

Molybdenum Kinetics in Men Differ during Molybdenum Depletion and Repletion¹

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ABSTRACT In this study we developed an expanded compartmental model of molybdenum (Mo) kinetics to determine rates of molybdenum distribution during molybdenum depletion and repletion. The model was based on a clinical study in which 4 men consumed a low-molybdenum diet of 22 $\mu\text{g/d}$ (0.23 $\mu\text{mol/d}$) for 102 d, followed by a high molybdenum diet of 467 $\mu\text{g/d}$ (4.9 $\mu\text{mol/d}$) for 18 d. Stable isotopes ¹⁰⁰Mo and ⁹⁷Mo were administered orally and intravenously, respectively, at several time points during the study, and serial samples of plasma, urine, and feces were analyzed for ¹⁰⁰Mo, ⁹⁷Mo, and total Mo. Based on plasma, urine, and fecal molybdenum levels, kinetic parameters of distribution and elimination were determined. The rates of molybdenum distribution and elimination were different during depletion and repletion. During high intake, urinary molybdenum excretion was greater than during low intake. In addition, fractional tissue storage of molybdenum was lower during high intake than during low intake. This suggests that low intake results in an adaptation to conserve body Mo, and that high intake results in an adaptation to eliminate Mo. The model also suggested that food-bound molybdenum was ~16% less bioavailable than purified Mo. Finally, under the conditions of this study, the model suggested that an intake of 43 $\mu\text{g/d}$ (0.45 $\mu\text{mol/d}$) would be sufficient to maintain plasma molybdenum levels at steady state. This is a minimum estimate because subjects in this study were in a molybdenum-sparing state. These findings provide an understanding of the adaptations in molybdenum metabolism that take place during depletion and repletion. *J. Nutr.* 136: 953–957, 2006.

KEY WORDS: • bioavailability • kinetics • modeling • mineral

Molybdenum (Mo) is a cofactor for at least 3 enzymes in humans: sulfite oxidase, xanthine oxidase, and aldehyde oxidase. It is considered essential because it is required for the function of these enzymes, which play a role in the catabolism of sulfur amino acids and compounds such as purine and pyrimidine (1). Although molybdenum deficiency has not been observed in healthy humans, a metabolic defect known as molybdenum cofactor deficiency results in severe neurological abnormalities and death at an early age (2,3). One instance of molybdenum deficiency attributed to inadequate intake has been documented (4). It occurred in a patient with Crohn's disease and short bowel syndrome who was on long-term total parental nutrition without molybdenum. The patient exhibited amino acid intolerance attributed to abnormal sulfur amino acid metabolism. The intolerance was reversed by adding molybdenum to the intravenous solution.

Reports of usual dietary intake of molybdenum vary widely because of differences in analytical methods and the molybdenum content of the soil (5). One study reported that the intake of molybdenum in the United States ranged from 120 to 240 $\mu\text{g/d}$ (1.2 to 2.5 $\mu\text{mol/d}$) (6), and another reported that the

mean intake for men was 109 $\mu\text{g/d}$ (1.1 $\mu\text{mol/d}$) (7). New dietary recommendations were established for molybdenum in 2002 (5). A minimum requirement of 25 $\mu\text{g/d}$ (0.26 $\mu\text{mol/d}$) was estimated, which was consistent with estimates for the minimum requirements of several animal species (8). A bioavailability factor of 75% was added to establish an estimated average requirement of 34 $\mu\text{g/d}$ (0.35 $\mu\text{mol/d}$). To cover the requirements for over 97% of people, an additional factor of 15% was added, resulting in a recommended dietary allowance of 45 $\mu\text{g/d}$ (0.47 $\mu\text{mol/d}$). The basis of these recommendations was balance studies (9). Although balance studies are useful for estimating retention of nutrients that are not altered in the colon, this approach treats the physiologic handling of the nutrient as a black box. Alternatively, kinetic modeling offers a unified hypothesis of absorption, distribution, and elimination of ingested nutrients, and therefore provides a wealth of additional information about nutrient metabolism. Thus, the goals of developing the kinetic model described here are to provide another approach for establishing dietary recommendations and to establish rates of flow among the pathways of molybdenum metabolism.

