Hazards of Short-Term Exposure to Arsenic Contaminated Soil

Washington State Department of Health

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EXECUTIVE SUMMARY

Arsenic-contaminated soil is a potential public health problem in many areas of Washington. The Washington State Department of Ecology asked the Washington State Department of Health to assess the potential hazards of acute exposure to arsenic-contaminated soil. Information regarding arsenic toxicity and human soil ingestion was evaluated and used to determine soil arsenic concentrations protective of public health for acute exposures. Best estimated soil concentrations of arsenic to protect the public from adverse health effects due to short-term exposure were developed for three scenarios:

1. Relatively common child exposure to contaminated soil from accessible areas, resulting in transient adverse health effects (37 milligrams of arsenic/kilogram soil),
2. Infrequent child exposure to deeply buried or relatively inaccessible, contaminated soil resulting in death (162 milligrams of arsenic/kilogram soil), and
3. Relatively common adult resident or worker exposure to subsurface or relatively inaccessible soil resulting in transient adverse health effects (175 milligrams of arsenic/kilogram soil).

Further work is necessary to determine where in Washington arsenic-contaminated soil may be a hazard and what actions would be appropriate to ensure protection of public health. It will be important to involve a wide range of stakeholders to develop approaches to these problems.

PURPOSE

Soil in many areas of Washington State is contaminated with arsenic from smelter operations or from arsenical pesticides and herbicides. Residential communities are located in some of these contaminated areas, and people are likely to be exposed to arsenic in the soil. This exposure could result in illness.

The Washington State Department of Ecology (Ecology) is responsible for determining whether, and how, to manage arsenic-contaminated soil in many areas of the state. A major consideration in this determination is the potential human health hazard of the soil. Ecology has asked the Washington State Department of Health (DOH) to assess the potential hazards of exposure to arsenic-contaminated soil. Specifically, what concentrations of arsenic in soil could cause adverse health effects in people and what concentrations are unlikely to be harmful. Both short-term (acute) exposure and long-term (chronic) exposure to contaminated soil could result in adverse health effects in people. The purpose of this document is to evaluate information on hazards of short-term exposure to arsenic-contaminated soil and to use the information to calculate soil arsenic concentrations protective of public health. Hazards of chronic exposure to arsenic-contaminated soil will be evaluated in another document.

PUBLIC HEALTH CONCERNS FROM ARSENIC-CONTAMINATED SOIL

The health hazard of arsenic-contaminated soil depends on both the toxicity of arsenic and the amount of arsenic to which people are exposed through contact with the soil. Studies of the toxicity of arsenic and of the potential for people to be exposed to arsenic in soil suggest that arsenic-contaminated soil could be a public health hazard in some contaminated areas. Exposure to arsenic can cause a wide spectrum of adverse health effects.(1) The primary route of exposure is expected to be ingestion of contaminated soil, by direct hand to mouth activity or by swallowing airborne soil and dust particles that enter the mouth and nose.

The potential health hazard of arsenic-contaminated soil is not limited to current populations. Future generations of residents may also be at risk since arsenic remains in soil for hundreds to thousands of years.(2) For example, at the Everett Smelter hazardous waste site in Everett, Washington, an area of contamination that appears to be composed of pure arsenic trioxide is still present 85 years after production was discontinued.(3) One estimate of the residence time for arsenic in soil is 9000 years.(2) Since arsenic is expected to remain in soil for centuries or longer, contaminated soil left at the site must be considered a potential source of exposure throughout this time frame.

APPROACH TO EVALUATING HAZARDS OF ARSENIC-CONTAMINATED SOIL FROM ACUTE EXPOSURE

Use of Scientific Information

Adequate scientific studies that directly assess the hazard of arsenic-contaminated soil to exposed populations have not been conducted. At this time, the hazard can be better evaluated indirectly through a synthesis of information from toxicity and exposure studies that, individually, address pieces of the overall question. To estimate what concentrations of arsenic may be left in soil and be protective of the health of current and future residents and workers, the following types of information are needed:

- How exposure could occur, and to whom,
- How much exposure might occur, and
- The potential consequences of exposure (as reflected by the toxicity of arsenic).

