 μg/L and the relative abundance (3.6345%) of ^{62}Ni isotope in total Ni (CRC 2009), or 0.012 μg/L. However, the latter value was substantially less than the (baseline) average plasma-^{62}Ni concentrations of 0.038, 0.20, and 0.092 μg/L calculated for the 5-, 10-, and 20-μg/kg bw dose groups, respectively. To address this issue, the mean baseline value calculated was added to each model prediction for that dose group and the corresponding baseline observation at time $t = 0$ was dropped from the comparison, yielding 14 time points per data set for each dose group (rather than 15 including time $t = 0$). This approach was adequate to obtain good fits to all of the fitted plasma data, as described above.

A total of 30 sets of measures of cumulative fraction of administered ^{62}Ni in urine at 10 time points following each of three PTS dosing scenarios were all approximately normally distributed ($p_{adj} \geq 0.30$). After values of the F_{GI} parameter were fit to data on ^{62}Ni in plasma as described above, each of three sets of resulting MS1-model predictions of cumulative fraction of administered ^{62}Ni in urine following each respective PTS dosing scenario became statistically consistent with the corresponding set of urinary ^{62}Ni data collected ($\chi^2 \leq 14.0$, df = 9, $p \geq 0.12$, for all three comparisons). Nevertheless, MS1-model predictions for the 20-μg/kg bw dose group systematically overestimate cumulative fractions of urinary ^{62}Ni that were measured for this dose group (Figure 4).

Inter-individual variability in urinary Ni excretion

Values of $\Delta\ln(C_{Pu})$ for 18 subjects in Data Set 1 at time = 120 h (the longest time period common to all 18 subject groups) correlate significantly with corresponding values for all earlier times T at which comparisons were feasible. Respective times T (in h), and the corresponding correlation coefficient *r* and its 2-tail p-value are summarized in Table 1. Because $\Delta\ln(C_{Pu})$ values pertaining to different times are significantly and rather highly correlated with those pertaining to 120 h, the within-subject data are highly redundant and so cannot independently inform an assessment of inter-individual variability in R. For this reason, only $\Delta\ln(C_{Pu})$ values measured at 120 h were used to characterize inter-subject variability exhibited in Data Set 1. Dose-specific subsets of the 18 values of 120-h $\ln(C_{Pu})$ have approximately equal variance ($p = 0.10$, by Bartlett's test). Although these subsets do not differ significantly by dose group ($p = 0.44$, by 1-way ANOVA), the combined set of $\Delta\ln(C_{Pu})$ values, defined in terms of the mean of the 18 values of $\ln(C_{Pu})$, are significantly non-normally distributed ($p = 0.047$, by Shapiro-Wilk test).