We developed an earlier kinetic model of molybdenum metabolism with low dietary molybdenum intake (10), but the model was limited insofar as the plasma compartment was a central feature of the model and no plasma data were available. The concentration of molybdenum in plasma is extremely low,

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and feasible methods to measure it were not available. We have since developed a method to determine plasma molybdenum by inductively coupled plasma mass spectrometry, and this has allowed us to measure the concentration of molybdenum and molybdenum isotopes in blood plasma (11). Measures reveal that plasma molybdenum rapidly reflects dietary intake (12). The addition of this new plasma data eliminates the serious limitation of our earlier model and allows a more accurate characterization of molybdenum metabolism through kinetic modeling. The analysis has revealed new and important information about molybdenum absorption, distribution, and elimination, including specific adaptations that occur to spare molybdenum during low intakes and to eliminate molybdenum during high intakes, differences in bioavailability of food-bound molybdenum compared to pure Mo, and more accurate values for the molybdenum requirement, steady-state molybdenum flow rates, and total body stores of Mo.

METHODS

Subjects, study design, and diet. Four healthy men participated in a study of molybdenum metabolism. All procedures were approved by the Human Subject Review Committee of the Letterman Army Institute of Research, and subjects gave written informed consent prior to participation. Subjects' characteristics (means \pm SD, $n = 4$) were as follows: 26 ± 3 y, 77 ± 12 kg, and BMI 25 ± 3 . Initial plasma molybdenum concentration ranged from 8.6 to 11.4 nmol/L, with a mean of 9.4 nmol/L.

The study design has been described previously (10). It consisted of 2 phases, a 102-d depletion phase followed by an 18-d repletion phase. Participants were confined to a metabolic research unit for the duration of the study. During the depletion phase, they consumed a low-molybdenum diet containing 22 μg Mo/d (0.23 $\mu\text{mol/d}$). The molybdenum content of the diet was the lowest that we could achieve using low-molybdenum foods and required administering purifying salts to remove molybdenum. On days 1 and 85, subjects received a 33 μg (0.34 μmol) intravenous dose of ^{97}Mo , and on days 13, 49, and 91 they received a 24 μg (0.25 μmol) oral dose of ^{100}Mo . During the repletion phase (which began on day 103), subjects consumed 467 μg Mo/d (4.9 $\mu\text{mol/d}$) as an ammonium molybdate supplement in addition to the base diet, and a 428 μg (4.5 μmol) oral dose of ^{100}Mo replaced the molybdenum supplement on day 109. This intake was chosen to ensure adequate molybdenum status by the end of the 18-d repletion period. It was a level well beyond the usual dietary intake, and a level at which there were no reports of toxic effects.

The base diet was a 3-d rotation comprised of low-molybdenum foods. The diet provided on average 11.4 ± 1.1 MJ/d, with 9% of energy from protein, 30% of energy from fat, and the remainder from carbohydrate. The base diet was supplemented with B vitamins and a formula beverage comprised of corn starch, dextrimaltose, cottonseed oil, sucrose, α -cellulose, and added salts and minerals (CaCO_3 , MgO , NaCl , KCl , KH_2PO_4 , and trace elements). The amount of energy in the beverage varied among subjects and was calculated to meet the energy requirement of each subject. If a subject gained or lost weight, the amount of energy was adjusted so that body weights of all subjects remained constant throughout the study. During the repletion phase, the ammonium molybdate supplement was added to the formula beverage. Diets plus supplements provided adequate levels of all essential nutrients except Mo. Deionized water was freely available throughout the study.

Stable isotopes. ^{100}Mo and ^{97}Mo were obtained from the Oak Ridge National Laboratory. Oral doses of ^{100}Mo were incorporated into the formula beverage described above for delivery. Polyethylene glycol was administered with each oral isotope dose as a fecal marker to monitor completeness of fecal collections. Polyethylene glycol analysis indicated all collections of unabsorbed isotope were complete. ^{97}Mo was delivered in solution after filtration and pH adjustment and was injected intravenously over a 2-min period.

