Nickel Absorption and Kinetics in Human Volunteers (42881)

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Abstract. **Mathematical modeling of the kinetics of nickel absorption, distribution, and elimination was performed in healthy human volunteers who ingested $NiSO_4$ drinking water (Experiment 1) or added to food (Experiment 2). Nickel was analyzed by electrothermal atomic absorption spectrophotometry in serum, urine, and feces collected during 2 days before and 4 days after a specified $NiSO_4$ dose (12 μg of nickel/kg, $n = 4$; 18 μg of nickel/kg, $n = 4$; or 50 μg of nickel/kg, $n = 1$). In Experiment 1, each of the subjects fasted 12 hr before and 3 hr after drinking one of the specified $NiSO_4$ doses dissolved in water; in Experiment 2, the respective subjects fasted 12 hr before consuming a standard American breakfast that contained the identical dose of $NiSO_4$ added to scrambled eggs. Kinetic analyses, using a compartmental model, provided excellent goodness-of-fit for paired data sets from all subjects. Absorbed nickel averaged 27 ± 17% (mean ± SD) of the dose ingested in water vs 0.7 ± 0.4% of the same dose ingested in food (a 40-fold difference); rate constants for nickel absorption, transfer, and elimination were not significantly influenced by the oral vehicle. The elimination half-time for absorbed nickel averaged 28 ± 9 hr. Renal clearance of nickel averaged 8.3 ± 2.0 ml/min/1.73 m^2 in Experiment 1 and 5.8 ± 4.3 ml/min/1.73 m^2 in Experiment 2. This study confirms that dietary constituents profoundly reduce the bioavailability of Ni^{2+} for alimentary absorption; approximately one-quarter of nickel ingested in drinking water after an over-night fast is absorbed from the human intestine and excreted in urine, compared with only 1% of nickel ingested in food. The compartmental model and kinetic parameters provided by this study will reduce the uncertainty of toxicologic risk assessments of human exposures to nickel in drinking water and food.**

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In previous studies, the absorption of nickel from the gastrointestinal tract has been investigated in healthy human volunteers or patients with nickel dermatisis who ingested capsules containing 0.6–5.6 mg of nickel as nickel sulfate (1–5). These studies have shown that nickel concentrations in serum or plasma generally peak at 2.5- to 3-hr postingestion and diminish to baseline by 72 hr, and that nickel elimination in urine is highest during the initial 12 hr and gradually returns almost to baseline within 72-hr posttreatment. Great variability has been reported for nickel levels in body fluids from subjects who ingested test doses of nickel sulfate (1–5), which probably reflects differences in fasting status, as well as the difficulty of nickel analysis and the problem of nickel contamination. This inference is based upon a study by Solomons *et al.* (6) who found that fasting human volunteers developed marked hypernickelemia within 4 hr after ingesting 5 mg of nickel as an aqueous solution of nickel sulfate, whereas no significant hypernickelemia occurred when the same quantity of nickel sulfate was added to standard meals.

In this investigation, mathematical modeling of the kinetics of nickel absorption, distribution, and elimination was performed for the first time in human subjects. The experimental protocol for this study was derived from that employed by Solomons *et al.* (6), but involved (i) more stringent precautions against nickel contamination during specimen collection and processing, (ii) quantification of nickel in serum, urine, and feces during 2 days before and 4 days after the admin-

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istration of nickel sulfate in water or food, and (iii) more sensitive and accurate nickel analyses by electrothermal atomic absorption spectrometry with Zeeman background correction.

Materials and Methods

This study was approved by the Human Experimentation Committee of the University of Connecticut Health Center, including proviso for written informed consent of the volunteers. The subjects (6 men, 4 women, ages 22–55 years) were volunteers who met the following criteria: (i) no serious illnesses during the past 5 years; (ii) no current illness, based on complete medical history and physical examination; (iii) no recent use of drugs, medications, or tobacco; (iv) no evidence of nickel sensitivity, based on negative history of contact dermatitis and negative response to dermal patch testing with $NiSO_4$; (v) negative pregnancy test in women; and (vi) consumption of a well-balanced North American diet, based on review of an itemized dietary log for 1 week.