This information can be used in the following equation to calculate the amount of arsenic in soil that is potentially harmful following short-term ingestion:

$$\textit{harmful soil arsenic concentration} = \frac{\textit{acutely toxic dose x body weight}}{\textit{acute soil ingestion rate x bioavailability}}$$

This was adapted from an equation used by Ecology to calculate soil cleanup levels.[4]

Exposure Scenarios

Another consideration when evaluating the hazard is the likelihood of exposure, which may depend on the location of the contaminated soil and the types of activities that occur on the contaminated property. Locational factors that could influence the potential for exposure include depth of the contaminated soil, the presence of an overlying structure such as a road or building, and the accessibility of the contaminated property to potentially exposed individuals.

Three scenarios, representing realistic sets of conditions whereby people could be exposed to arsenic-contaminated soil, were developed based on who would be exposed (adults versus children), the likelihood of exposure, and the potential consequences of exposure. The conditions of each scenario guide the choice of appropriate values for parameters in the above equation to calculate potentially harmful soil arsenic concentrations.

The three short-term exposure scenarios that will be considered in this document are:

1. Relatively common child exposure to arsenic-contaminated soil located in accessible areas, resulting in adverse health effects that are not permanent. For example, a child is exposed in a residential yard while playing in a pile of contaminated dirt excavated for a garden or to install a fence post.
2. Atypical child exposure to deeply buried or relatively inaccessible arsenic-contaminated soil resulting in death. For example, a child is exposed while playing in a pile of contaminated dirt excavated to repair a utility pole or install a foundation for a home addition.
3. Relatively common adult resident or worker exposure to arsenic-contaminated soil resulting in nonpermanent adverse health effects. For example, a homeowner or worker is exposed while landscaping or performing plumbing repairs in the crawl space under a home.

In consultation with Ecology, DOH determined that these scenarios could be used to determine appropriate cleanup activities for most currently foreseeable exposure situations where protection of public health from arsenic-contaminated soil is the primary concern.

Addressing Uncertainties and Limitations of Available Scientific Data

For this document, the evaluation of the hazards of arsenic-contaminated soil was based on published scientific information related to soil exposure and arsenic toxicity. However, information on these topics is incomplete, resulting in uncertainties in predicting exposure, as well as the consequences of exposure, for potentially affected populations. Scientific studies have limitations that must be recognized and evaluated before relying on them to protect public health in real-world situations. Limitations of the studies raise concerns such as the following:

- Are study results sufficiently reliable and reproducible to assume that they accurately reflect the real world?
- Can results of toxicity and exposure studies in other groups of people or animals be assumed to accurately reflect results that would be expected in people at the site in question (due, for example, to differences in populations or study conditions)?
- People vary in sensitivity to the toxic effects of arsenic. Do study results adequately reflect the variability in sensitivity that may be present in people at the site in question, now and in the future?
- Individuals have a wide variety of behaviors, habits, and activities that can affect their amount of exposure to contaminated soil. Do study results adequately reflect the variability in exposure that may occur in people at the site in question, now and in the future?
- Do studies evaluate hazards based on the most sensitive indicator of toxicity, or are less sensitive indicators used? Has the most sensitive indicator of toxicity been identified?

Important information deficiencies and uncertainties must be identified and addressed to evaluate the hazards of arsenic-contaminated soil. The goal of DOH is to protect public health. Therefore, if the information used to estimate public health hazards is of questionable accuracy and reliability, protective assumptions will be made when interpreting the data in order to prevent illness. If a range of possible interpretations is consistent with data from scientific studies (for example, there was a range of responses or a range of behaviors identified in the studies), protective values in the range will be selected for the purpose of estimating public health hazard.

Information on toxicity and exposure can be used to estimate harmful concentrations of arsenic in soil. To determine a soil arsenic concentration that is not expected to cause illness, the potentially harmful level will be adjusted with a safety factor.