Sample collection and analysis. During the first 24 h following each intravenous infusion of ^{97}Mo , urine was collected in 8-h pooled

samples. For fecal samples and all other urine samples, 6-d composite pools were collected for each subject. Urine collections were verified for completeness by creatinine content using a Technicon Autoanalyzer IIC Plus System (Technicon Instruments). Blood was collected on days 1, 14, 25, 50, 76, 92, 103, 110, and 121.

Isotopic enrichments of urine, fecal, and diet samples were determined by magnetic sector thermal ionization mass spectrometry after separation and purification of sample molybdenum by previously described methods (13). Plasma molybdenum was determined by inductively coupled plasma mass spectrometry, also previously described (11). The amounts of molybdenum and isotope tracers in the samples were determined by isotope dilution, which added a weighed amount of a ^{94}Mo solution to each weighed sample.

Kinetic modeling. Using the WinSAAM software package, a compartmental model was developed to determine kinetic parameters describing molybdenum distribution during low-molybdenum intake and the early stages of repletion. The kinetic model developed earlier (10) was based on fecal and urine data from these subjects. The model presented here was expanded to include recently available plasma molybdenum data.

The initial model (for both tracer and tracee) and parameter estimates that were used for fitting the data were based on the model published by Thompson and Turnlund (10). Initial conditions for the tracee model were based on the tracee outcome from that model. A simplified version of the model was promptly investigated based on the principle of parsimony, and 1 tissue compartment and 2 GI tract compartments were eliminated because they were not needed to fit this data set. Experimental data were compared with the model prediction for plasma, urine, and fecal ^{100}Mo , ^{97}Mo , and total Mo, and the model structure and parameters were adjusted to improve agreement of the model prediction with that of the measured data. Adjustments were mathematically driven (e.g., if model-predicted urinary molybdenum was less than experimentally observed urinary Mo, then the flow of molybdenum from plasma to urine was increased), and only adjustments that were in accord with a general knowledge of physiologic functioning were investigated.

The model included a loose statistical constraint to account for the lack of information concerning the short-term kinetics of the labeled doses. Because data describing the initial decrease of molybdenum from plasma after a dose were not available, we used data from a previous study (14) to establish loose statistical guidelines for the flow of molybdenum from plasma to tissues. Rosoff and Spencer (14) administered ^{99}Mo intravenously into 4 adults and determined plasma and whole blood ^{99}Mo levels at several time points for 24 h. In the first hour, plasma ^{99}Mo fell 95–98%. Using this data with a single exponential decay function, it was possible to estimate the rate coefficient for the transfer of molybdenum from plasma to tissues to be $\sim 85.4 \text{ d}^{-1}$. Thus, this information was added mathematically to the model.

Model parameters were adjusted until the predictions for ^{100}Mo , ^{97}Mo , and total molybdenum in plasma, urine, and feces agreed with the observed data. Once the model and parameters provided a visual fit, a least-squares fitting procedure was used to minimize the difference between model prediction and observed data. The WinSAAM population tool was used to calculate the population values.

Statistical methods. All data values are presented as means \pm SD. Differing parameter values for the depletion and repletion phases were compared by a paired t test, using Microsoft Excel 2003. $P < 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

The structure of the final model is illustrated in **Figure 1**. The model consisted of a stomach compartment for the entry of oral doses, a single gastrointestinal compartment, a plasma compartment, and a tissue compartment. Molybdenum exited the system through urine from the plasma compartment and through feces from the gastrointestinal compartment. Bile flow transferred Mo from the tissue compartment into the gastrointestinal compartment. An additional plasma compartment

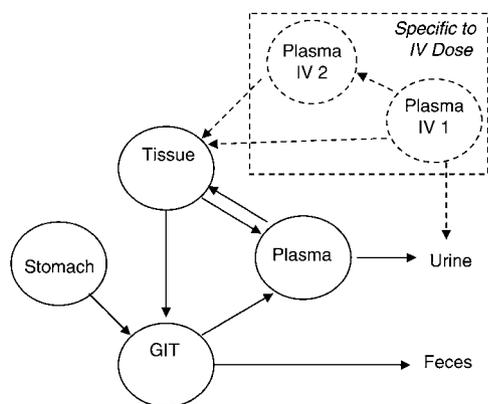


FIGURE 1 Schematic of the molybdenum kinetic model. Circles represent distinct kinetic compartments, and arrows indicate pathways of flow. Structures in dashed lines are specific to intravenous dosing.

was needed to fit the ⁹⁷Mo data. This compartment, specific to the infusion, was included only for fitting the ⁹⁷Mo data and the total molybdenum data (which included the infused ⁹⁷Mo). Because ¹⁰⁰Mo was not infused intravenously, this intravenous compartment was not included in the ¹⁰⁰Mo modeling.