The protocol included two experiments, each lasting 6 days (2 days predose and 4 days postdose). In Experiment 1, each of the subjects fasted overnight (for 12 hr) prior to drinking water (1.5 ml/kg body wt) that contained one of the specified doses of $NiSO_4$. Fasting was continued for 3-hr postdose; thereafter, the subjects returned to their usual diets. In Experiment 2, the respective subjects fasted overnight (for 12 hr) prior to consuming a standard American breakfast (6) that contained the identical dose of $NiSO_4$ added to scrambled eggs prior to cooking in a Teflon-lined skillet. The breakfast comprised two eggs, two pieces of bacon, two slices of white bread toast with margarine and jam, 100 ml of orange juice, and 150 ml of coffee. Six weeks elapsed between the two experiments. One man withdrew from the study after Experiment 1 and was replaced in Experiment 2 by a man of equal age and similar habitus. The $NiSO_4$ dosages in both of the experiments were (i) 50 μg of nickel/kg body wt in one man, (ii) 18 μg of nickel/kg body wt in four subjects (two men, two women), and (iii) 12 μg of nickel/kg body wt in four subjects (two men, two women).

In each experiment, blood specimens (10 ml) were obtained by venepuncture (using metal-free polyethylene intravenous cannulas and polypropylene syringes) at nine precisely timed intervals, as follows: 24- and 1-hr pretreatment and 1-, 3-, 7-, 10-, 24-, 48-, and 72-hr posttreatment. The total output of urine during each experiment was voided directly into metal-free polypropylene jars during 15 precisely timed intervals, as follows: four 3-hr collections immediately after the nickel dose and eleven 12-hr collections (during 48-hr pretreatment and 12- to 96-hr posttreatment). The total output of feces was deposited directly into polyethylene pails, using a portable plastic commode, during 48-hr pretreatment and 96-hr posttreatment. Serum, urine, and fecal specimens were processed as previously described (7), and nickel concentrations were determined by electrothermal atomic absorption spectrophotometry with Zeeman background correction, using a Perkin-Elmer model 5000-Z spectrometer (7). Creatinine concentrations in serum and urine were analyzed by the picric acid reaction (8) and creatinine clearances were normalized according to body surface area (9).

Paired data sets for the eight subjects who participated in both experiments were analyzed by a linear, compartmental, toxicokinetic model (Fig. 1), adapted from the model of Onkelinx *et al.* (10, 11). The model included two inputs of nickel: (i) the single oral dose of $NiSO_4$ administered in water or food at 7 a.m. on the third day of each experiment, and (ii) the baseline dietary ingestion of nickel. For each subject and each experiment, the following kinetic parameters were estimated: (i) a first-order rate constant (k_{01}) for intestinal absorption of nickel from the oral dose of $NiSO_4$; (ii) a pseudo-zero order rate constant (k_f) for fractional absorption of dietary nickel, based upon analyses of urine and feces during the control (predose) periods; (iii) a first-order rate constant (k_{10}) for urinary elimination of nickel; (iv) two first-order rate constants (k_{12} and k_{21}) for transfer of nickel between the compartments; and (v) the mass fraction (F) of nickel absorbed from the oral dose of $NiSO_4$. The mathematical model was based upon three simultaneous equations, as follows:

$$C = \frac{F \cdot D \cdot k_{01}}{V_1} [A_1 e^{-L_1 t} + A_2 e^{-L_2 t} + A_3 e^{-k_{01} t}] + C_O; \quad [1]$$