HOW EXPOSURE COULD OCCUR

Numerous studies suggest that people ingest soil from their environment (5-17) during daily activities, including soil that forms the surface of their yard. Concern for acute toxicity of arsenic-contaminated soil is related to the occasional ingestion of large amounts of soil.(18-23) When surface soil in a residential area is contaminated, it is expected that chronic exposures to the contaminants will occur and that cleanup of this soil will be based on an evaluation of long-term exposure. However, contaminants are rarely confined to just the surface layer of soil, but may be present beneath the surface as well as in relatively inaccessible areas such as in crawl spaces of buildings and under structures such as roads, driveways, barns, and sheds. While it is not expected that people will have regular contact with this material, it is occasionally brought to the surface where exposure can occur. For example, gardening, digging by children and pets, and other common activities and projects involving an excavation could result in contact with contaminated soil that was previously not available for human exposure. Piles of soil excavated during single or multi-day projects and left at the surface may attract children and could become sources of exposure. Residents and workers who go into crawl spaces and under decks for inspection or repair work could also be exposed to contaminants. Short-term contact with this soil could be hazardous unless contact with the soil is controlled and the soil is handled and disposed of properly.

The following list of activities that could result in exposure to subsurface contaminants is based on consultation with people who live and work in the Everett, Washington area:

- gardening,
- digging by children and pets,
- planting trees and shrubs,
- resodding,
- installing or repairing utility lines and utility poles,
- digging holes for fence posts,

- installing and repairing a sprinkler system,
- removing and installing heating oil tanks,
- bioturbation (disturbance of soil by worms, ants, moles, etc.),
- repairing roads and driveways,
- construction of structures such as decks, sheds, barns, home additions, and
- new home construction.

Many of these activities commonly occur on residential properties and would likely result in disturbance of soil to a depth of 12 to 24 inches. Construction activities and work on utility lines and oil tanks may involve deeper excavations.

SHORT-TERM EXPOSURE RATE

Soil Ingestion Rate

Children 18-24 months of age are generally believed to ingest the most soil per kilogram of body weight.[20] Studies suggest that, over time, the upper 95th percentile for soil ingestion in children 1 to 6 years of age is approximately 200 - 250 milligrams per day.[7] However, these studies found that the amount of soil ingested varied greatly from child to child and also from day to day for each child. On a particular day, a child may ingest significantly more soil than his or her average. An analysis of soil ingestion studies [13] suggests that, over the course of a year, most children will occasionally ingest 1,000 to 2,000 milligrams in a day, and that the upper 95th percentile of the average daily soil ingestion is 1751 milligrams. In a study of 64 children, one child ingested approximately 20,000 milligrams of soil on each of two separate days.[20] Psychological problems and mental retardation may lead to behaviors that include ingestion of large amounts of soil. In one study, a retarded child was estimated to ingest greater than 48,000 milligrams of soil on three out of four days.[20]

Soil ingestion rates in adults have not been well documented. One small study estimated that the upper 95th percentile for adult soil ingestion was 330 milligrams per day, and the maximum one-day ingestion was approximately 2,000 milligrams.[16] Information was not found regarding short-term soil ingestion rates for adults whose work involves significant contact with soil or generation of dust.

For the purposes of this document, the following will be assumed:

- For scenario 1, the range of commonly occurring short-term soil ingestion rates for children is 1000 to 2000 milligrams per day. The upper 95th percentile of 1751 milligrams per day is the best estimate.

- For scenario 2, where atypical children occasionally ingest very large amounts of soil, the range of soil ingestion rates is 20,000 to 50,000 milligrams per day. Because of the expected low probability of occurrence of this scenario, a best estimate of 20,000 milligrams per day was chosen.
- For scenario 3, the range of commonly occurring short-term soil ingestion rates for adults working in the soil is 100 to 2,000 milligrams per day. A best estimate of 2,000 milligrams per day was chosen based on the assumption that this would best reflect exposures in adult workers with significant soil contact, a population of concern that was not specifically targeted in the adult soil ingestion study.(16)

Bioavailability

When a chemical is ingested, some may be absorbed into the body by the gut and enter the blood stream to be distributed throughout the body. The remainder is not absorbed and is excreted in the feces without having a chance to damage the body, except by directly affecting the lining of the gut. The bioavailability of a chemical is the percentage of the ingested amount that is absorbed by the gut.

