In Vivo Percutaneous Absorption of Arsenic from Water and CCA-Treated Wood Residue

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Abstract

This study was conducted to evaluate the dermal absorption of arsenic from residues present on the surface of wood preserved with chromated copper arsenate (CCA). The research reported herein used methods parallel to those of earlier research on the dermal absorption of radiolabeled arsenic (Wester 1993), with modifications to allow use of environmental matrices that are not radiolabeled. These modifications include the surface area of application and dietary intake of arsenic, and they maximize the potential for detection of dermally absorbed arsenic in exposed animals above background levels of exposure.

Two forms of arsenic were administered in this work. The first, arsenic in solution, was applied to the skin of monkeys to calibrate the model against prior absorption research and to serve as the basis of comparison for absorption of arsenic from CCA residues. The second substrate was residue collected from the surface of CCA-treated wood. Results from this research indicate that this study methodology can be used to evaluate dermally absorbed arsenic without the use of a radiolabel. Urinary excretion of arsenic above background levels can be measured following application of soluble arsenic, and absorption rates (0.6%–4.1% absorption) are consistent with prior research using the more sensitive, radiolabeled technique. Additionally, the results show that arsenic is poorly absorbed from CCA residues (i.e., does not result in urinary arsenic excretion above background levels).

Key Words: dermal arsenic absorption, CCA, arsenic exposure, environmental arsenic

Introduction

Prior research on the dermal absorption of soluble arsenic administered in water, and soluble arsenic mixed with soil, in Rhesus monkeys (Wester et al. 1993) produced mean dermal absorption rates for soluble arsenic in the range of 2.0–6.4 percent of the applied dose. Percent absorption did not vary across five orders of magnitude in the applied dose. Also, in Wester et al. (1993), the absorption rates for arsenic from the test soil fell within the range of the rates for percutaneous absorption of the arsenic administered in water. The research method was based on dermal application and subsequent urinary excretion of radiolabeled arsenic (As^{73}), thereby permitting detection of very small amounts of absorbed arsenic in the urine. Subsequent to this research, questions arose as to whether the data on dermal absorption of soluble arsenic mixed with soil immediately prior to dermal application are representative of arsenic absorption from environmental media (U.S. EPA 2001). Specifically, this issue affects the ongoing discussion of dermal absorption of arsenic from wood treated with chromated copper arsenate (CCA). This paper used a methodology similar to that used by Wester et al. (1993) to assess dermal arsenic absorption from CCA-treated wood.

Among several challenges associated with studying exposure to arsenic from environmental media is the large degree of exposure to background levels of arsenic from the diet (Schoof 1999a,b; Yost et al. 2003). Typical daily urinary arsenic excretion for Rhesus monkeys consuming the standard diet of Purina monkey chow is 5–15 μg As/day. In the Wester et al. (1993) research, the use of a radiolabeled arsenic source circumvented the confounding effects of concomitant dietary exposures and associated difficulties in data interpretation. For

study of environmental samples (e.g., soils or treated wood), it is not practicable to use a radiolabeled source. Therefore, a new research methodology was developed that incorporates a low-arsenic diet. Urine samples were analyzed using inductively coupled plasma/mass spectrometry, which provided an adequately sensitive detection limit for total arsenic in urine. This alteration in the study design allows for the evaluation of dermal arsenic absorption from natural environmental media.

The research reported herein describes the use of the Rhesus monkey model to measure the dermal absorption of arsenic from water and from residues present on the surface of CCA-treated wood. The Rhesus monkey is a relevant animal model for *in vivo* human percutaneous absorption (Wester and Maibach 1975; 1989).

Materials and Methods

Formulations and Dosing Rates

An open crossover design was used, in which each animal is dosed in each of three trials (soluble arsenic in solution applied to the skin and CCA residue applied to the skin), with a washout period of at least 14 days between each dose. This design allows for each animal to serve as its own internal control.