$$AUC(t) = \frac{F \cdot D \cdot k_{01}}{V_1} \left[\frac{A_1}{L_1} (1 - e^{-L_1 t}) + \frac{A_2}{L_2} (1 - e^{-L_2 t}) + \frac{A_3}{k_{01}} (1 - e^{-k_{01} t}) \right] + C_O t; \quad [2]$$

$$A_u(t) = k_{10} \cdot V_1 \cdot AUC(t); \quad [3]$$

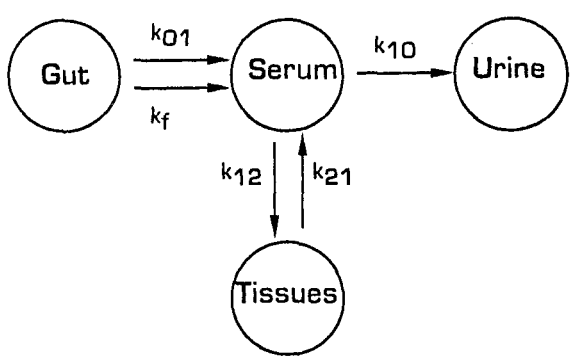

Figure 1. Schematic diagram of the compartmental model of nickel metabolism (k_f = zero-order rate constant for fractional absorption of dietary nickel; k_{01} = first-order rate constant for intestinal absorption of nickel from the oral dose of $NiSO_4$, k_{12} = first-order rate constant for nickel transfer from serum (Compartment 1) to tissues (Compartment 2); k_{21} = first-order rate constant for nickel transfer from tissues to serum; k_{10} = first-order rate constant for nickel excretion in urine).

where

C = serum nickel concentration (μg/liter) at time t after the oral dose of $NiSO_4$;

D = dose of nickel (μg) ingested as $NiSO_4$ in water or food;

t = time (hr) after the oral dose of $NiSO_4$;

C_o = baseline concentration of serum nickel, [$=f(K_f)$], established during the predose control period;

V_1 = Plasma volume (liter), derived from standard nomograms based on sex, height, and weight (12);

$A_1 = \frac{(L_1 - k_{21})}{(k_{01} - L_1 - L_2)}$ = an algebraic constant derived for the first exponential term of Equation 1;

$A_2 = \frac{(k_{21} - L_2)}{(k_{01} - L_2)(L_1 - L_2)}$ = an algebraic constant derived for the second exponential term of Equation 1;

$A_3 = -(A_1 + A_2)$, = an algebraic constant derived for the third exponential term of Equation 1;

L_1 and L_2 = hybrid rate constants, which are functions of the intercompartmental rate constants (k_{10}, k_{12}, and k_{21});

$AUC(t)$ = Cumulative area under the serum nickel concentation curve to time t; and

$A_u(t)$ = Cumulative urinary elimination of nickel (μg) from t_0 to time t.

Computations were performed on a Compaq DeskPro computer, using an iterative, least-squares program, PCNONLIN, to fit the equations to the data (13), and a polyexponential curve-stripping program, CSTRIP, to obtain the initial parameters (14). Goodness-of-fit was assessed by the Spearman correlation coefficients (r) for calculated vs observed values for serum nickel concentration and cumulative urinary excretion of nickel. Renal nickel clearance was calculated as the product of the urinary elimination rate constant (k_{10}) and the plasma volume, which was estimated from standard nomograms (12). The elimination half-time ($t_{1/2}$) for absorbed nickel was calculated by dividing the natural logarithm of 2 by L_2, using observations when the mass fraction of absorbed nickel exceeded 1.2% of the administered dose. Statistical calculations and tests (SD, correlation coefficient, linear regression, paired t test, ANOVA) were performed according to Sachs (15).