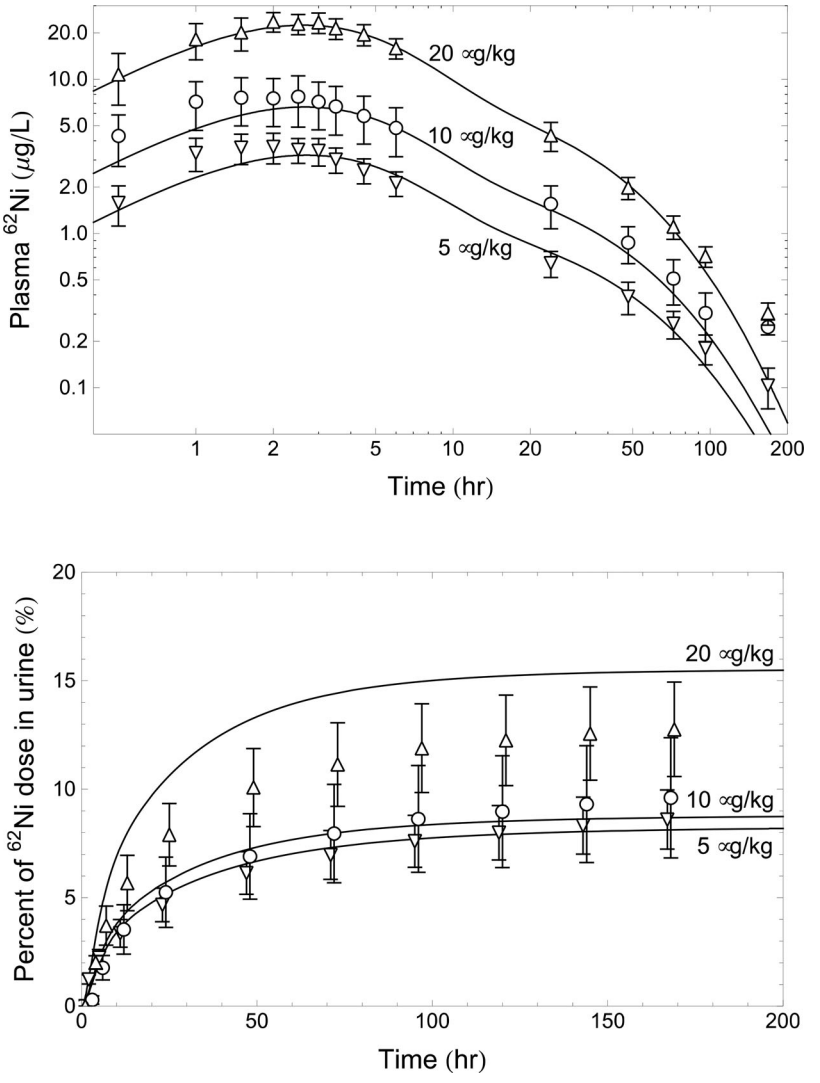

Figure 4. Measures of ^{62}Ni in samples of plasma and urine obtained by NiPERA (Patriarca and Taylor 2010a, 2010b, 2011a, 2011b) for a total of 14 subjects administered 5, 10, or 20 μg/kg bw of soluble ^{62}Ni after a 10–12-h fast (open points). Error bars denote ±1 SEM. Predictions made by the MS1 model, as optimized to the serum Ni data of Sunderman et al. (1989), were fit to the corresponding NiPERA data on ^{62}Ni in plasma by optimizing values of the parameter F_{GI} for each dose group. The bottom panel compares corresponding fitted MS1 model predictions for cumulative ^{62}Ni excretion to the respective measures of cumulative ^{62}Ni excretion in urine.

Table 1. Correlation of subject-specific $\Delta\ln(C_{Pu})$ for times T vs. time = 120 h.

Time T (h)	Number of subjects	*r*	2-tail p-value
3	16	0.659	0.0055
6	18	0.969	∼0
12	17	0.979	∼0
24	18	0.992	∼0
48	18	0.998	∼0
72	18	0.999	∼0

After excluding data for the middle dose group subject with the lowest and most extreme C_{Pu} and $\Delta\ln(C_{Pu})$ value relative to others (as further discussed below), variances among dose-specific subsets of $\ln(C_{Pu})$ are approximately equal ($p = 0.76$) and normally distributed ($p > 0.16$). Although the 17 $\ln(C_{Pu})$ values differ somewhat by dose group ($p = 0.015$, by 1-way ANOVA), this dose-related difference is (as noted above) not present using all 18 subjects and is not evident between the two highest dose groups that differ in dose by the largest absolute amount ($p = 0.21$, by 1-way ANOVA). This difference across dose groups is not linearly proportional to dose (2-tail $p = 0.26$, by linear regression), nor are dose-related differences in C_{Pu} (and thus also in $\ln(C_{Pu})$) expected based on biokinetic analysis of similar data obtained over a dose range of 12 to 50 μg/kg bw (e.g., Sunderman et al. 1989). Consequently, $\ln(C_{Pu})$ values were assumed to be independent of dose for the purpose of modeling their variance and distribution.

