

1  $\mu\text{g}/\text{dL}$  have remained at that value for two years. Supported by NIEHS grant #ES04762 to C R Angle.

#### 71 A NON HUMAN PRIMATE MODEL FOR LEAD KINETICS IN GERIATRIC HUMAN POPULATIONS

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The purpose of the investigation was to study lead (Pb) kinetics in a non human primate model of aging using K XRF measurements of Pb in bone. Rhesus monkeys (*Macaca mulatta*) were administered Pb acetate daily in drinking water for six years during adulthood; controls were given no Pb. Pb content in tibia was measured using <sup>109</sup>Cd K XRF techniques at  $28 \pm 2$  yrs of age and again approximately 10 months later. Pb intake ended 10 years prior to the first bone measurement. Bone Pb content was significantly elevated for the Pb-treated monkeys and there were no significant changes over the repeated measurements. The accumulation rate of Pb into tibia was similar to that measured in humans, 0.1 mcg Pb/(g bone mineral)/mcg/dl yr) in monkey and 0.05 to 0.1 in human. A half-life of Pb in a single bone compartment for the Pb treated monkeys was calculated to be  $3.0 \pm 1.0$  years. Endogenous Pb exposure from bone was low at the time of bone Pb measurements but may have been higher from cortical than from trabecular bone. The rhesus monkey appears to be an excellent model of human bone Pb metabolism studies needed for further understanding of Pb kinetics in geriatric populations. Supported by EPA CR-817425 and CR-817156.

#### 72 TRENDS IN BLOOD LEAD VALUES IN UNCHELATED CHILDREN WITH MODERATE LEAD POISONING

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This study determined contributions of environmental Pb exposure and Fe status to changes in BPb levels over six months in moderately Pb poisoned children (initial BPb: 25–55  $\mu\text{g}/\text{dL}$ ). Chelation therapy was not administered: all children had negative lead mobilization tests (Pb-MT) indicating limited response to CaNa<sub>2</sub>EDTA. Children received these interventions: three home visits to assess lead paint hazards; notification of the D.O.H. to remediate lead hazards; educational information about the routes of lead exposure, its toxicity and treatments; Fe therapy for children with ferritin levels < 16  $\mu\text{g}/\text{dL}$ ; and 10 clinic visits over the six month period to reassess clinical status, reinforce educational information and obtain BPb levels. Other than a single dose on the day of a Pb-MT, no child received chelation. To quantify lead paint hazards, a visual rating of the surfaces (intact to peeling) was combined with x-ray fluorescence measurements. The sum of these assessments was termed the home environmental score (HES). Data were analyzed from 79 children. BPb levels declined by 27% over the six months. HES was correlated with BPb at enrollment but neither the initial nor later HES measurements predicted BPb. The HES was highest at enrollment and declined by 50% and 75% at the second and third home visits, respectively. Only a minority of children (20%) achieved a HES of 0, indicating no lead paint hazards. Despite some ongoing Pb exposure, a parallel fall in BPb levels was observed in subgroups of children with initially low or high HES. Fe status did not account for the change in BPb levels: Fe deficient and sufficient children had comparable rates of decline in BPb concentrations. These indicate that: 1) the HES is quantifiably related to BPb levels; 2) this correlation is significant only prior to intervention, and, 3) BPb levels decline in moderately lead poisoned children after they are enrolled in a comprehensive intervention program, even in the absence of chelation therapy and in the presence of some ongoing lead paint exposure and Fe deficiency.

#### 73 PHARMACOKINETICS OF DRINKING WATER EXPOSURE TO SELECTED CHROMIUM (III AND VI) COMPOUNDS IN HUMAN VOLUNTEERS

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This study examines chromium uptake and excretion following ingestion of a single oral dose of three different chromium compounds in water ( $\text{CrCl}_3$ ,  $\text{K}_2\text{CrO}_4$  reduced in orange juice, and  $\text{K}_2\text{CrO}_4$ ). Adult volunteers ingested a single dose of 5 mg chromium in a 0.5 liter volume. Blood and urine samples collected for up to two weeks following the dose were analyzed for total chromium. Plasma and red blood cell (RBC) chromium concentrations were transiently elevated for all three chromium compounds within 8 hours after