For the soluble arsenic dose, arsenic was administered in water onto the monkey's skin at an application rate of 5 μl/cm^2 evenly applied across 100 cm^2 of skin, to achieve a total dermal dose of 1430 μg arsenic (Table 1). The solution was prepared from sodium arsenate heptahydrate in de-ionized (DI) water, which was acidified with 1% nitric acid (trace-metal

grade). The soluble arsenic dose was designed to match the arsenic dose applied in the CCA-treated wood residue.

The residue used in this study was collected from the surface of treated wood that had been weathered in the environment. The residue, in the form of a fine particulate, was supplied by the American Chemistry Council (ACC 2003). To collect the material, CCA-treated boards consisting of either Southern Yellow Pine, or Ponderosa Pine were removed from in-service residential decks in Michigan and Georgia. Deck structures ranged from 1 to 4 years of age and had no coatings applied. A total of 1456 board sections (each 2 ft long) were collected and shipped to Michigan State University, where the residue was collected as a single composite from multiple boards. The residue was collected by brushing the boards with a soft-bristle test-tube brush while rinsing with DI water. The rinsate and residue collected in this manner were filtered through glass wool, concentrated by rotary evaporation under vacuum at 46 °C, and then air dried in a fume hood at 22 °C and 65% humidity. The dried residue was irradiated using Cobalt-60 irradiation for 3 hours, to eliminate possible microbial contamination of the sample.

Duplicate aliquots of the residue material used in the dermal dosing studies were analyzed for arsenic, chromium, copper, iron, and manganese concentrations, which involved digestion in refluxing nitric acid and analysis by inductively coupled plasma mass spectroscopy (ICP-MS) spectroscopy (EPA Method 6010B; U.S. EPA 1997). This analytical methodology was used to ensure adequate sensitivity for all metals of interest. As a means of comparing the composition of the CCA residue with the composition of treated wood, samples of newly treated wood (top 0.3 cm of wood surface) and a sample of weathered wood from a 5-year-old

CCA-treated residential deck (top surface, 0.3 cm thick) were subjected to identical digestion and analyses.

For very fine soil (i.e., silty clay), a loading of 5.4 mg/cm^2 of skin results in a monolayer (U.S. EPA 2001). Because the residue appears similar in particle size distribution to silty clay, and a loading rate of 4 mg/cm^2 of the residue provides complete coverage on a flat surface, a loading rate of 4 mg/cm^2 was selected for this study. Application of 4 mg/cm^2 on 100 cm^2 of skin area resulted in a total dose of 1422 μg arsenic (Table 1). The residue was applied as a dry powder, and spread in an even layer across the exposure area.

In Vivo Model

Female Rhesus monkeys were selected for this research because of their ability to duplicate the biodynamics of percutaneous absorption in humans, and because previous studies of percutaneous arsenic absorption have used this same model. The monkeys were approximately 20 years old, which is the same approximate age as the monkeys used in the previous dermal arsenic absorption research (Wester et al. 1993). The animals reside within the monkey colony maintained by the University of California, San Francisco, and have not been used for active research for 18 months. Prior to the beginning of the current series of studies, no topical doses had been applied to the skin of these animals for more than 4 years.

Each topical dose was applied to a pre-measured 100-cm^2 area of abdominal skin of three monkeys. The dosing area was demarked by "masking" the boundaries with a single layer of Tegaderm™ (a water-vapor-permeable adhesive membrane available from 3M) and then was dosed by spreading the fluid (5 μl/cm^2) or residue (4 mg/cm^2) evenly across the 100-cm^2

dosing area. The dosing area was then covered with a layer of Tegaderm™ [1] to ensure that the material remained in contact with the skin. The Tegaderm™ patch over the dosing area extended well beyond the boundaries of the exposure area. In addition to the Tegaderm™ patch, the abdomen of each monkey was wrapped with Spandage Instant Stretch Bandage[2] to ensure that the applied dose was kept in direct contact with the skin throughout the dosing period. This bandage is of a web construction; most of the Tegaderm™ was exposed to the open air for moisture and air exchange. Following application of the topical doses, the monkeys were placed in metabolic restraint chairs for the duration of the 8-hour dosing period. During this time, the monkeys had free access to water, but were restricted from touching their abdominal area. Researchers remained in the room and interacted with the monkeys, and the monkeys were hand fed bananas and liquid diet during this stage.