The combined set of 17 $\Delta\ln(C_{Pu})$ values, all calculated without regard to dose group, are approximately normally distributed ($p = 0.63$) with SD = 0.531, implying that C_{Pu} for this group at 120 h is approximately lognormally distributed with a geometric standard deviation (GSD) of 1.70. Under this normality assumption, the single outlier excluded (as noted above) had a $\ln(C_{Pu})$ value that differs significantly from the mean of the remaining 17 values ($p = \sim 0$, by t-test). The set of 17 $\Delta\ln(C_{Pu})$ values is not linearly associated with any of the covariates examined by multivariate linear regression (age, sex, or the ratio of total body mass to LBM, with or without including the additional variable dose) ($p > 0.20$, by ANOVA). The C_{Pu} value (1.37%) associated with the excluded data point lies significantly below (and is ~12% of) the geometric mean (GM) value (11.4%) of C_{Pu} measures obtained for the remaining 17 subjects at time = 120 h ($p = \sim 0$, by 2-tail t-test). This outlier represents approximately $p_o = 5.6\%$ of the total set of 18 subjects for which data were available in Data Set 1. Therefore, in the absence of additional information pertaining to inter-individual variability in R that might better characterize in particular the lower tail of the R distribution that can be estimated from Data Set 1, the ln(R)-distribution was modeled as bi-normal, i.e., R was modeled as a weighted mixture of two lognormal distributions, one with GM = 1, GSD = 1.70, and likelihood $1–p_o$, and the other with GM = 0.12, GSD = 1.70, and likelihood p_o (Figure 5). In particular, the 5th and 95th percentiles of (i.e., the 1-tail 95% confidence limits on) R so characterized are $R_5 = 0.2164$ (or $1/R_5 = \sim 4.62$-fold below the median value of R that by definition is 1) and $R_{95} = 2.358$, respectively. Very similar results obtained from an analysis of Data Set 2 are summarized in Appendix 2.

Illustrative BEAL derivation

Figure 6 plots MM1-model estimates of net urinary Ni output above that model's estimated background level (also plotted) for a reference 70-kg adult under each of the two work-week schedules and two daily Ni-intake patterns considered. Under the "M–F 8-hr shift" work-week schedule of occupational exposure to non-dietary Ni, this figure implies that he workplace equivalent of daily oral exposure to the WHO TDI of 11 μg Ni/kg is expected to result in a net rate of urinary Ni excretion due to occupational exposure equal approximately to $RU_{M–F\ 8\text{-}hr} = 2.2$-μg/hr, above excretion due to dietary exposure, regardless of whether daily occupational exposure occurs as a 6-min pulse at

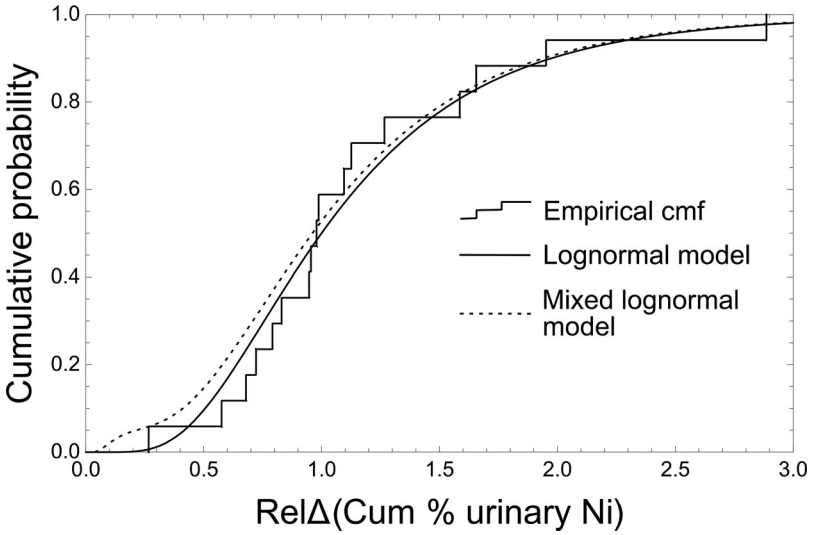

Figure 5. Models of inter-individual variability in R (the ratio of observed to median percentage of orally ingested soluble Ni that is excreted to urine, plotted along the X-axis) consistent with data obtained for a total of 18 male and female subjects studied by NiPERA, and for 20 control women (not sensitized to Ni) who were studied by Nielsen et al. (1999). The empirical cumulative probability mass function (cmf) pertains to 17 NiPERA and Patriarca et al. (1997) study subjects, and data from these studies were also used to derive the lognormal and mixed-lognormal models shown.

