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# Chapter 10

# RISK CONSIDERATIONS RELATED TO ARSENIC EXPOSURE: DRINKING WATER INGESTION VERSUS DIETARY INTAKE OR SOIL EXPOSURE

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## ABSTRACT

The February 2010 release of the Draft Toxicological Review of Inorganic Arsenic by the U.S. Environmental Protection Agency provoked discussion of a potential significant downward revision of the arsenic cancer slope factor (CSF), which would be applicable to many oral exposure evaluations. Given the extreme variability in soil cleanup guidelines that are in use throughout the United States and internationally for arsenic, it may be appropriate to more seriously consider bifurcating the manner in which arsenic is evaluated in environmental media. In much the same fashion by which manganese and cadmium presently are evaluated from a risk perspective, arsenic may lend itself to similar evaluation from a drinking water exposure standpoint separately from a dietary or an environmental soil route of exposure. This paper examines the basis for the current oral toxicological guidance with respect to specific exposure route and environmental medium of exposure, and addresses possible means for alternative toxicity guidance related to arsenic, based on differences in exposure through soil or the diet.

Keywords: arsenic, soil, organic, inorganic, drinking water, cleanup guidelines, risk, relative bioavailability

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## 1. INTRODUCTION

Arsenic is the perennial number one entry in the CERCLA Priority List of Hazardous Substances (ATSDR, 2007a), and is listed as a constituent of concern at more than 40% of NPL sites (ATSDR, 2007b). Although the CERCLA list is not based solely on toxicity, and the NPL occurrence is based primarily on exceedance of often artificially low cleanup guidelines, the perception is such that arsenic, no matter the medium, accessibility, or concentration, is a serious human health concern. As with most meaningful health questions that are posed, the true answer to the question of whether arsenic is a concern is "It depends". It depends on the arsenic form (inorganic, organic). It depends on the exposure medium (soil, food, air, water). It depends on the intake route (oral, dermal, inhalation). It depends on the exposure magnitude (concentration, duration). Any one of these factors, or more likely, a combination of them all, determines whether arsenic can exert its ability to cause toxic effects.

In the case of arsenic toxicity, particularly from exposure to soils, health-based screening levels and some cleanup guidelines are derived using conclusions largely based upon long term, high concentration drinking water studies, resulting in sub part per million protective soil targets. Human exposures to soil arsenic at concentrations far in excess of these health-based screening levels occur frequently in all parts of the U.S. and worldwide. However, reports conclusively connecting exposures to arsenic in soil with adverse health effects are not readily found in the toxicological literature.

## 2. NATURAL OCCURENCE

Many, if not a substantial majority of, areas in the U.S. contain soils that have measurable levels of arsenic. Often, these detectable levels are referred to as "elevated." Of course, elevated is the operative word defining the discussion. Depending on the screening level that is considered, even naturally occurring background concentrations of arsenic in surface soil may be viewed as "elevated." By way of example, a 2009 study by Vosnakis, et al. evaluated more than 1,600 samples from 189 sites in seven states in the northeastern U.S. (KY, MD, NY, OH, PA, VA, WV). The authors found that, following data validation and site screening, the retained arsenic in soil results ranged from 1.1 mg/kg to 89 mg/kg (Vosnakis, et al., 2009; see Table 1). When compared with each state's soil screening level for arsenic, the reported background concentrations were from 2x to 40x greater than the respective screening levels, and the highest background level was approximately 60x the lowest screening level.

*Table 1.* Arsenic Background vs Soil Screening Levels for 7 States

| State | Frequency of Detection | 95th Percentile Surface Soil As (mg/kg) | Risk Based Screening Level (mg/kg) |
|---|---|---|---|
| **Kentucky** | 57 of 57 | 15.6 | 0.39 |
| **Maryland** | 28 of 32 | 10.1 | 0.39 |
| **New York** | 42 of 50 | 22.8 | 13 |
| **Ohio** | 94 of 143 | 21.7 | 6.8 |
| **Pennsylvania** | 219 of 220 | 23.7 | 12 |
| **Virginia** | 91 of 98 | 13.6 | 0.39 |
| **W Virginia** | 314 of 316 | 15 | 8.64 |

Each of these states allows for some consideration of background in their cleanup guidance, and a few incorporate background directly into the screening levels. However, the fact remains that large areas of soil in the U.S. exceed health-based screening levels for arsenic.