Results

During the control (predose) periods, the following baseline nickel levels (mean ± SD) were obtained in the 10 subjects: serum nickel = 0.32 ± 0.17 μg/liter (range, 0.1–0.6); urine nickel = 2.0 ± 0.9 μg/liter (range, 0.4–3.1), and 2.4 ± 1.1 μg/day (range, 0.9–4.6); fecal nickel = 1.5 ± 0.5 μg/g wet wt (range, 1.0–2.2) and 158 ± 75 μg/day (range, 69–289). These nickel concentrations and nickel excretion rates are all within the reference values for nonexposed, healthy subjects, as previously reported by our laboratory (16).

Seven hours after ingesting $NiSO_4$ in drinking water (50 μg of nickel/kg body wt), the first subject, a 55-year-old man developed left homonymous hemianopsia, which lasted 2 hr. Since the hemianopsia occurred soon after the peak concentration of serum nickel in this subject, a causal relationship between the hypernickelemia and the transient neurologic disturbance was suspected. The dosages of $NiSO_4$ for subsequent volunteers were reduced to 18 or 12 μg of nickel/kg body wt, and no adverse symptoms or signs were noted in any of these subjects.

Nickel concentrations in serum specimens and nickel excretions in urine collections from the subjects are plotted in Figure 2. When $NiSO_4$ was ingested in water, the peak nickel concentrations in serum and urine averaged, respectively, 33 and 22 times the corresponding values when $NiSO_4$ was ingested in food. The cumulative urinary eliminations of nickel during 4 days after ingesting $NiSO_4$ in water and food are compared in Figure 3. Fecal elimination of nickel during 4 days posttreatment, corrected for each subject's baseline fecal elimination of nickel, averaged 76 ± 19% of the dose ingested in water vs 102 ± 20% of the dose ingested in food ($P < 0.05$). Total recovery of the nickel dose in urine plus feces during 4 days posttreatment averaged 102 ± 8% in Experiment 1, which did not differ significantly from the corresponding value of 104 ± 21% in Experiment 2.

Parameters for nickel kinetics, derived by the mathematical model, are listed in Table I. Graphs of calculated vs observed data for serum nickel concentration and cumulative urinary elimination of nickel are shown in Figures 4 and 5, to demonstrate the goodness-of-fit. Correlation coefficients (r) for the calculated vs the observed data were 0.983 for serum nickel concentrations and 0.9996 for cumulative urinary eliminations of nickel. Absorbed nickel averaged 27 ± 17% of the dose ingested in water, compared with 0.7 ± 0.4% of the dose ingested in food ($P < 0.001$). However, the rate constants for nickel absorption, transfer, and elimination for each subject did not differ significantly when nickel was administered in water vs food. The elimination half-time ($t_{1/2}$) for absorbed nickel averaged 28 ± 9 hr (range, 17–48). No significant differences in any of the parameters were found in men vs women.

The subjects' renal clearances of nickel did not differ significantly after ingestion of $NiSO_4$ in water vs food (Table I). The renal clearance of nickel did not correlate with the mass fraction of the nickel dose that was absorbed, but it did correlate directly with the renal clearance of creatinine ($r = 0.856$, $P < 0.01$). The equation of the regression line was $y = -4.76 + 0.134x$, where y is the nickel clearance and x is the creatinine clearance, expressed as milliliters per minute.