the dose. Total urinary chromium excretion within 4 days after the dose was less than 1% of the dose for  $\text{CrCl}_3$  and  $\text{K}_2\text{CrO}_4$  reduced in orange juice, but was considerably higher for the same dose of  $\text{K}_2\text{CrO}_4$  in water. Despite the greater systemic chromium uptake and excretion following ingestion of  $\text{K}_2\text{CrO}_4$  in water, no sustained elevation of chromium was observed in red blood cells — a marker for systemic uptake of the hexavalent form. The data suggest that ingestion of trivalent chromium as  $\text{CrCl}_3$  or as a probable organic complex in orange juice leads to low level systemic uptake, indicated by transient elevations in RBC chromium content and slightly increased urinary chromium excretion. The magnitude of total chromium uptake is increased when  $\text{K}_2\text{CrO}_4$  is administered in water, but the absence of any sustained elevation of RBC chromium levels indicates reduction intragastrically followed by systemic absorption of the trivalent form.

#### 74 DERMAL UPTAKE OF HEXAVALENT CHROMIUM IN HUMAN VOLUNTEERS MEASURES OF SYSTEMIC UPTAKE FROM IMMERSION IN WATER AT 22 PPM

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This study examines the systemic uptake of chromium in four human volunteers following 3 hours of contact with water containing hexavalent chromium [ $\text{Cr(VI)}$ ] at a concentration of 22 ppm (mg/L). Volunteers were immersed below the shoulders (about 13,000  $\text{cm}^2$ ) in the water at  $91 \pm 2.5^\circ \text{F}$ . On the day prior to the experiment and for six days afterwards, samples of urine, plasma, and red blood cells were collected and analyzed for total chromium. Red blood cell chromium concentrations were used as a specific biomarker for systemic uptake of hexavalent chromium. No sustained elevation of chromium concentrations was observed in red blood cells of the volunteers tested; thus, no appreciable  $\text{Cr(VI)}$  was systemically absorbed. Small increases were observed in the concentration of chromium in urine within 48 hours of exposure, indicating some  $\text{Cr(III)}$  may have penetrated the skin at a rate of about  $3.5 \times 10^{-5}$  to  $5.2 \times 10^{-4} \mu\text{g}/\text{cm}^2\text{-hr}$ . In short, dermal exposure of humans for 3 hours at 22 ppm  $\text{Cr(VI)}$  did not result in systemic uptake of measurable amounts of  $\text{Cr(VI)}$ , but a very small quantity of chromium may have penetrated the skin where it was subsequently reduced to  $\text{Cr(III)}$  before systemic uptake and distribution.

#### 75 HANDDUST LEAD LOADING ( $\mu\text{g}/\text{m}^2$ ) AS AN IMPROVED PREDICTOR OF CHILDHOOD BLOOD LEAD (PbB) IN LONGITUDINAL STUDIES

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Handwipe lead (PbHW) is often evaluated as an exposure index reflecting the exchange between soil and dust lead and childhood blood lead (PbB). Since PbHW, usually obtained by 2 wipes of both sides of both hands, increases with surface area (SA), PbHW/5% body SA (PbHWSA  $\mu\text{g}/\text{m}^2$ ) may better reflect Pb loading in longitudinal studies of growing children. Circulating PbB (8% wt kg x PbB) similarly reflects the effect of growth on body burden: while PbB declines with age, PbBcirc may be stable or increase. In the 12 month Omaha Study of 21 urban children, 2–3 y.o., PbHW was  $5.6 \mu\text{g} \pm 4.5$  (SD); PbHWSA was  $3.4 \mu\text{g}/\text{m}^2 \pm 2.9$  ( $n = 244$ ); PbB was  $6.4 \pm 3.1 \mu\text{g}/\text{dL}$ ; PbBcirc was  $73.2 \pm 35.1 \mu\text{g}$  ( $n = 82$ ). Although the prediction of PbB by PbHW and age (ANOVA correlated for repeat measures) was not statistically significant, PbBcirc was significantly predicted by PbHWSA:  $p = .011$ , SEE 0.6. Physiologic models may provide more valid correlates of environmental exposure than the use of age as a predictive covariable in multiple regression analyses, particularly in longitudinal studies of environmental lead and the body burden of childhood lead. Supported by NIEHS #ES04762.