Parameters representing fractional transfer coefficients are outlined in **Table 1**. The fractional transfer coefficient represents the fraction of material in a compartment transferred along a specified path in the given time unit. A value >1 indicates that the compartment turns over more than once during the specified time interval. All parameter values were determined with fractional standard deviations on individual parameters were below 10%, indicating statistical certainty on all parameter values. A sample of the model fitted to experimental data is demonstrated in **Figures 2–4**.

Three pathways were affected by the increased molybdenum intake during the repletion phase: absorption efficiency, tissue uptake, and urinary output. These paths were identified by examining the deviation of model prediction from experimental observation. The model under-predicted urinary molybdenum during repletion, which suggested that the urine output had changed. Fecal molybdenum was overestimated during repletion, suggesting that the absorption efficiency had increased. Changing those 2 paths alone still resulted in an underestimation of plasma peak concentration during repletion, and suggested that tissue storage may have been decreased. Adjustments in the paths produced agreement between model prediction and experimental data.

A comparison of differing fractional transfer coefficients is outlined in **Table 2**. During the repletion phase, fractional

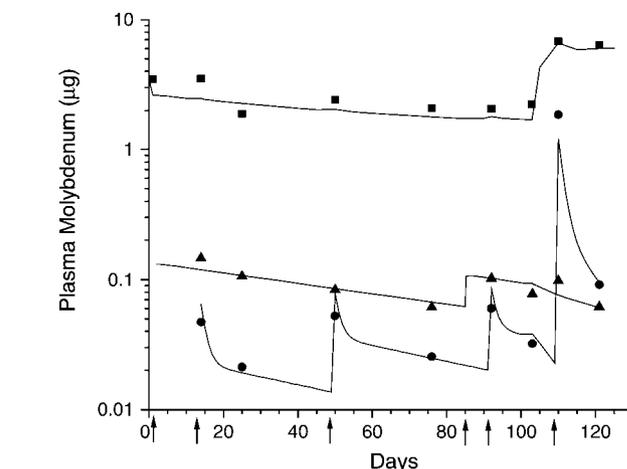


FIGURE 2 Model prediction (line) and experimental observations (symbols) for mass of plasma ¹⁰⁰Mo (circles), ⁹⁷Mo (triangles), and total Mo content (squares) for a sample subject. Mass is expressed in micrograms (multiply by 0.0104 to convert to µmol, and divide by 3.15 L plasma to estimate concentration). Mo intake was 22 µg/d for days 0–102, and 467 µg/d for days 103–120. Isotope doses (marked by arrows) were 24 µg ¹⁰⁰Mo administered orally on days 13, 49, and 91; 428 µg on day 109; and 33 µg of ⁹⁷Mo administered intravenously on days 1 and 85.

urinary output increased substantially. The fraction of plasma molybdenum excreted in urine per day increased almost 6-fold, and the mean fractional transfer coefficient from plasma to urine was 10.5 d⁻¹ for the low-molybdenum diet (equivalent to 0.73% of plasma molybdenum transferred to urine per min) and 67.9 d⁻¹ for the higher-molybdenum diet (equivalent to 4.7% of plasma molybdenum transferred to urine per min). Fractional tissue uptake of molybdenum from plasma decreased substantially during the higher-molybdenum intake. The mean fractional transfer coefficient for the transfer of molybdenum from plasma to tissue was 125.3 · d⁻¹ for the depletion diet (equivalent to 8.7% of plasma molybdenum taken up by tissues per min) and dropped to 50.3 · d⁻¹ during the repletion phase (equivalent to 3.5% of plasma molybdenum taken up by tissues per min). Both of these changes suggest an adaptation toward rapid elimination of molybdenum during the repletion phase compared with the depletion phase. These differences could also