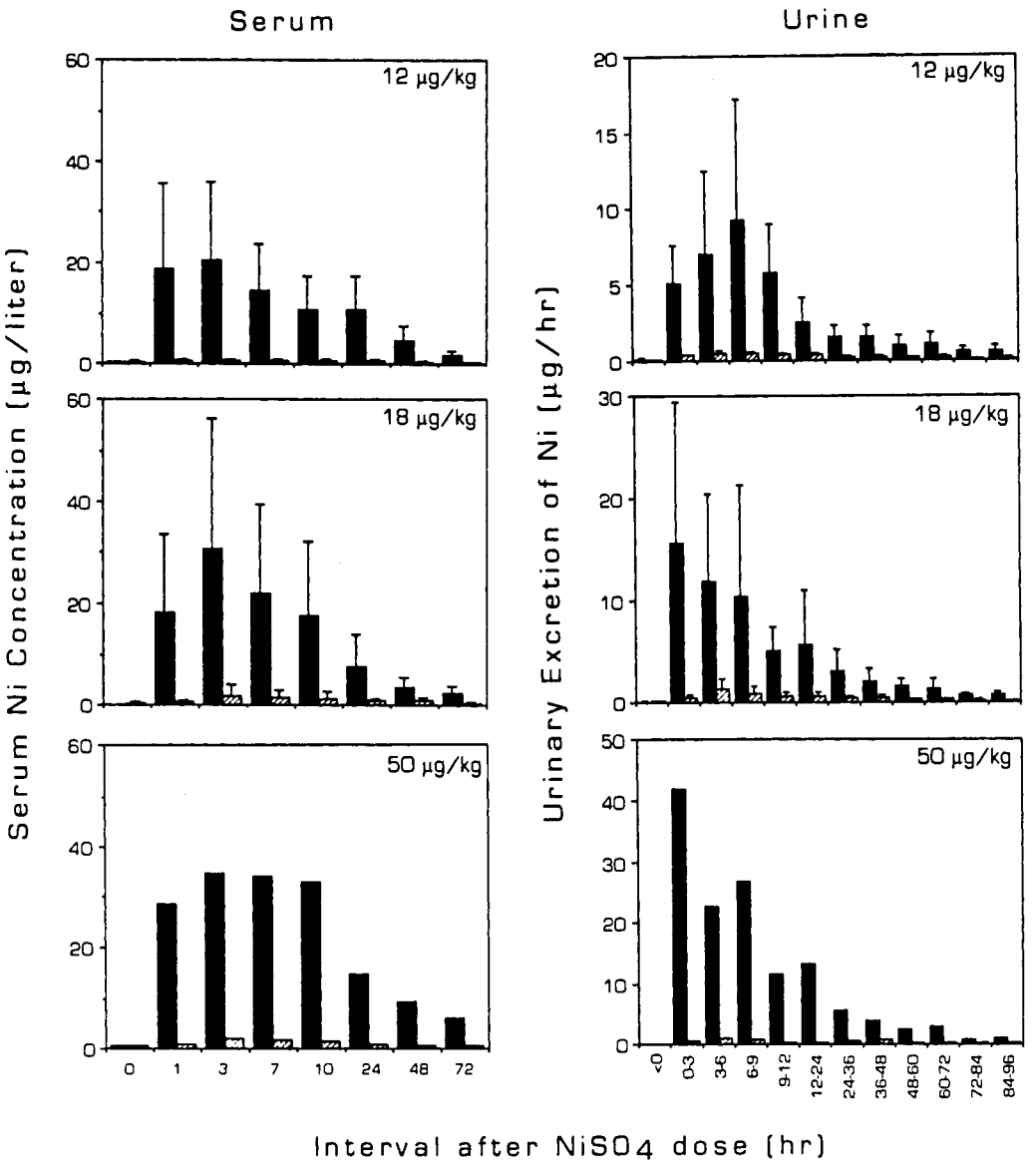

Figure 2. Mean nickel concentration in serum (µg/liter) and mean nickel excretion in urine (µg/hr) of subjects at specified intervals after ingestion of $NiSO_4$ in drinking water (solid bars) or food (hatched bars) at dosages of 12 µg of nickel/kg body wt (n = 4), 18 µg of nickel/kg (n = 4), and 50 µg of nickel/kg (n = 1). The error bars designate 1 SD above the mean.