the beginning of, or continuously at a constant rate throughout, each work day. In contrast, if occupational Ni exposure occurs under the "2-2-3 12-hr shift" work-week schedule, the assumed daily single-pulse or constant-rate patterns of net (occupational-specific) Ni intake imply approximate net rates of urinary Ni excretion due to occupational exposure to the WHO TDI of 11 μg Ni/kg of approximately $RU_{2\text{-}2\text{-}3\ 12\text{-}hr,\ pulse} = 1.5\,\mu g/hr$ or $RU_{2\text{-}2\text{-}3\ 12\text{-}hr,\ constant} = 1.0\,\mu g/hr$, respectively. Given a worker orally exposed occupationally to Ni under the two work-week schedules and two daily exposure patterns considered, assumed to have a body weight of W (kg) and participate in a urinary Ni biosurveillance program with $T_{collect}$ measured in hours, it follows that a conservative urinary Ni BEAL (B, in μg Ni in urine) for this worker implied by the MM1 biokinetics/variability model defined above can be approximated as

$$B = RU \times T_{collect} \times R_5 \times \left[W/(70kg)\right], \tag{2}$$

where RU is one of the three net rates of urinary Ni excretion due to occupational equivalent of oral Ni exposure mentioned above, and the time $T_{collect}$ and ratio value $R_5 = 0.2164$ are discussed above. For example, assuming $T_{collect} = 2\,hr$ and $W = 60\,kg$, protective urinary Ni BEAL values of approximately 0.82, 0.56, and 0.37 μg Ni are implied for the M–F 8-hr, 2-2-3 12-hr (pulse), and 2-2-3 12-hr (constant) work schedule/exposure pattern combinations discussed above, respectively.

Discussion

The MS1 human biokinetic model for Ni presented here was determined to predict patterns of Ni exhibited in plasma and in urine of adult male and female volunteers

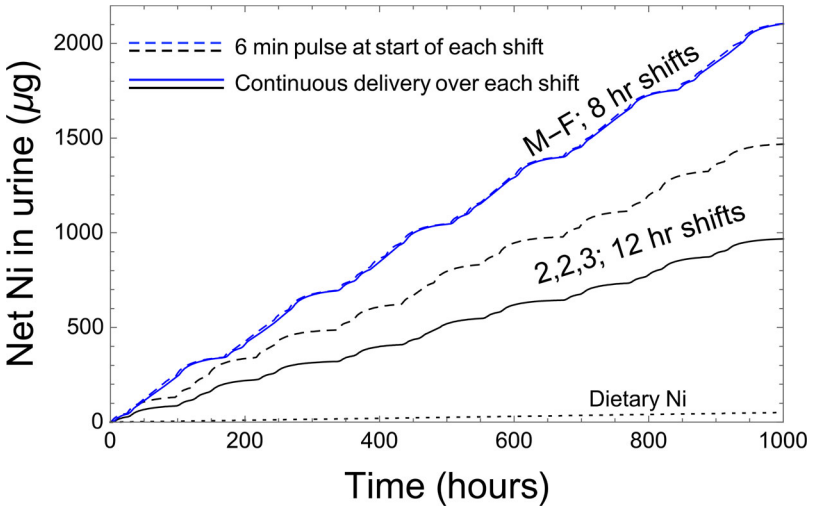

Figure 6. Cumulative total net Ni excreted in urine predicted by the biokinetic model assuming that oral-equivalent occupational nickel exposures occur on each assumed exposure day at the WHO TDI of 11 μg/kg, for M–F (blue curves) and 2,2,3 (black curves) exposure scenarios, above the background rate (1.22 μg/d) of Ni excretion (dotted line) that is implied by the MS1 model for a reference 70-kg adult due to dietary Ni intake.

administered a single oral 5- to 20-μg/kg bw dose of soluble Ni in studies by Sunderman et al. (1989), by Patriarca et al. (1997), and more recently by PTS, although using fits to the latter data involving dose-specific adjustments of the parameter F_{GI} governing modeled Ni absorption after oral exposure. Melo and Leggett (2017) predicted relative Ni clearance in plasma and in urine using a similar and also a more complex biokinetic model for Ni, but compared these predictions only to "representative" or summary data reported by Sunderman et al. (1989) and Patriarca et al. (1997), nor did Melo and Leggett (2017) address inter-individual variability in Ni clearance.

