

Quantitative estimates of the reducing capacity of key body fluids and tissues may represent detoxification thresholds which provide insights on the probability of health effects at lower doses. The purpose of this study is to illustrate how the detoxification thresholds vary for inhalation versus ingestion exposures in a manner consistent with the relevant sources of reducing agents for these routes of exposure. Estimates of the overall Cr(VI) reducing capacity of some conceptual body compartments were made by relating the specific reducing activity of these tissues or fluids to their average volume, number, or weight in an average adult. Our route-specific calculations illustrate that plausible Cr(VI) detoxification thresholds via ingestion are substantial, involving sequential contact with three conceptual compartments that have high capacity, regenerable sources of exogenous and endogenous reducing agents. In contrast, the plausible Cr(VI) detoxification thresholds via inhalation are comparatively low for lung tissue, the well-characterized target organ for occupational settings. Calculated thresholds for the conceptual compartments in this study correspond well with the observation that chronic doses of Cr(VI) in the high milligram per kilogram range are required via ingestion to induce appreciable tissue damage to the gastrointestinal tract, whereas chronic inhalation doses of Cr(VI) in the low microgram per kilogram range have been associated with objective deficits in pulmonary function tests. We conclude that these quantitative estimates of Cr(VI) detoxification thresholds for oral and inhalation exposures are consistent with published observations on acute and chronic toxicity in animals and humans.

**1711** STEADY-STATE OBSERVATIONS IN BLOOD AND URINE OF HUMAN VOLUNTEERS FOLLOWING INGESTION OF HEXAVALENT CHROMIUM IN DRINKING WATER.

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This study examines the uptake and elimination of Cr(VI) in a male volunteer who ingested two liters per day of 2 mg/L for 17 consecutive days. Total chromium was measured in urine, plasma, and red blood cells (RBCs) for 4 days prior to and two weeks after dosing (34 days total). The estimated bioavailability (2%) and the plasma elimination half-life (36 hrs) were consistent with our previous studies of Cr(VI) ingestion in humans. Steady-state chromium concentrations in urine and blood were achieved after 7 days of Cr(VI) ingestion. Both plasma and RBC chromium concentrations returned rapidly to background levels within a few days of cessation of dosing. Since the concentration of chromium in the RBC should not decrease quickly if the chromium had entered the RBC as Cr(VI), these data support our prior work suggesting that concentrations of 10 mg Cr(VI)/L or less in drinking water of exposed humans appears to be reduced to Cr(III) prior to systemic distribution.

**1712** EFFECTS OF SUCCIMER ON TISSUE Pb AND Pb EXCRETION IN RHESUS MONKEYS DETERMINED USING A STABLE <sup>204</sup>Pb ISOTOPE TRACER.

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A sensitive stable lead isotope (<sup>204</sup>Pb) tracer methodology is being used to investigate the endogenous sources of Pb mobilized and removed by succimer (Chemet®) chelation in Rhesus monkeys (*Macaca mulatta*). Infant monkeys (12 months age) exposed to Pb or vehicle since birth were administered a stable <sup>204</sup>Pb tracer i.v. and subsequently placed on a treatment regimen of succimer or placebo for 19 days. Blood, liver (biopsy), and bone (biopsy) samples were collected using trace metal clean techniques at T=0 and 5d of treatment. Complete 24 hr urine collections were conducted over the first 5 days of treatment. All samples were analyzed for total Pb and <sup>204</sup>Pb tracer by inductively coupled plasma - magnetic sector mass spectrometry. This design possesses advantages over previous studies because each animal is sampled prospectively to evaluate changes in organ and blood lead content over the course of treatment. Preliminary results (n = 3 animals/group) from Pb + placebo versus Pb + succimer groups indicates that succimer treatment increased the total 5 day urinary excretion of Pb and <sup>204</sup>Pb by 150% - 170% over the placebo group. In the placebo group, the percentage reduction (± SD) in blood, liver, and bone Pb levels after 5 days treatment was 35% (± 19%), 39% (± 3%), and 30% (± 37%), respectively, while in the succimer treated group, blood, liver, and bone Pb levels were reduced by 44% (± 10%), 64% (± 11%), and 17% (± 14%), respectively. The <sup>204</sup>Pb tracer provided

additional important information on the metabolism and excretion of Pb over the course of treatment. (Supported by NIEHS Grant #06918).