Urine was collected during the 8-hour dosing period in a pan under the metabolic chair. After 8 hours, the monkeys were removed from the chairs, the Spandage bandage and Tegaderm™ patch were removed, and the applied doses were removed using a soap and water wash (50/50 v/v, soap and water, followed by water, soap, and two final water washes). The monkeys were then transferred to metabolic cages for continued urine collection over the following 7 days.

As with humans, significant exposure to arsenic occurs from the normal diet (Schoof 1999a,b; Yost 2003). Urinary excretion of total arsenic for Rhesus monkeys on the standard diet of Purina Monkey Chow falls in the range of 5 to 15 μg/day—levels that would obscure accurate detection of the arsenic that might be absorbed following topical application of arsenic.

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[1] 3M Tegaderm™ (1629) (3M Health Care, St. Paul, Minnesota 55144).

Therefore, the monkeys were provided a low-arsenic diet (Primate Liquidiet from BioServe, Inc.) for 7 days prior to each dose. The powdered Liquidiet formulation also was prepared into meal bars, which were provided *ad libitum* to the monkeys during the research period (7 days prior to dosing through 7 days after dosing). The diet was supplemented with pieces of banana and apple, which are both known to be low in total arsenic (Schoof et al. 1999a). De-ionized water was provided *ad libitum*. The liquid diet was provided as both liquid and solid forms. Preference was for the solid form. The monkeys maintained their body weight during the study.

The monkey urine samples were preserved with nitric acid (2%) at the time of collection, and shipped to Battelle Pacific Northwest Laboratories in Sequim, Washington, for analysis. At Battelle, the urine samples were acidified with an additional 2% (by volume) of concentrated nitric acid and analyzed for total arsenic by inductively coupled plasma/mass spectrometry (ICP/MS; Method 1638, U.S. EPA 2002). This method provides a method detection limit (MDL) of approximately 0.1 μg/l arsenic in monkey urine. Quality assurance and quality control (QA/QC) samples included a method blank, duplicates, matrix spikes, and a laboratory control sample at a 5% frequency of analysis.

Results

Total metals concentrations of arsenic, chromium, and copper in the residue are presented in Table 2, along with corresponding data for a sample of newly treated wood (recently purchased from a local retailer), and a sample of weathered wood from a 5-year-old

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[2] Spandage Instant Stretch Bandage (MEDI-TECH International Corp. Brooklyn, New York 11242).

residential deck. The relative concentrations of these three metals are similar for all three samples, indicating that the residue contains a proportion of the CCA metals that is similar to both freshly treated and aged wood. Concentrations of all three metals are lower in aged wood than in residue. This is likely due to the removal of larger wood fragments during preparation of the residue, when the residue is filtered through glass wool.

Data for the mass of urinary arsenic excreted by the monkeys following dermal dosing are presented in Table 3 (soluble arsenic) and Table 4 (CCA residue). Data on the background arsenic excretion for each monkey for the days prior to the dosing period are included. The value reported for the 0- to 24-hour period is the combined arsenic mass from the urine collected during the 8-hour dosing period, a wash of the urine collection pan, and the urine collected from 8 hours to 24 hours after the monkeys were returned to their cages. The right-most column in each of these tables presents the mass of arsenic excreted for each 24-hour period, corrected for background levels of arsenic in urine by subtracting out the median of the five background data points for each monkey, on a monkey-specific basis. (In other words, the five background values for each monkey were compiled, and the median calculated for each monkey. The median value of 5.73, 5.79, and 4.40 for monkey 1, 2, and 3, respectively, was subtracted out of the 24-hour urine value to yield the "background-corrected" value). This correction was applied to the data to reduce the influence of dietary arsenic on the excreted mass. The mass of arsenic excreted that is associated with the dermally applied dose is calculated by adding the mass excreted from the time of dosing through 96 hours after dosing. After 96 hours, the arsenic excretion has returned to background levels.