The use of ^{62}Ni in the PTS protocol, rather than total Ni, does not appear to explain key discrepancies between PTS data patterns and those reported by Sunderman et al. (1989) and Patriarca et al. (1997), because Patriarca et al. (1997) also used the ^{62}Ni dosing whereas Sunderman et al. (1989) did not. The Sunderman et al. (1989) data at all dose groups were fit by the MS1 model using a single F_{GI} estimate of 0.30, and this same F_{GI} value also fit the Patriarca et al. (1997) study data. The two lower F_{GI} values estimated for the 5- and 10-μg/kg bw PTS dose groups are nearly identical (∼0.11), whereas the high-dose estimate (0.19) is substantially larger. This could be due to chance. With only three doses, one cannot fit a dose-related pattern reliably. However, one factor that can reduce F_{GI} by up to ∼100-fold is food intake that precedes soluble Ni ingestion by 2–12 h (Sunderman et al. 1989; Patriarca et al. 1997). Thus, even relatively minor, unplanned deviations from the PTS study protocol, including a similar 10–12-hr fast prior to soluble ^{62}Ni ingestion, may explain why the PTS data are otherwise consistent with the MS1 model. Alternatively, a more complex Ni biokinetic model, or measurements in greater numbers of individuals, may jointly explain the combined data considered. For example, such a more detailed model may reflect differences in

nickel binding proteins or in the extent of entero-hepatic recirculation or fecal excretion of Ni in certain individuals that might affect Ni-biokinetic study results, particularly with sample sizes as small as those used to date. Until more extensive Ni biokinetic data become available, however, the MS1 model and associated statistical analyses described can be used to characterize and predict human Ni biokinetics after ingestion of Ni doses $\leq$ 20 µg/kg bw and associated inter-individual variation in urinary Ni excretion.

Worker-specific BEALs based on a systemic Ni exposure that can be experienced by humans on a daily basis without adverse health effects can provide health-based reference values for urinary nickel to complement but not replace existing industrial hygiene air monitoring programs. Here the MS1 model was applied illustratively to estimate a protective occupational BEAL for Ni in urine, conditional on a reference level of oral Ni intake such as the WHO oral TDI of 11 µg Ni/kg bw/d (developed to protect against potential reproductive toxicity based on oral dosing in animals). The model application was also conditional on assumed individual worker characteristics including shift schedule, a pattern of occupational oral-equivalent exposure to Ni (equivalent to the oral TDI), duration of urine accumulation prior to sample collection, and body weight.

To the extent that the route of nickel exposure in the occupational setting of concern is partly, primarily, or exclusively respiratory, it is important to bear in mind that the observed kinetics of human nickel uptake and systemic distribution that occur with respiratory exposure differ substantially from those observed after oral ingestion of soluble nickel under fasting conditions (Yu et al. 2001; Schaller et al. 2007). Inhaled nickel can be retained in the lung for extended periods, with relatively slow systemic absorption of some inhaled mass via the lymphatic system, and relatively more rapid transit of some inhaled mass by mucociliary clearance to the gastrointestinal tract (Yu et al. 2001; Schaller et al. 2007). It is expected that the difference in between respiratory absorption kinetics and oral uptake kinetics affects ultimate urinary excretion kinetics. Additionally, the WHO (2007) TDI of 11 μg/kg (as an example of a conservative TDI for Ni) as well as specific assumptions concerning work-week schedule, Ni-exposure pattern and route, urine sampling schedule, and body weight were combined here to illustrate BEAL derivation using the biokinetic/variability model developed. Application of an alternative TDI value and other assumptions would likely generate different results.

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drawn in the paper are the exclusive professional product of the authors and are not necessarily those of NiPERA, Exponent (or any of its clients), the Istituto superiore di sanità, or the Royal Surrey County Hospital.

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Data availability statement

De-identified data corresponding to tables and figures in this study will be made available to assist in related academic scientific research upon written request to the corresponding author.

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Appendix 1: Biokinetic model summary

The human Ni biokinetic model of Sunderman et al. (1989) and the modified (MS1) version of this model fit to three Ni biokinetic data sets in this study are summarized in Figure A1. The Sunderman et al. (1989) model is a two-compartment model that assumes exponential injection of an absorbed fraction F_{GI} of an administered oral dose M_o (μg/kg bw) soluble Ni from the GI into a relatively rapid-exchange Blood compartment (here representing serum or plasma), from which Ni is lost to urine with first-order kinetics, and which otherwise exchanges Ni with a relatively slowly exchanging Tissues compartment. Plasma volume was assumed to be 3.0 liters (L) for a 70-kg body weight (bw) reference adult (ICRP 1975). Using the estimates reported by Sunderman et al. (1989) for all other model parameters, baseline dietary Ni ingestion at a rate of 4.45 μg/d per 64 kg average bw for the nine dosed subjects studied by Sunderman et al. is required by their model to predict the corresponding average serum Ni concentration (C_{po} = 0.32 μg/L) reported for 10 non-dosed subjects in that study.