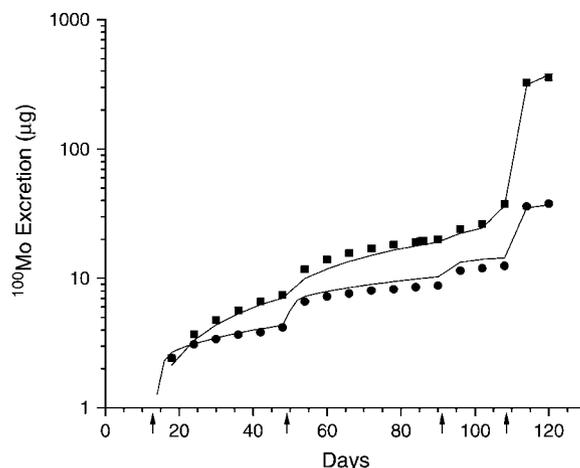


FIGURE 3 Model prediction (lines) and experimental observations (symbols) for excretion of ¹⁰⁰Mo in urine (squares) and feces (circles) for a sample subject. Mass is expressed in micrograms (multiply by 0.0104 to convert to µmol). The subject received 24 µg ¹⁰⁰Mo orally on days 13, 49, and 91, and 428 µg on day 109 (marked by arrows).

TABLE 1

Fractional transfers and flow rates of molybdenum disposition during depletion in men¹

Donor compartment	Recipient compartment	Fractional transfer coefficient, d ⁻¹	Transfer of donor compartment, %/min
GIT	Plasma	0.61 ± 0.01	0.042 ± 0.001
Plasma	Tissue	125.3 ± 9.1	8.7 ± 0.6
Tissue	Plasma	0.12 ± 0.03	0.008 ± 0.002
Tissue	GIT	0.027 ± 0.005	0.0019 ± 0.0003
GIT	Fecal	0.064 ± 0.012	0.0044 ± 0.0008
Plasma	Urine	10.5 ± 1.2	0.73 ± 0.08

¹ Values are means ± SD, n = 4.

TABLE 3

Predicted flow rates for 2 molybdenum intakes in men¹

Donor compartment	Recipient compartment	0.23 $\mu\text{mol/d}$ (22 $\mu\text{g/d}$)	4.9 $\mu\text{mol/d}$ (467 $\mu\text{g/d}$)
GIT	Plasma	0.57 \pm 0.02	5.19 \pm 0.14
Plasma	Tissue	2.07 \pm 0.19	3.35 \pm 0.36
Tissue	Plasma	1.67 \pm 0.20	2.71 \pm 0.33
Tissue	GIT	0.39 \pm 0.02	0.64 \pm 0.07
GIT	Fecal	0.06 \pm 0.01	0.31 \pm 0.07
Plasma	Urine	0.17 \pm 0.01	4.55 \pm 0.07

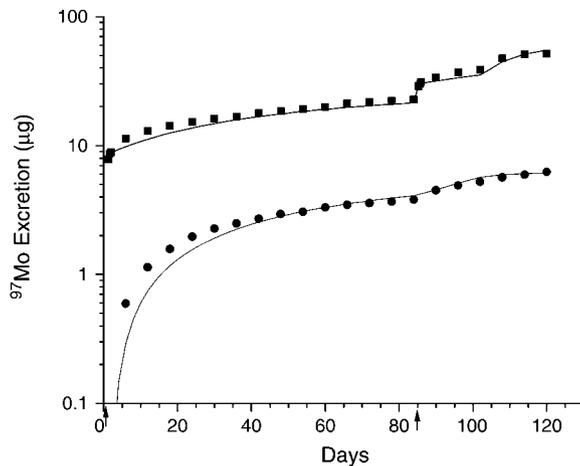
¹ Values are means \pm SD, $n = 4$.