#### 76 TESTING FOR DNA-PROTEIN CROSSLINKING AFTER DRINKING WATER EXPOSURE TO CHROMIUM (III AND VI) IN HUMAN VOLUNTEERS

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Increased DNA-protein crosslinking (DPX) in circulating lymphocytes has been proposed as a potential biomarker for exposure and potential genotoxic

damage caused by inhalation of certain reactive chemicals, such as hexavalent chromium. This study was designed to determine whether ingestion of a single dose of chromate alone [Cr(VI)] or chromate fully reduced to Cr(III) with orange juice causes an increase in DPX of circulating lymphocytes in humans. Five adult male volunteers ingested a dose of 5 mg chromium in a 0.5 liter volume of water, and blood samples were collected at 0, 30, 60, 120, 180, and 240 minutes afterwards for analysis of lymphocyte DPX. Blood and urine samples were also collected for up to two weeks following the dose to examine the pattern of uptake and excretion of chromium. The results demonstrated that no significant change in DPX was observed following either Cr(VI) or Cr(III) ingestion, even though blood and urine chromium measurements indicated systemic uptake and urinary excretion of a substantial fraction of the ingested chromium within 4 days after the dose. Since Cr(III) does not possess DPX-inducing properties while Cr(VI) does, these results suggest that the Cr(VI) was reduced to Cr(III) intragastrically prior to absorption.

#### 77 REDUCTION KINETICS OF HEXAVALENT CHROMIUM IN HUMAN BLOOD

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Available literature suggests that both plasma and red blood cells are capable of reducing hexavalent chromium to the less reactive trivalent form. However, the rate of reduction and the maximum capacity for reduction in blood have not been well characterized. To evaluate these parameters, fresh human blood stabilized with EDTA was separated into red blood cell and plasma pools. The plasma was spiked with Cr(VI) at concentrations ranging from 0.2 to 10.0 ppm. The blood was then reconstituted and incubated at body temperature. Timed samples were removed for total chromium and hexavalent chromium analyses in both red blood cells and plasma. Cr(VI) spiked into plasma alone was stable for several hours at 0.003 - 0.025 ppm, indicating a lack of appreciable reductive capacity in isolated plasma. Red blood cells exhibited a large capacity to reduce Cr(VI) and accumulate chromium (perhaps greater than 15 ppm). The rate of Cr(VI) reduction in whole blood is extremely rapid and complete at concentrations below 2.0 ppm, but plasma compartment reduction processes apparently are overwhelmed at a concentration of 10 ppm Cr(VI). The studies indicate that the blood provides a significant buffer or barrier to prevent the distribution of Cr(VI) in the body via chromium reduction in plasma (in the whole blood matrix) and rapid uptake and reduction inside red blood cells.

#### 78 BIOAVAILABILITY OF SOIL-BORNE LEAD IN ADULTS, BY STABLE ISOTOPE DILUTION

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Using stable isotope dilution, we determined the bioavailability of soil-borne lead in human adult volunteers. Soil from a residential yard at a mining-impacted federal Superfund site, which had negligible amounts of other priority pollutants, was dried and screened through a 250  $\mu$ m mesh sieve. The < 250  $\mu$ m fraction, which likely represents that ingested via hand-to-mouth activity, was then sterilized by exposure to radiation. Ten replicate samples yielded a mean (SD) soil lead concentration of 2924  $\pm$  36 ppm, and a mean <sup>206</sup>Pb/<sup>207</sup>Pb ratio of 1.1083  $\pm$  0.0002, indicating remarkable soil homogeneity. Six adults with <sup>206</sup>Pb/<sup>207</sup>Pb ratios of > 1.190 were admitted to the Clinical Research Center and fasted overnight prior to dosing with 250  $\mu$ g Pb/70 kg body wt (i.e., 85.4 mg soil/70 kg) in a gelatin capsule. Blood for Pb and <sup>206</sup>Pb/<sup>207</sup>Pb ratios was obtained at 14 time points through 30 hours. Isotopic analyses from two subjects have been completed and indicate that 35.6% and 22.6%, respectively, of the administered dose was absorbed. (Supported by EPA Agreement CR 822793 and EPA Region II.)

#### 79 DISPOSITION AND METABOLISM OF OCTAMETHYL-CYCLOTETRASILOXANE (D<sub>4</sub>) IN F-344 RATS: EFFECT OF CLASSICAL INDUCING AGENTS