The modified Sunderman et al. (MS) model developed adds a Bone compartment assumed to sequester Ni from the Tissues compartment irreversibly, at a rate sufficient to generate a Ni mass of 10.39 mg (U.S. EPA 1986; ICRP 1994) in a 70-kg reference adult. To implement the MS1 model, it was assumed that this target adult reference Ni mass was attained by age 30. For a 70-kg reference adult at age 30, MS1 model parameters were optimized to yield a background Serum Ni concentration of C_{po} = 0.32 μg/L (i.e., the same as that reported by Sunderman et al. 1989), and imply a corresponding background rate of dietary Ni absorption equal to 2.167 μg/d, a corresponding urinary Ni output of 0.05079 μg/h or 1.22 μg/d, and a retained percentage of total absorbed Ni equal to 43.7%. The fraction F_{GI} of post-fasting ingested soluble Ni absorbed from the GI tract was visually optimized to a value of 0.30, which is slightly greater than the F_{GI} estimate of 0.27 reported by Sunderman et al. (1989) using their model.

The MS model parameter k_1 governing urinary Ni + ^{62}Ni excretion is a saturable, nonlinear (Michaelis-Menten) function of total nickel (i.e., total Ni + ^{62}Ni) in Serum, not just of ^{62}Ni in

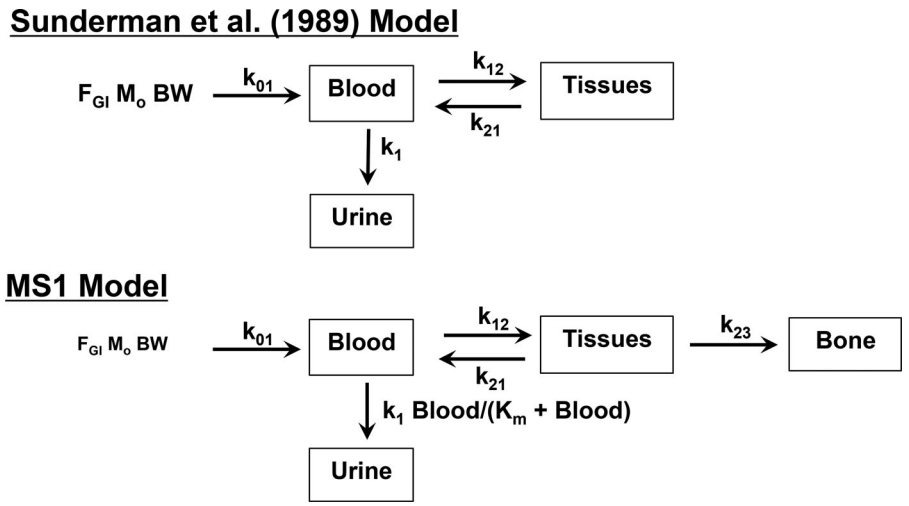

Figure A1. The Sunderman et al. (1989) biokinetic model for oral Ni uptake, distribution, and urinary excretion (top); and a "modified Sunderman et al." (MS1) model that adds a Ni sink (Bone) compartment representing long-term sequestration of Ni in bone, and replaces first-order urinary excretion kinetics with saturable (Michaelis-Menten) kinetics. The Blood compartment here represents plasma or serum. Ni mass X(t) in each compartment X at time t, is modeled as being subject to first-order loss at a rate k; i.e., to total loss at rate k X(t), for rates k noted next to each arrow exiting that compartment. The net rate of change of Ni mass in each compartment is thus modeled as the sum of all such corresponding rates of gain into, minus the sum of all rates of loss from, that compartment. Oral Ni intake-per-unit body weight (bw), M_o, including Ni from daily food ingestion and any initial experimental dose of soluble Ni administered in water, was assumed to be deposited in the GI tract, from which absorption into the Blood compartment was assumed to occur at rate k_{01}.