FIGURE 4 Model prediction (lines) and experimental observations (symbols) for excretion of ⁹⁷Mo in urine (squares) and feces (circles) for a sample subject. Mass is expressed in micrograms (multiply by 0.0104 to convert to μmol). The subject received 33 μg ⁹⁷Mo intravenously on days 1 and 85 (marked by arrows).

reflect adaptations to spare molybdenum during low-molybdenum intakes. We also found that absorption efficiency of molybdenum was slightly higher during the high-molybdenum intake (94%) compared with that during the low-molybdenum intake (91%), as expressed by the difference in the fractional transfer of molybdenum from the gastrointestinal compartment to the plasma compartment. This may represent a lower fraction of molybdenum bound tightly to undigested dietary components, but could also be due to a biophysical phenomenon in the gastrointestinal lumen or to a change in gastrointestinal function during the higher-molybdenum intake.

Flow rates were calculated for intakes of 22 $\mu\text{g/d}$ (0.23 $\mu\text{mol/d}$) and 467 $\mu\text{g/d}$ (4.9 $\mu\text{mol/d}$) (Table 3). The effect of changing fractional transfer coefficients on molybdenum flows can be seen when comparing the depletion and repletion periods. Increasing intake over 20-fold from the depletion to repletion diets resulted in a <100% increase in tissue storage of molybdenum.

Simulations showed that repletion of molybdenum stores occurred very rapidly at an intake of 467 $\mu\text{g/d}$ (4.9 $\mu\text{mol/d}$), which is not surprising at this high-intake level. As demonstrated in Figure 1, total plasma molybdenum rose immediately upon the increase in daily intake. Extending the simulation confirmed that the total plasma molybdenum had reached a plateau by day 115 (after 12 d of repletion). A plot of the

TABLE 2

Differing fractional transfers rates for molybdenum disposition during depletion and repletion in men^{1,2}

Donor compartment	Recipient compartment	Depletion fractional transfer coefficient, d^{-1}	Repletion fractional transfer coefficient, d^{-1}
GIT	Plasma	0.61 \pm 0.01	0.63 \pm 0.01
Plasma	Tissue	125.3 \pm 9.1	50.3 \pm 9.5
Plasma	Urine	10.5 \pm 1.2	67.9 \pm 5.7

¹ Values are means \pm SD, $n = 4$.

² Fractional transfer coefficients above for the depletion and repletion phases differed, $P < 0.05$. Other fractional transfer coefficients were the same for both the depletion and repletion phases and are listed in Table 1.

predicted tissue molybdenum during repletion showed that tissue molybdenum reached its predepletion level by day 126 (after 23 d of repletion).

The model was used to estimate the daily molybdenum intake that would be required to maintain the initial plasma molybdenum levels (mean of 9.4 nmol/L) prior to the dietary treatment periods. It was estimated that an intake of 0.45 $\mu\text{mol/d}$ (43 $\mu\text{g/d}$) would sustain the initial plasma molybdenum concentrations. For this calculation, fractional transfer coefficients characteristic of the 22 $\mu\text{g/d}$ (0.23 $\mu\text{mol/d}$) intake level were used. Based on the comparison of rate parameters for the depletion and repletion phases, it appears that these subjects may have been in a molybdenum-sparing state. If molybdenum excretion is higher at higher intakes, then this estimate would be low. Kinetic studies at other intakes are needed to explore this conclusion. This finding confirms the newly established Dietary Reference Intake values for molybdenum, which were partially based on the urine and fecal losses from these subjects. The Estimated Average Requirement was set at 34 $\mu\text{g/d}$ (0.35 $\mu\text{mol/d}$), and the Recommended Dietary Allowance was set at 45 $\mu\text{g/d}$ (0.47 $\mu\text{mol/d}$) (5).