Prior research (Wester et al. 1993) indicates that, for female Rhesus monkeys, urinary excretion of an intravenous dose of arsenic is 80 ± 6.7% of the administered dose. This value was used to adjust the assumed total mass of arsenic excreted over the 96-hour collection period, by dividing the calculated mass excreted by 0.8. This calculated mass excreted was then divided by the applied dose to calculate the percent of the applied dose that was absorbed for each animal and each dosing substrate. Thus, the percent absorption of arsenic was calculated in the following manner:

$$\frac{Percent\ absorption = (Corrected\ mass\ excreted_{0-96hours} \div 0.8) \times 100}{Applied\ dose}$$

For the soluble dose, absorption rates were 3.6%, 0.55%, and 4.1% for the three monkeys in the study (Table 3). Dosing levels used in our earlier research on the dermal absorption of arsenic are compared to those used in this study in Table 1. Despite the nearly 7-fold difference in the dermal loading rate between the two studies, the average absorption rate for the group dosed with soluble arsenic (2.8%) is consistent with results from Wester et al. (1993). These results are consistent with the previous study, wherein absorption rates were relatively consistent (range of 2%–6.4%) despite five orders of magnitude change in the dose levels (i.e., an applied dose range of 0.000024 to 2.1 $\mu g/cm^2$). These data strongly support the suggestion that the difference in the measured absorption rates in the Wester et al. (1993) research reflects experimental variability rather than dose-related differences in absorption (U.S. EPA 2001). This is consistent with what we know about individual variability in percutaneous absorption in humans and animals (Wester and Maibach 1991, 1997).

Converse to the results for soluble arsenic, data from dermal application of CCA residue indicate virtually no absorption. Absorption rates following dermal application of residue are presented in Table 4. These data show that urinary excretion of arsenic following dermal application of the CCA residue does not cause a detectable increase in urinary arsenic excretion, despite the fact that equivalent doses of arsenic were applied for both soluble arsenic and residue.

The time profiles for urinary arsenic excretion by each monkey are provided in Figure 1. These charts show a consistent time course for the three monkeys; peak excretion of arsenic occurs within 24 hours of the dermal application of the soluble dose, with a rapid return to near-background levels of excretion within 48 to 72 hours. Peak 24-hour urinary arsenic excretion following the soluble dose ranged up to a maximum value of 41.6 μg. The time profile for arsenic excretion following dermal application of the CCA residue is also consistent across all three monkeys. The figures depict that following application of the CCA residue, there is no increase in urinary arsenic excretion, followed out through time.

To determine whether the difference in the results for the two exposure groups was statistically significant, an ANOVA analysis followed with a Tukey's multiple comparison test was conducted. Using an overall significance level of 0.05, results indicate that the urinary arsenic excretion levels in the animals exposed to the CCA residue are not significantly greater than background. Additionally, the urinary arsenic excretion in the animals exposed to soluble arsenic in solution is significantly greater than background, and significantly greater than the residue exposure group. In this analysis, the monkey number

was treated as a random effect, time as an ordered effect, and "treatment" (i.e., dose group) as the factor of interest.

Discussion

The results from this research indicate that the methodology described above can be used to evaluate dermally absorbed arsenic from environmental samples. The development of this method was challenging because of the high degree of background arsenic exposure from the diet, and the potential for that background exposure to obscure any signal from a dermally applied dose. Use of the low-arsenic diet resulted in an approximately four-fold decrease in urinary arsenic excretion relative to the standard primate diet, and allowed for detection above background of a dermally applied dose of arsenic.