Table A1. Parameter values of the Sunderman et al. (1989) human biokinetic model for Ni, and of the MS model fit to data from that study, from Patriarca et al. (1997), and from NiPERA.[a]

Model[a]	Data set[a]	*n*	M_o (μg/kg bw)	k_{01} (h^{-1})	k_1 (h^{-1})	k_{12} (h^{-1})	k_{21} (h^{-1})	k_{23} (y^{1})	K_m (μg/L)	F_{GI} (unitless)
Sunderman et al. (1989)	S89	9	12, 18, 50	**0.28**	**0.21**	**0.38**	**0.08**	–	–	**0.27**
MS1	P97	4	10	**0.28**	**0.21**	**0.38**	**0.08**	85.15	2.85	0.30
MS1	NiP	6	5	**0.28**	**0.21**	**0.38**	**0.08**	85.15	2.85	0.105
MS1	NiP	4	10	**0.28**	**0.21**	**0.38**	**0.08**	85.15	2.85	0.11
MS1	NiP	4	20	**0.28**	**0.21**	**0.38**	**0.08**	85.15	2.85	0.19

[a]MS = modified Sunderman et al. biokinetic model for Ni. Parameters values listed in bold are the estimates reported by Sunderman et al. (1989). See Figure 1 for model and parameter explanations; *n* = number of subjects studied. Data sets to which models were fit were: S89 = Sunderman et al. (1989), P97 = Patriarca et al. (1997); NiP = NiPERA (Patriarca and Taylor 2010a, 2010b, 2011a, 2011b). Experimental oral doses (M_o) of soluble Ni or ^{62}Ni were administered in water after a 12-hour (h) fast (10 h in the case of NiPERA study data). Parameter estimates were conditioned on values of baseline rates of dietary Ni absorption of 4.45 μg/d per 64 kg average bw (Sunderman et al. model) or 2.167 μg/d for a reference 70-kg adult (MS1 model), and also on k_{23} (MS1 model), that are required to predict the assumed baseline plasma Ni concentration of 0.32 μg/L (see text). FGI estimates based on the S89 and NiP data sets are approximated by the following function of ingested soluble-nickel dose D (μg/kg): $F_{GI} = 0.104 + 0.146/[1 + \exp\{-0.35132(D - 18.975\ \mu g/kg)\}]$.

Serum. At only dietary levels of nickel intake with no added ^{62}Ni dose, urinary output of nickel is expected to exhibit background Ni-isotope ratios, with ^{62}Ni constituting a fraction $p = 0.036345$ of total Ni. The background Serum concentration of ^{62}Ni is thus expected to be p