## 3. HEALTH EFFECTS

Given the intrinsic toxicity of arsenic, the very low soil screening levels theoretically required to protect human health, and the presence in most soil of arsenic far exceeding health-based guidelines, where are all of the reports of arsenic-related illness, disease and death? Going briefly back to the Vosnakis, et al. (2009) study of elevated background arsenic, we can look at selected state soil concentrations and compare those with reported cancer incidences. As shown on Table 2, even though statewide soil arsenic concentrations are twice or three times the national average, and up to 60-times greater than the lowest RBSL, cancer incidence rates for bladder, liver and skin cancer are not significantly different from national rates.

Clearly, establishing a causal link between *any* factor and the development of cancer is a highly complex undertaking, but at the theoretical doses (and the associated grossly elevated risk levels) suggested by the above soil concentrations, the logical conclusion would be that rates broadly elevated beyond screening levels would be associated with noticeably elevated cancer incidences. In further attempts to support that hypothesis, Hinwood et al. (1999), in an Australian study of residential areas having soil arsenic concentrations greater than 100 mg/kg, did not show a statistically significant increase in relevant cancer incidences.

*Table 2*. Selected State Cancer Incidence Rates (NCI, 2010)
(cases per 100,000 population per year, 2004-2008)

| **Location (background As)** | **Bladder Cancer Incidence** | **Liver Cancer Incidence** | **Skin Cancer Incidence** |
|---|---|---|---|
| **U.S.** (7.2 mg/kg; ATSDR, 2007b) | 21.2 | 6.2 | 18.8 |
| **Kentucky** (15.6 mg/kg) | 22.6 | 5.1 | 22.3 |
| **New York** (22.8 mg/kg) | 23.9 | 7.6 | 15.8 |
| **Pennsylvania** (23.7 mg/kg) | 25.2 | 6.1 | 17.7 |

The above observation is consistent with the opinion of multiple authors who have proposed a sublinear or threshold basis for arsenic carcinogenicity, irrespective of medium of exposure (Rudel, et al., 1996; ERG, 1997; ATSDR, 2007b).

Consistent with the lack of evidence supporting cancers resulting from common soil arsenic exposures, no articles or studies were found citing systemic effects following human exposure to arsenic in soil under normal circumstances. In a German study of the potential transfer of arsenic from the environment to humans, it was observed that hair and urine arsenic levels actually were lower in the study area of elevated arsenic than in the reference area of low arsenic concentrations (Gebel, et al, 1998). Soil levels in the former mining region ranged from 2 to 605 mg/kg, but drinking water had low arsenic, and no occupational exposure was noted. Although a slight increase in hair and urine levels was associated with increasing soil levels, the most significant factor contributing to the observed levels was seafood consumption.

## 4. WHY THE DISCONNECT?

So, it is clear that arsenic occurs naturally and frequently in soils at levels much greater than health-based regulatory guidelines. There also is some evidence that cancer incidence is not elevated in areas of elevated soil arsenic, and there is a notable lack of evidence that elevated soil arsenic results in adverse systemic effects.

Many authors have reported on the various aspects that are involved in arsenic occurrence in soil, exposure, toxicokinetics, and toxicity, but very little consensus has developed at this point. Over the past several years, even the recognized certainty that arsenic methylation in the human body is a key detoxification step has been shown to be less than reliable (Thomas, et al., 2001; 2007; Hughes, et al., 2011; Steinmaus, et al., 2000). Other key areas of debate include whether arsenic is indeed a linear, nonthreshold carcinogen, or, as offered by many authors, a threshold carcinogen, or at the least a sublinear carcinogen (ERG, 1997; Abernathy, et al., 1996; Carlson-Lynch, et al., 1994; Lamm, et al., 2004). Separate from further refinement of the fundamental question of carcinogenicity from drinking water exposure, this paper pursues a solution to the

disparity between the observed drinking water toxicity and the lack of reported health effects from exposure to elevated soil arsenic.