Although the results indicate that the urinary arsenic levels following topical administration of arsenic in CCA residues are not distinguishable from background, the non-zero values for background urinary arsenic excretion, and the variability of the measured background values, impose some limits regarding the sensitivity of the model to detect an absorbed dose. A statistical evaluation using a comparison of means (t-test) for our data indicates that the absorbed dose would need to be in the range of 0.02% to 0.2% of the applied dose in order for daily arsenic excretion levels to be detectable above background. Thus, while these data suggest that there may not be any dermal absorption of arsenic from CCA residue (data for the three monkeys were 0.00%, 0.00%, and 0.01%, respectively), the uncertainty associated with this research model tells us that dermal absorption of arsenic from CCA residues is at least 10- to 100-fold less than absorption of soluble arsenic from solution.

Extensive chemical analyses indicate that the arsenic present in the CCA residue used in this study is structurally and chemically identical to the arsenic present on the surface of newly treated or aged CCA-treated wood (Nico et al. 2003), thus making it an appropriate study substrate for understanding the potential dermal absorption of arsenic following contact with CCA-treated wood. The negligible absorption of arsenic from the CCA residues derives from the fact that this arsenic is chemically bound with other metals (particularly chromium) and ultimately to the wood structure (Bull 2000; Nico et al. 2003). The physico-chemical conditions on the surface of the skin do not result in the liberation of arsenic from the residue, thus precluding absorption. These results indicate that percutaneous absorption of arsenic from environmental media is significantly different from soluble arsenic or even soluble arsenic mixed with environmental media. Therefore, it is not appropriate to apply generic assumptions regarding dermal absorption to these unique matrices, and medium-specific analysis may be required to understand the dermal absorption from them (and potential associated risks). This appears to be true for arsenic, and may be true for other metals that form similarly stable complexes in the environment. The latter point should not be overgeneralized until additional metals have been thoroughly studied.

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Figure

Figure 1. Urinary arsenic mass excretion in 24-hour increments

Tables

Table 1. Applied dose for dermal application of arsenic

Table 2. Metal concentrations in CCA residue and wood

Table 3. Urinary arsenic data following dermal application of arsenic in soluble dose

Table 4. Urinary arsenic data following dermal application of arsenic in CCA residue

Table 1. Applied dose for dermal application of arsenic

		Arsenic	Volume	Arsenic Mass (μg)	Arsenic Mass per Unit Area (μg/cm^2)
Soluble dose		2,860 mg/L[a]	0.5 mL	1,430	14.3
CCA residue		3,555 mg/kg[a]	400 mg	1,422	14.2
Soluble dose:	High dose	--	--	76	2.1
Wester et al. (1993)	Low dose	--	--	0.00086	0.000024

[a] Average of duplicate analyses

Table 2. Metal results in CCA residue and wood

Sample	Arsenic (mg/kg)	Chromium (mg/kg)	Copper (mg/kg)
CCA residue			
Sample 1	3,600	4,120	2,260
Sample 2	3,510	4,070	2,220
Weathered CCA-treated wood			
WD0001	1,760	2,700	942
Freshly treated CCA wood			
WD-002	2,730	3,080[a]	1,545[a]

[a] Average of lab duplicates

Table 3. Urinary arsenic data following dermal application of arsenic in soluble dose