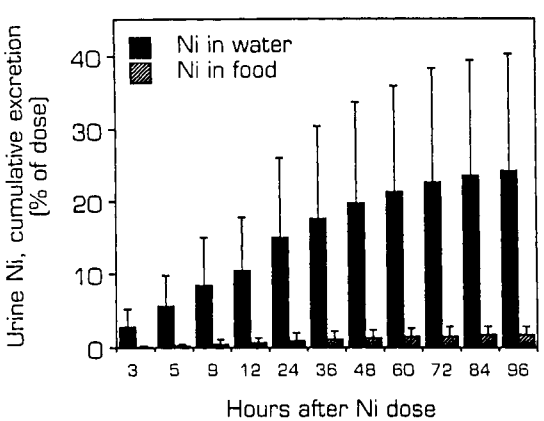

Figure 3. Cumulative nickel excretion (% of dose) in urine of subjects after ingestion of $NiSO_4$ (12, 18, or 50 µg of nickel/kg body wt) in water (solid bars) or food (hatched bars), corrected for each subject's baseline excretion of nickel during the predose control periods. The error bars designate 1 SD above the mean.

Discussion

This is the first report of a compartmental model for nickel kinetics based upon data in humans. The present compartmental model was adapted from a model for $^{63}Ni^{2+}$ kinetics in rats and rabbits, reported by Onkelinx *et al.* (10, 11). The model described in this article provides a satisfactory fit of the experimental data for the human subjects. By empirical trials, the present authors found that optimal fit of the mathematical model to the experimental data was obtained when the baseline gastrointestinal uptake of nickel from the daily diet was treated as a pseudo-zero order process (k_f), and the uptake of the administered $NiSO_4$ dose was treated as a first-order process (k_{01}). This approach can be justified by considering the pseudo-zero order constant (k_f) to represent the steady-state summation of multiple first-order Ni inputs from foods and bev-

Table I. Parameters for Nickel Absorption, Distribution, and Elimination in Human Volunteers

Parameters (with symbols and units)	Experiment 1[a] ($NiSO_4$ in water)	Experiment 2[a] ($NiSO_4$ in food)	P[b]
Mass fraction of nickel dose absorbed from the gastrointestinal tract (F, %)	27 ± 17	0.7 ± 0.4	<0.001
Rate constant for alimentary absorption of nickel from the $NiSO_4$ dose (k_{01}, hr^{-1})	0.28 ± 0.11	0.33 ± 0.24	NS
Rate constant for alimentary absorption of dietary nickel intake (k_f, μg/hr)	0.092 ± 0.051	0.105 ± 0.036	NS
Rate constant for nickel transfer from compartments 1 to 2 (k_{12}, hr^{-1})	0.38 ± 0.17	0.37 ± 0.34	NS
Rate constant for nickel transfer from compartments 2 to 1 (k_{21}, hr^{-1})	0.08 ± 0.03	—[c]	
Rate constant for urinary elimination of nickel (k_{10}, hr^{-1})	0.21 ± 0.05	0.15 ± 0.11	NS
Renal clearance of nickel (C_{Ni}, ml/min/1.73 m^2)	8.3 ± 2.0	5.8 ± 4.3	NS
Renal clearance of creatinine ($C_{creatinine}$, ml/min/1.73 m^2)	97 ± 9	93 ± 15	NS
Nickel clearance as % of creatinine clearance ($C_{Ni}/C_{creatinine}$, ×100)	8.5 ± 1.8	6.3 ± 4.6	NS

[a] Data are listed as mean ± SD.
[b] P computed by ANOVA (NS = not significant).
[c] Indeterminate value, owing to the small mass of nickel absorbed from the alimentary tract and transferred from Compartment 1 (serum) into Compartment 2 (tissues).

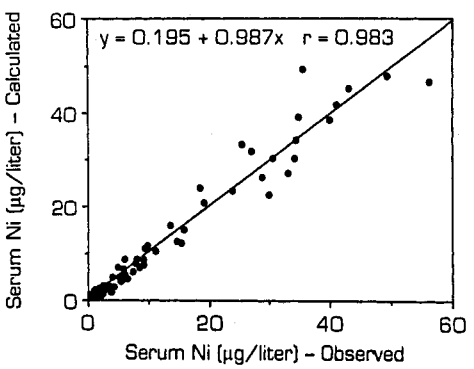

Fig. 4. Scatter plot of *observed* values for serum nickel concentrations (abcissa) vs *calculated* values by the two-compartment model of nickel kinetics (ordinate), to demonstrate the goodness-of-fit for all of the data (n = 126). The equation of the least-squares regression line and the correlation coefficient (r) are indicated at the top of the graph.