Two additional intravenous dose compartments were needed to fit the plasma ⁹⁷Mo data. One compartment, labeled "Plasma IV 1" in Figure 1, was used to deliver the intravenous dose. The tissue uptake of molybdenum from this compartment was assumed to match that of the main plasma compartment. It was necessary to transfer molybdenum from this compartment to urine \sim 3 times more rapidly than from the main plasma compartment to urine, otherwise plasma molybdenum was overestimated and urinary molybdenum was underestimated. We propose that this simply represents a difference in the kidney's handling of the intravenous form of molybdenum compared with molybdenum incorporated into the blood stream via the gastrointestinal tract. The kinetic data also showed that a small percentage of the intravenous dose remained resident in the plasma longer than would be expected given the turnover rate of the main plasma compartment. We assumed that the compartment labeled "Plasma IV 2" in Figure 1 represented molybdenum extrinsically bound to red blood cells. Evidence for this type of interaction in rats was presented by Lener et al. (15) and Kselikova et al. (16). Kselikova et al. (16) examined blood partitioning of ⁹⁹Mo after administering ammonium molybdate subcutaneously. Of the administered dose, 0.15% was associated with red blood cells 1 h after the dose. We found, on average, that 0.21% of the dose needed to be transferred to this compartment to fit the data, which complies with the findings of Kselikova et al. (16). Assuming that this molybdenum was associated with red blood cells, we assigned a residence time of 120 d to this compartment, the average lifespan of a red blood cell.

TABLE 4

Tissue/pool masses for 2 molybdenum intakes in men¹

Tissue	0.23 $\mu\text{mol/d}$ (22 $\mu\text{g/d}$)	4.9 $\mu\text{mol/d}$ (467 $\mu\text{g/d}$)
Plasma	0.017 \pm 0.002	0.067 \pm 0.006
Tissue	14.9 \pm 2.5	24.1 \pm 3.8
GI Tract	0.93 \pm 0.03	8.2 \pm 0.1

¹ Values are means \pm SD, $n = 4$.

The tissue compartment likely represents mainly liver and kidney, because those tissues are known to store large amounts of molybdenum following a dose (17). Molybdenum stores were calculated for an intake of 0.45 $\mu\text{mol/d}$ (the intake level calculated to maintain initial plasma molybdenum concentrations) and the fractional transfer coefficients characteristic of the depletion period. For this study population, the model predicted 2711 \pm 103 μg (28.2 \pm 1.1 μmol) for total body molybdenum. Schroeder et al. (17), who analyzed molybdenum levels in tissues of 381 humans after accidental or disease-related death, found total body molybdenum to range between 2286 and 2378 μg (\sim 24 μmol). In Schroeder's analysis, the highest concentrations of molybdenum were found in the liver, kidney, and adrenals. Molybdenum was also consistently present (though sometimes in very low levels) in fat, blood, and the intestine, lungs, and heart. Pool sizes for the 2 dietary intakes can be seen in Table 4. Intakes of 22 $\mu\text{g/d}$ (0.23 $\mu\text{mol/d}$) and 467 $\mu\text{g/d}$ (4.9 $\mu\text{mol/d}$) would result in total body molybdenum stores of 1519 μg (15.8 μmol) and 3115 μg (32.4 μmol), respectively. Residence time for total body molybdenum was estimated to be 67 d.

To fit the plasma total molybdenum data, we found it necessary to slightly reduce the bioavailability of molybdenum from the background diet in relation to the ¹⁰⁰Mo oral dose. Without the reduction in bioavailability, plasma total molybdenum was consistently overestimated, resulting also in the overestimation of urinary total molybdenum. The model predicted the mean bioavailability of molybdenum from food sources to be 76%, which is 16% lower than the bioavailability of the purified ¹⁰⁰Mo dose (91%) during the depletion phase. Incorporating this bioavailability reduction into the model allowed the total plasma and urine molybdenum predictions to be in accord with measured data. A previous study of foods intrinsically labeled with molybdenum showed that the food matrix can interfere with molybdenum bioavailability (18). In that study, the kale matrix did not inhibit the absorption of molybdenum, whereas the soy matrix reduced molybdenum bioavailability by 37% compared with the purified dose. The reduction in bioavailability in our study represents an average affect on bioavailability for the general background diet and falls within the range reported by Turnlund et al. (18).

In conclusion, the kinetic analysis presented here provided a clearer understanding of molybdenum absorption, distribution, and elimination during molybdenum depletion and repletion. The analysis demonstrated that 3 pathways are responsible for sparing molybdenum when intake is low and eliminating it rapidly when intake is high. This new evidence suggested that food-bound molybdenum has lower bioavailability than purified molybdenum.

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