Many effects of ingested arsenic are due only to the arsenic that is absorbed and not the arsenic that passes through the gut without being absorbed.(1) However, some effects can be caused by direct contact of arsenic with tissues, and absorption is not necessary.(1,24) For example, ingestion of arsenic can lead to irritation of mucous membranes and damage to the gastrointestinal tract leading to diarrhea, vomiting, and abdominal pain.(1,24,25)

Intestinal absorption of purified compounds of arsenic and of arsenic from contaminated soil has been studied. Bioavailability studies in humans show that purified arsenic compounds are absorbed almost completely (90-100%) when ingested.(26-28) Tests of the bioavailability of purified arsenic compounds in animals (29-31) have found that absorption is frequently significantly less than in humans, suggesting that these animals may not be accurate models for arsenic bioavailability in humans.

No human studies of the bioavailability of arsenic from contaminated soil have been published. Studies in animals suggest that bioavailability of arsenic from contaminated soil is less than bioavailability of purified compounds.(28-32) However, as described in Appendix A (Evaluation of Bioavailability Studies) of this report, results of arsenic bioavailability studies in animals appear to be greatly influenced by the choice of animal model and test conditions. It remains to be demonstrated whether differences in bioavailability reported in these studies reflect actual soil-specific differences in bioavailability or were due to differences related to animal models, study conditions and protocols. For example, one possible explanation for the results is that bioavailability may decrease as larger amounts of soil are ingested. These studies represent interesting first steps toward understanding the bioavailability of arsenic from soil. However, limitations of these studies, as well as findings in animals that differ from humans, suggest that the animals and experimental protocols used may not be appropriate models of human response. It remains to be demonstrated that these studies accurately and reliably reflect bioavailability in humans. Furthermore, the soils tested came from small areas of specific contaminated sites, and it has not been shown that it is appropriate to generalize the results to soil from other sites.

Without accurate information on bioavailability of arsenic from Washington soils, or even a proven and reliable method to obtain that information, it is appropriate to assume that relative bioavailability of arsenic from soil is 100% when small amounts (<5,000 milligrams) of soil are ingested. This value is supported by studies of the absorption of arsenic in humans and represents a protective choice that considers the limitations of published studies of arsenic bioavailability from contaminated soils. Lacking adequate data, an assumption of 100% bioavailability for larger amounts of ingested soil (5,000 to 50,000 milligrams) is defensible. Alternatively, based on Figure 1 and the discussion in Appendix A (Evaluation of Bioavailability Studies), it may be reasonable to assume that relative bioavailability is lower, perhaps 20-60%, when larger amounts of soil are ingested. See Appendix A for a more complete discussion of studies of arsenic bioavailability.

For the purposes of this document, the following will be assumed:

- For scenarios 1 and 3, bioavailability is 100%.
- For scenario 2, bioavailability is between 20 and 60%, with a best estimate of 40%. These values were chosen based on the discussion in Appendix A (Evaluation of Bioavailability Studies) and the expected low probability of occurrence of this scenario.

Body Weight

Due to the frequency of mouthing activity, young children are believed to be the population most likely to ingest large amounts of soil. Mouthing activity is reported to be greatest in children 18 to 24 months of age. For calculations in this document the body weight of an 18 to 24 month old child is assumed to be 13 kilograms.(34)

Assumed adult body weight is 70 kilograms.(34)

POTENTIAL CONSEQUENCES OF EXPOSURE (TOXICITY)

Numerous health effects in humans have been documented after short-term exposure to arsenic. The most sensitive reported indicators of toxicity appear to be transient (edema, conjunctivitis, liver enlargement, irritation of the mucous membranes, and gastrointestinal problems such as vomiting, diarrhea, cramps, and pain).(1,25,35,36) Permanent effects such as nervous system damage and death (1,25,35,37) have been documented after several such doses or single higher doses. Information from studies documenting doses of arsenic that caused health effects on short-term exposure is presented in Appendix B (Analysis of Acute Arsenic Toxicity) of this report.