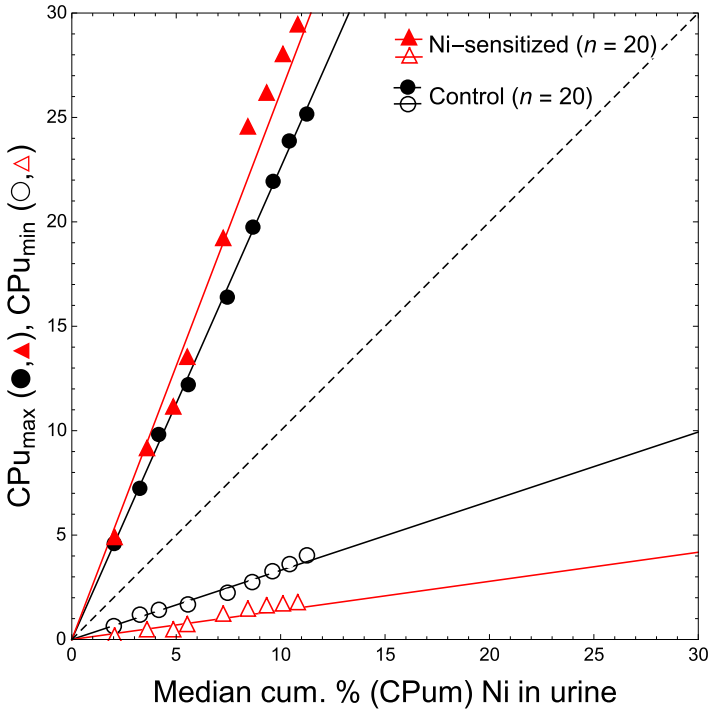

Figure A2. Minimum and maximum values of cumulative percentage of Ni in urine (C_{Pu}) measured at nine post-exposure time points in 20 control women and 20 Ni-sensitized women studied by Nielsen et al. (1999), in relation to corresponding median values (C_{Pum}). The lower and upper lines of each color represent the functions $C_{Pu\ min} = C_{Pum}/R_{loHat}$ and $C_{Pu\ max} = R_{hiHat} \times C_{Pum}$, which involve the parameters R_{loHat} and R_{hiHat} defined in Methods. The dotted line shows the value of C_{Pum} plotted along the Y-axis.

$C_{po} = 0.0116\,\mu g/L$, and the rate of urinary ^{62}Ni loss is expected to be $0.0443\,\mu g/d$. Therefore, to evaluate the MS model in relation to measured levels of ^{62}Ni made after ^{62}Ni dosing scenarios, an inflated baseline rate of dietary ^{62}Ni ingestion was used, equal to the entire assumed MS baseline rate of $2.167\,\mu g/d$ for total dietary Ni. MS model predictions for ^{62}Ni in Serum and in Urine were therefore adjusted downward to account for overestimates equal to $(1–p)\ C_{po}$ in Serum, and to $1.175\,\mu g/d$ in Urine, made conditional on the assumed (inflated) baseline rate of ^{62}Ni absorption. Equivalent model predictions for ^{62}Ni-exposure scenarios could be obtained without such adjustments by using a model more complex than MS, which accounts separately for each Ni isotope of interest.

Model parameter values reported, assumed, or estimated for the Sunderman et al. (1989) model and the MS model appear in Table A1.

Appendix 2: inter-individual variation in Ni excretion based on data set 2

The $Min(C_{Pu})$ and $Max(C_{Pu})$ measures from Data Set 2 for 20 control women and Ni-sensitized women at nine time points post-exposure are plotted in Figure A2, in relation to corresponding C_{Pum} values. This plot also shows 0-intercept slopes associated with each of the four data sets ($Min(C_{Pu})$ and $Max(C_{Pu})$ vs. C_{Pum} for control women, and likewise for Ni-sensitized women). These slopes were estimated as $1/R_{loHat}$ and R_{hiHat} for each subject group (see Methods), rather than by linear regression, because this approach relies on the parameters R_{loHat} and R_{hiHat} used to analyze this data set (see Methods) and because this alternative approach is adequately

predictive for these data sets (Figure A2). Corresponding zero-intercept and unconstrained linear regressions all indicate significant positive correlations ($r \geq 0.94$, $p < 10^{-6}$) with estimated slopes that all have small relative error ($\leq$6%). The unconstrained regressions include Y-intercepts that do not differ significantly from 0 at a 99% confidence level, except for a significant but small positive intercept (1.6%) estimated for R_{hi} values pertaining to Ni-sensitized women.

Figure A2 shows that values of $Min(C_{Pu})$ and $Max(C_{Pu})$ clearly diverge farther from the axis of symmetry (dashed line, denoting C_{Pum} measured at each time point) for the Ni-sensitized group than for the control group of women studied. Values of $Min(C_{Pu})$ also diverge farther than those of $Max(C_{Pu})$; consequently, R_{lo} values tend to exceed R_{hi} values for both groups of subjects ($p < 10^{-6}$, by Welch's t-test). The mean (±1 SD) values of R_{loHat} and R_{hiHat} obtained are 3.02 (± 0.215) and 2.26 (± 0.052) respectively for the 20 control women, and 7.18 (± 1.93) and 2.61 (± 0.208) respectively for the 20 Ni-sensitized women. Corresponding parameter estimates obtained for a bi-lognormal model (Methods) to characterize inter-individual variation in R for control women are: $R_g = 2.615$, $\sigma = 0.5147$, and $k = 1.157$. Because the estimated value of k is not much greater than 1, the R-distribution is also approximately lognormal with GM = 1 and $GSD = \exp(\sigma) = 1.67$ (Figure A2). Notably, the latter GSD estimate is very close to that of 1.70 estimated from the analysis of Data Set 1, indicating consistency in variability-characterization results obtained based on two independent data sets examined.