The list of possible explanations for the disconnect is long, and includes at least the following:

- arsenic form (inorganic, organic);
- exposure medium (soil, food, air, water);
- methylation and other toxicokinetic processes (absorption, detoxification or activation);
- intake route (oral, dermal, inhalation); and,
- exposure magnitude (concentration, duration).

Any one of these factors, or more likely, a combination of them all, determines whether arsenic can exert its potential to cause toxic effects.

## 5. POSSIBLE SOLUTIONS

In order to resolve the inconsistency observed between the adverse effects from exposure to arsenic in drinking water and the lack of actual or reported harm from elevated soil arsenic, three of the most readily quantifiable influences were evaluated: 1) relative bioavailability, to address intake route and exposure medium; 2) analogy to cadmium and manganese, to address absorption and exposure medium; and, 3) inorganic versus organic form of exposure.

### 5.1 Relative bioavailability adjustment

As noted earlier, a few state environmental agencies (e.g., Florida Department of Environmental Protection) explicitly acknowledge the oft-reported reduced relative oral bioavailability of arsenic in soil within their cleanup guidelines development process (FDEP, 2005). The most frequently reported range for relative bioavailability adjustment (RBA) is on the order of 20 to 60 percent (ATSDR, 2007b; Roberts, et al., 2002; Bradham, et al., 2011; Freeman, et al., 1993; 1995), while ranges from 5 to 75 percent are not unheard of. Thus, taking 30 percent as the midrange estimate, and 5 and 75 percent as the low and high estimates, respectively, Table 3 presents plausible risk based screening levels (RBSLs) for arsenic that would be calculated using procedures consistent with development of the USEPA regional screening levels (RSLs; USEPA, 2011a).

*Table 3*. Arsenic RBSLs based on estimated RBA

| Reported RBA Estimates | Default EPA RBSL mg/kg | RBA-Based RBSL mg/kg |
|---|---|---|
| **Default (100%)** | 0.39 | 0.39 |
| **Upper (75%)** | 0.39 | 0.52 |
| **Mid (30%)** | 0.39 | 1.3 |
| **Lower (5%)** | 0.39 | 7.8 |

As shown on Table 3, the midrange RBA estimate results in a possible RBSL of 1.3 mg/kg. While this value is scientifically defensible, health-based, and it provides considerable relief from default guidelines, it does not remotely approach naturally occurring arsenic levels in most soils in the U.S. Thus, adjustments for RBA are appropriate, based on a multitude of studies, but RBA adjustment is likely only a piece of the puzzle.

### 5.2 Exposure medium/route adjustment

In the case of cadmium and, to a lesser extent, manganese, the route of exposure dictates the applicable toxicological guidance that is recommended for use in risk assessment and cleanup activities. The oral RfD for cadmium when the exposure medium is water is 5E-4 mg/kg•day, and the oral RfD for cadmium in food is 1E-3 mg/kg•day (IRIS; USEPA, 2011b), or twice that for water. The IRIS profile for cadmium reports that the difference in RfD values is based on observed differences in absorption (i.e., 2.5% absorption of Cd from food or 5% from water; USEPA, 2011b). Specifically, it states "Since the fraction of ingested Cd that is absorbed appears to vary with the source (e.g., food vs. drinking water), it is necessary to allow for this difference in absorption when using the toxicokinetic model to determine an RfD." For cadmium, the differences in toxicological guidance typically are reflected in differential media screening levels through use of the water RfD when calculating the tapwater level and through use of the food RfD when calculating the soil level (FDEP, 2005; USEPA, 2011a).