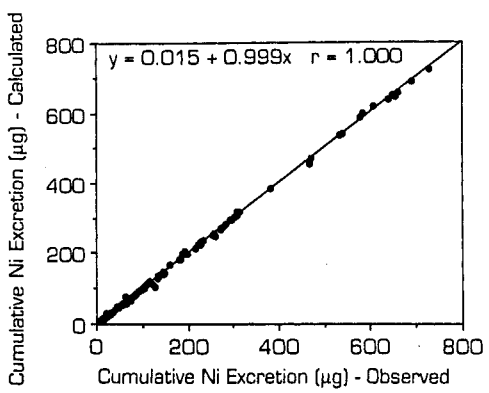

Figure 5. Scatter plot of *observed* values for cumulative urinary excretion of nickel (abcissa) vs *calculated* values obtained by the two-compartment model of nickel kinetics (ordinate), to demonstrate the goodness-of-fit for all of the data (n = 176). The equation of the least-squares regression line and the correlation coefficient (r) are indicated at the top of the graph.

erages consumed throughout the day. The model does not include parameters for possible biliary elimination and intestinal reabsorption of nickel, since the data gave no indications of an enterohepatic cycle, such as secondary peaks of nickel concentrations in serum or urine, and since biliary excretion of nickel has been shown to be quantitatively insignificant in rats (17). It is possible that biliary excretion of exogenous nickel could be significant in humans, since bile specimens obtained postmortem from nonexposed persons contain 2.3 ± 0.8 μg of nickel/liter (18). However, constraints of human experimentation prevented the present authors from performing biliary drainage to estimate the biliary elimination of nickel in the volunteers.

Compartmental modeling efforts were initially performed by use of the SAAM program of Berman and Weiss (19), based upon a more complex multicompartment model. This model incorporated (i) separate kidney, liver, and lower gut compartments, (ii) transfer parameters for possible enterohepatic circulation, and (iii) timing parameters for possible physiologic effects queued by the dietary regimens. The more complex model provided a good fit to serum nickel data for most of the subjects and a very good fit to cumulative urinary elimination data for all of the subjects. This was achieved, however, by use of subject-specific post hoc modifications (e.g., time-dependent urinary elimination rates). The authors decided that the results of such model tinkering were unsuitable for inclusion in this article.

Based upon analyses on nickel in foods and meas-

urements of nickel concentrations in prepared diets (20–22), the breakfast that was consumed by the volunteers in Experiment 2 contained <60 μg of nickel, equivalent to <~1 μg of nickel/kg body wt. Since the administered doses of $NiSO_4$ ranged from 12 to 50 μg of nickel/kg, the background nickel content of the consumed breakfast probably had little effect on the gastrointestinal absorption rates of the added nickel. Studies by Foulkes and McMullen (23, 24) on the transepithelial movement of Ni^{2+} in the isolated rat jejunum show that nickel absorption is a saturable process. In the rat, nickel uptake deviates from a first-order process at Ni^{2+} concentrations <0.1 m*M* (23, 24) in the perfusate (23, 24), whereas the present study indicates that nickel uptake in humans did not deviate from first-order kinetics following ingestion of water containing Ni^{2+} at concentrations up to 0.6 m*M* (which was, of course, substantially diluted postingestion by the gastrointestinal juices). The absorption rate constant for nickel in humans was not significantly different at dosages of 12, 18, or 50 μg of nickel/kg body wt. These findings do not exclude the possibility that nickel absorption could be saturated at higher dosages, which would restrict the applicability of the present compartmental model. To test whether or not the compartmental model of nickel kinetics can be applied to oral nickel exposures at toxic levels, two of the authors (K. R. S., F. W. S., Jr.) are using the model to analyze data for nickel concentrations in body fluids of 10 electroplating workers, who developed nickel poisoning after accidentally drinking water contaminated with nickel chloride and nickel sulfate (25). Applications of the present model to the absorption, tissue distribution, and elimination of $^{63}Ni^{2+}$ in mice, rats, and rabbits are being initiated in our laboratory, in order to undertake allometric analyses and interspecies scaling (26, 27). Such comparisons of nickel kinetics in experimental animals with those in humans should reduce the uncertainties of toxicologic risk assessments of nickel exposures that rely upon extrapolations from rodents to humans.