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Previous studies in our laboratory have shown repeated inhalation exposure to high levels of octamethylcyclotetrasiloxane (D<sub>4</sub>) causes liver enlargement with significant induction of P450 2B1 and a slight induction of P450 1A1

in rats. In order to evaluate the potential role of induction on the metabolism of D<sub>4</sub>, female rats were pretreated with either phenobarbital (PB) (80 mg/kg, i.p.), 3-methylcholanthrene (3-MC) (30 mg/kg, i.p.), or vehicle once a day for four consecutive days. On the following day, rats were administered a single dose of <sup>14</sup>C-D<sub>4</sub> (70 mg/kg, i.v.). Urine, feces and expired air were collected over the next 72 hr. PB treated rats excreted  $\approx$  50% of the administered dose in the urine, while 3-MC and control rats excreted  $\approx$  20% over the same 72 hr period. However, only  $\approx$  5% of the dose was excreted as expired volatiles in PB treated rats, while 3-MC and control rats excreted  $\approx$  30% over the 72 hr period. At 72 hr following administration of D<sub>4</sub>,  $\approx$  30% of the dose remained in the control and 3-MC pretreated carcass compared with  $\approx$  5% in the PB treated rats. HPLC analysis of urine revealed no qualitative change in PB or 3-MC pretreated animals when compared to controls. A similar profile of at least 6 metabolites of D<sub>4</sub> and no parent compound was detected in all samples. However, pretreatment with PB did increase the formation of a novel polar metabolite, methylsilane triol at later time points when compared to controls. The results of this study indicate PB pretreatment increased the excretion rate and the metabolism of D<sub>4</sub> which lead to an increased formation of methylsilane triol as a urinary metabolite. These results suggest P450 2B1 is one of the potential isozymes involved in the metabolism of D<sub>4</sub>.

#### 80 EVALUATION OF UDP-GLUCURONOSYL TRANSFERASE, $\alpha$ -GLUTATHIONE-S-TRANSFERASE, & EPOXIDE HYDROLASE IN RAT LIVER FOLLOWING REPEATED INHALATION EXPOSURES TO OCTAMETHYLCYCLOTETRASILOXANE (D<sub>4</sub>)

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Previous studies in this laboratory have shown that D<sub>4</sub> induces at least two classes of P450 isozymes (1A1 and 2B1). *In vivo* metabolism studies suggest that D<sub>4</sub> is reduced to low molecular weight, water soluble components. However, the role of glucuronide and glutathione conjugation in the metabolism of D<sub>4</sub> has not been examined. The purpose of the present study was to evaluate changes in hepatic  $\alpha$ -Glutathione-S-transferase ( $\alpha$ -GST), UDP-Glucuronosyltransferase (UDPGT), and Epoxide Hydrolase (EH) following exposure to D<sub>4</sub>. Male and female Fischer 344 rats were exposed to 0, 70, and 700 ppm D<sub>4</sub> in whole body inhalation chambers for 6 hr/day, 5 days/week, for 28 days. Animals were sacrificed on day 28 and hepatic microsomes and cytosol were prepared by differential centrifugation. Changes in microsomal UDPGT activity were assessed using p-nitrophenol as substrate. No significant differences in UDPGT activity were observed in control versus treated groups. In addition, D<sub>4</sub> exposure did not change  $\alpha$ -GST levels in cytosol, as determined by ELISA. The effect of D<sub>4</sub> on microsomal EH was evaluated by measuring changes in EH mRNA levels. Analysis of EH mRNA showed a significant increase in female 70 and 700 ppm groups ( $\sim$  3-4 fold) compared to controls. No significant differences between control and treated groups were observed in males. Whether or not EH is directly involved with the breakdown of D<sub>4</sub> or induced by indirect mechanisms is unknown. Overall, these findings are in agreement with *in vivo* D<sub>4</sub> metabolism studies and suggest that phase II conjugation reactions may not play a major role in the metabolism of D<sub>4</sub>.

#### 81 INDUCTION OF HEPATIC P450 1A1 AND 2B1 FOLLOWING REPEATED INHALATION EXPOSURE TO DECAMETHYLCYCLOPENTASILOXANE (D<sub>5</sub>)

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D<sub>5</sub> is one member of a group of cyclic siloxanes which are used in a variety of commercial and industrial applications because of their physical and functional performance. Previous studies from this laboratory have shown that exposure to octamethyl-cyclotetrasiloxane (D<sub>4</sub>), increases liver size and induces P450 1A1 and 2B1 in a dose-dependent manner. The purpose of the present study was to determine if exposure to D<sub>5</sub> by inhalation would produce a similar increase in hepatic P450 1A1 and 2B1 isoenzymes. Female Fischer rats were exposed to 0 and 160 ppm D<sub>5</sub> in whole body inhalation chambers for 6 hr/day, 7 days/week, for 28 days. Following exposure, liver was removed and microsomes prepared by differential centrifugation. In D<sub>5</sub> animals liver to body weight ratios increased 17% over controls. After 14 days post-