	24-Hour Mass Excreted (μg)	24-Hour Mass Excreted (corrected)[a] (μg)
SOLUBLE DOSE		
Animal #1		
Background (24–48 hr)	5.07	0.00
Background (0–24 hr)	1.56	0.00
(0–24 hr)	41.58[b]	35.85
(24–48 hr)	7.22	1.48
(48–72 hr)	8.08	2.35
(72–96 hr)	7.21	1.48
Total arsenic mass excreted (0–96 hr):		41.16
Total arsenic mass excreted with urinary arsenic excretion fraction correction (0–96 hr):		51.45
Percent absorption (0–96 hr):		**3.6%**[c]
Animal #2		
Background (24–48 hr)	6.30	0.51
Background (0–24 hr)	7.08	1.29
(0–24 hr)	10.22[b]	4.43
(24–48 hr)	6.96	1.17
(48–72 hr)	5.32	0.00
(72–96 hr)	6.53	0.73
Total arsenic mass excreted (0–96 hr):		6.33
Total arsenic mass excreted with urinary arsenic excretion fraction correction (0–96 hr):		7.92
Percent absorption (0–96 hr):		**0.55%**[c]
Animal #3		
Background (24–48 hr)	5.20	0.80
Background (0–24 hr)	3.07	0.00
(0–24 hr)	30.35[b]	25.95
(24–48 hr)	20.98	16.58
(48–72 hr)	4.52	0.11
(72–96 hr)	9.16	4.76
Total arsenic mass excreted (0–96 hr):		47.40
Total arsenic mass excreted with urinary arsenic excretion fraction correction (0–96 hr):		59.25
Percent absorption (0–96 hr):		**4.1%**[c]

[a] Corrected mass calculated by subtracting median of the 5 background arsenic masses for each monkey. If corrected mass is calculated less than zero, corrected mass is set to zero.

[b] Sum of (0–8 hr), pan wash, and (8–24 hr). Pan wash concentration is calculated using pan wash concentration minus average of wash water concentrations.

[c] Percent absorption calculated using soluble applied dose mass of 1,430 μg.

Table 4. Urinary arsenic data following dermal application of arsenic in CCA residue

	24-Hour Mass Excreted (μg)	24-Hour Mass Excreted (corrected)[a] (μg)
SOLUBLE DOSE		
Animal #1		
Background (96–120 hr)	7.88	2.14
Background (48–72 hr)	6.44	0.71
Background (0–24 hr)	5.73	0.00
(0–24 hr)	4.84[b]	0.00
(24–48 hr)	4.90	0.00
(48–72 hr)	4.86	0.00
(72–96 hr)[c]	5.89	0.16
Total arsenic mass excreted (0–96 hr):		0.16
Total arsenic mass excreted with urinary arsenic excretion fraction correction (0–96 hr):		0.20
Percent absorption (0–96 hr):		**0.01%**[d]
Animal #2		
Background (96–120 hr)	5.79	0.00
Background (48–72 hr)	1.92	0.00
Background (0–24 hr)	4.59	0.00
(0–24 hr)	4.17[b]	0.00
(24–48 hr)	2.93	0.00
(48–72 hr)	3.77	0.00
(72–96 hr)	3.78	0.00
Total arsenic mass excreted (0–96 hr):		0.00
Total arsenic mass excreted with urinary arsenic excretion fraction correction (0–96 hr):		0.00
Percent absorption (0–96 hr):		**0.00%**[d]
Animal #3		
Background (96–120 hr)	4.40	0.00
Background (48–72 hr)	4.88	0.48
Background (0–24 hr)	3.44	0.00
(0–24 hr)	4.24[b]	0.00
(24–48 hr)	3.26	0.00
(48–72 hr)	3.94	0.00
(72–168 hr)	3.39	0.00
Total arsenic mass excreted (0–96 hr):		0.00
Total arsenic mass excreted with urinary arsenic excretion fraction correction (0–96 hr):		0.00
Percent absorption (0–96 hr):		**0.00%**[d]

[a] Corrected mass calculated by subtracting median of the 5 background arsenic masses for each monkey. If corrected mass is calculated less than zero, corrected mass is set to zero.

[b] Sum of (0–8 hr), pan wash, and (8–24 hr). Pan wash concentration is calculated using pan wash concentration minus average of wash water concentrations.

[c] Mass excreted is estimated as one-fourth of (72–168 hr) mass.

[d] Percent absorption calculated using soluble applied dose mass of 1,422 μg.