**1713** THE SKELETON AS AN ENDOGENOUS SOURCE OF Pb EXPOSURE AND THE EFFECTS OF BONE Pb AND THERAPEUTIC TREATMENTS ON BONE LOSS DUE TO OSTEOPENIA.

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The skeleton is the major repository of Pb in the body and is an important target organ for Pb toxicity. However, little is known regarding both the mobilization of skeletal Pb during bone loss related to age or pathological conditions, or the effects of bone Pb levels on the physiological response of the skeleton to therapeutic treatments (i.e., estrogen replacement) used to reduce the development of osteopenia in post-menopausal women. To address this, we are utilizing a stable Pb isotope tracer method in a rodent model of hormone depletion-induced osteopenia to label the skeleton with a Pb isotope tracer signature distinguishable from soft tissues, in order to specifically identify Pb in soft tissues and urine that originated from the skeleton. Animals have been exposed to low (10ppm) and high (100ppm) Pb levels via drinking water and biweekly injections of tracer <sup>204</sup>Pb for 12 wks prior to ovariectomy (OVX). Following OVX, animals underwent one of three therapeutic treatment regimes, and were sacrificed at 4 and 8 weeks post-OVX. Blood, plasma, kidney, brain, tibia, femur, vertebrae, and urine samples have been collected for analyses of both Pb and tracer <sup>204</sup>Pb content. Plasma, urine and bone samples will also be analyzed for osteocalcin, alkaline phosphatase, and pyridinoline x-links to determine the effects of Pb and on bone remodeling processes. Preliminary data on bone <sup>204</sup>Pb tracer enrichment (≈ 6% <sup>204</sup>Pb) supports the suitability of this tracer method in this model. (Supported by NIEHS Grant# ES07535).

**1714** MONTE CARLO MODELING OF CHILDHOOD LEAD EXPOSURE: DEVELOPMENT OF A PROBABILISTIC METHODOLOGY FOR USE WITH THE U.S. EPA IEUBK MODEL FOR LEAD IN CHILDREN.

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An integrated stochastic exposure (ISE) model using microexposure techniques was developed to characterize short-term variability and uncertainty in residential childhood lead exposure. The ISE model was linked to the biokinetic module of the U.S. EPA Integrated Exposure, Uptake, and Biokinetic Model (IEUBK) for Lead in Children so that the predicted PbB distribution reflects variability in exposure and uptake variables. Probability distributions were assigned to exposure and uptake variables to characterize variability and uncertainty in age-specific physiology and activity patterns, demographic and housing conditions, and concentrations of lead in paint, soil, dust, and tap water. The linked model was used to conduct an uncertainty analysis of childhood lead risks at the census tract level in Syracuse, NY. Output from the linked ISE/IEUBK model was compared with output from the IEUBK Model run in batch mode using central tendency point estimates for exposure variables and an assumed GSD PbB. Modeling time steps ranging from 2 weeks to 1 year were simulated to demonstrate the effect that assumptions regarding temporal inter- and intra-individual variability (including seasonal variability) in exposure variables may have on the predicted PbB distribution. A sensitivity analysis was conducted to quantify the relative contributions of input variables to the predicted GM and GSD PbB. The ISE model demonstrates how the predicted GSD varies as a function of age and exposure topology. Future model development will quantify uncertainty and variability at smaller spatial scales, and link the ISE model to stochastic biokinetic models to explore the relative contributions of exposure, uptake, and biokinetic variables to the predicted GM and GSD PbB.

**1715** USE OF A MONTE CARLO EXPOSURE MODEL TO ESTIMATE BLOOD LEAD DISTRIBUTIONS IN U.S. CHILDREN.

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A Monte Carlo model was developed to estimate lead intake for children (age 0-6) from various media: food, water, air, and soil. For lead in food,