With respect to human absorption of arsenic, very little consensus is available, but there does appear to be a reduced absorption rate in animal studies when comparing insoluble, bound arsenic forms (i.e., those most often found in soil) with soluble, unbound arsenic forms (i.e., those most often found in drinking water; ATSDR, 2007b; NRC, 1999). Freeman et al. (1993) reported that, in rabbits, approximately 80% of the arsenic from an ingested soil bolus (primarily smelting soil in the form of sulfides) was eliminated (i.e., approximately 20% absorption). In contrast, 50% of a soluble oral dose and 10% of an injected dose were eliminated (i.e., 50% and 90% absorption, respectively). Thus, arsenic absorption from soil may range from 30-70% less than absorption from more soluble forms. This conclusion is consistent with results from

Roberts et al. (2002) who reported that between 60% and 80% of an ingested arsenic dose in soil was eliminated by *Cebus apella* monkeys, suggesting absorption of 20% to 40%.

Although much work is needed to refine knowledge regarding human absorption differences based on medium of exposure, the likely impact would be in the same general magnitude as that presented for adjustments based on relative bioavailability (e.g., 1.5 to 20 fold; see Table 3).

### 5.3 Form of arsenic adjustment

One promising potential solution to the presence/significance conundrum may lie in being able decisively to identify the form of arsenic, inorganic or organic, to which an individual is exposed. Determining which form is present in the soil, and, more importantly, identifying which form ultimately is present in the body following human exposure, is a subject of considerable debate. However, as presented by ATSDR (2007b), distinct chronic human oral minimal risk levels (MRLs) are available for inorganic and organic forms of arsenic, thus providing a potential mechanism for development of screening levels, if consensus on typical exposure forms in specific media can be reached.

The inorganic MRL is 3E-4 mg/kg•day and that value was derived from a human drinking water study. For the organic arsenic compounds monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA), the chronic human oral MRLs are 1E-2 mg/kg•day and 2E-2 mg/kg•day, respectively (ATSDR, 2007b), and both of these values are based on feeding studies in mice. The MRL development process is conceptually similar to that which is used to produce Reference Doses, including the application of uncertainty and modifying factors. Thus, analogous to the development of USEPA default RSLs, risk based screening levels (RBSLs) may be developed for arsenic in soil using the MRLs for inorganic arsenic and organic arsenic compounds. As shown on Table 4, the proposed RBSLs for organic arsenic in soil range from nearly 30 times greater to more than 50 times greater than the RBSL for inorganic arsenic in soil.

*Table 4*. Arsenic RBSLs based on form-specific toxicological guidance

| As Form | Chronic Oral MRL mg/kg•day | Default EPA RSL mg/kg | MRL-Based RBSL mg/kg |
|---|---|---|---|
| **Inorganic** | 0.0003 | 0.39 | 22 |
| **Organic (MMA)** | 0.01 | NA | ~600 |
| **Organic (DMA)** | 0.02 | NA | ~1,200 |

## 6. DISCUSSION

Significant monetary and human resources are expended on the characterization and mitigation of arsenic in soil, based primarily on the fundamental assumption that its potential toxicity following soil exposure is consistent with its potential toxicity following drinking water exposure. No conclusive reports were found to support that position, and an increasing body of evidence is available to undermine the conclusion. While the exact mechanisms and processes that result in the disparity remain unclear, it is time to begin refining an approach to the multiple potential solutions to the problem. As presented in this paper, the most promising and straightforward solutions lie in adjustments to the numerical toxicological guidance based on several factors including: 1) relative bioavailability; 2) differences in absorption between the water and soil matrices; and/or, 3) differences in the toxicity between inorganic and organic forms of arsenic.

Possible recommendations for future health investigations, as well as a few critical areas for continued toxicological study include the following:

- inorganic vs organic determination whenever soil investigations take place;
- refined toxicokinetics to conclusively identify methylation or other relevant processes and their importance;
- inexpensive, rapid *in vitro* methods for site-specific determinations of relative bioavailability; and,
- more conclusive determination of the mode of action for arsenic carcinogenicity.

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