The transient homonymous hemianopsia that occurred in one subject after ingesting the highest dosage of $NiSO_4$ in drinking water may possibly reflect acute cerebral vasospasm, since coronary vasoconstriction has been reported in dogs following intravenous administration of $NiCl_2$ (28). In 10 electroplating workers who developed acute nickel poisoning after ingesting nickel-contaminated water, the neurologic symptoms were giddiness, lassitude, and headache (25).

The most striking outcome of this study was the finding that the mass fraction of nickel absorbed from water averaged 40 times the corresponding value for nickel absorbed from food. The rate of nickel absorption (μg/hr) equals the product of the mass fraction of absorbed nickel (FD) and the absorption rate constant for nickel (k_{01}). The rate constants for absorption of nickel from water and food, as estimated by the mathematical model, did not differ significantly in the two experiments, indicating that nickel absorption rates directly reflected the different mass fractions of nickel absorbed from water and food. A plausible explanation is that the concentration of Ni^{2+} dissolved in gastrointestinal fluids and available for alimentary absorption was substantially diminished when $NiSO_4$ was added to scrambled eggs and consumed with a standard American breakfast, owing to chelation or reduction of Ni^{2+} by dietary constituents. Constraints of human experimentation prevented the investigators from performing intestinal intubation to test this inference by analyzing the concentrations of nickel dissolved in specimens of intestinal juice. However, the inference is consistent with the findings of Solomons *et al.* (6) that certain dietary constituents (e.g., ascorbic acid) and beverages (e.g., milk, coffee, tea, orange juice) reduce the bioavailability of orally administered nickel in humans, and the findings of Foulkes and McMullen (23) that skimmed milk and Zn^{2+} reduce the absorption of nickel in isolated segments of perfused rat jejunum.

The present measurements of fecal elimination of nickel during the control (predose) periods are noteworthy because there are only two previous reports of such data. Based upon analyses of 3-day collections of feces, Nodiya (29) found fecal excretion of nickel to average 258 ± 23 μg/day (range, 219–278) in 10 Russian students who consumed a school diet, and Horak and Sunderman (30) found fecal excretion of nickel to average 258 ± 126 μg/day (range, 80–540) in 10 American adults who consumed meals prepared in their homes. Slightly lower results for fecal excretion of nickel (158 ± 75μg/day; range, 69–289) were observed for the 10 subjects in this study. For comparison, Myron *et al.* (20) reported that nine diets in American institutions contained 168 ± 11 μg of nickel/day; Smart and Sherlock (21) found that dietary nickel intake averaged 150 μg/day (range, 60–310) in 30 British adults and Veien and Andersen (22) reported that dietary nickel intake averaged 130 μg/day (range, 60–260) in eight volunteers who consumed typical Danish diets. Based on these observations and the present study, the authors infer that approximately 1% of nickel in food is absorbed from the human alimentary tract, with the balance passing directly into the feces; in contrast, approximately one-quarter of the nickel ingested in drinking water after overnight fasting can be absorbed from the intestine and excreted in urine.

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