Transient adverse health effects have been reported in people who ingested 0.035 to 0.071 milligrams of arsenic per kilogram of body weight as a single dose, or over the course of one day.(25,35,36) One reference states that health effects commonly occur when such a dose is ingested.(25) Effects appear to be transient, but this cannot be confirmed from information provided in the publications.

Lethal doses of arsenic have been reported as 0.32 milligrams of arsenic per kilogram of body weight (a single dose in one individual) (25) and approximately 0.37 to 2.37 milligrams of arsenic per kilogram of body weight per day (about one week exposure for two individuals).(37)

For the purposes of this document, the following will be assumed:

- For scenarios 1 and 3, transient adverse health effects commonly occur when doses between 0.035 and 0.071 milligrams of arsenic per kilogram of body weight are ingested. The best estimate is 0.05 milligrams of arsenic per kilogram of body weight.
- For scenario 2, lethality can occur from doses between 0.32 and 2.37 milligrams of arsenic per kilogram of body weight, with a best estimate of 1 milligram of arsenic per kilogram of body weight.

CALCULATING HARMFUL SOIL ARSENIC CONCENTRATIONS FOR SHORT-TERM EXPOSURE

With the information presented in previous sections, it is possible to calculate concentrations of arsenic in soil that could cause adverse health effects in exposed populations under various short-term exposure conditions, or scenarios. Three different exposure scenarios, presented below, represent the exposure conditions of greatest public health concern. The evaluations of soil exposure and arsenic toxicity presented provide ranges of possible values for exposure and toxicity. These ranges reflect documented variability in humans with respect to sensitivity to the toxic effects of arsenic as well as documented variability in behaviors that lead to different amounts of exposure to soil.

For each scenario, ranges and best estimates of arsenic concentrations in soil potentially causing health effects are shown in the associated tables below. For the rows labeled "Best Estimate," potentially harmful soil arsenic concentrations were calculated using protective values for toxicity and exposure parameters that were chosen based on degree of support in the scientific literature and consideration of likelihood of occurrence of the scenario. In the rows labeled "More Protective," values from the more protective parts of the published ranges for toxicity and exposure were used. In the rows labeled "Less

Protective," values from the less protective parts of the published ranges for toxicity and exposure were used. For each scenario, the range of soil arsenic concentrations bounded by the more protective and less protective estimates reflects a reasonable expression of uncertainty in applying the information to populations.

Scenario 1

Children are exposed to arsenic-contaminated soil by playing in piles of dirt excavated in residential yards as a consequence of typical homeowner activities such as gardening, planting trees and shrubs, digging fence posts, and installation and maintenance of a sprinkler system. Digging activity by children, pets, and other animals (moles, gophers, ants, earthworms) could also bring contaminated soil to the surface where exposure could occur. These activities are expected to occur commonly in a residential area. Occasional ingestion by children of 1,000 to 2,000 milligrams of this excavated contaminated soil is expected.

Scenario 1	Body weight (kg)	Soil ingestion rate (mg soil/day)	Bioavailability (%)	Toxicity (mg arsenic/kg body weight)	Arsenic concentration in soil causing health effects (mg/kg)
Best Estimate	**13**	**1751**	**100**	**0.05**	**371**
More Protective	13	2000	100	0.035	228
Less Protective	13	1000	100	0.071	923

Scenario 2

Children are exposed to arsenic-contaminated soil in relatively inaccessible areas or deep beneath accessible areas. Contact with these soils would be expected as a result of activities such as construction of additions for existing homes, new home construction, road repair, and utility repair). These activities are expected to be relatively common in a residential area. Compared to Scenario 1, children are less likely to be exposed since people performing the excavations are expected to follow instructions in proper handling and disposal of these soils. However, this scenario evaluates unlikely conditions under which failure to properly handle highly contaminated soil could result in an exposure leading to death of a child.

Scenario 2	Body weight (kg)	Soil ingestion rate (mg soil/day)	Bioavailability (%)	Toxicity (mg arsenic/kg body weight)	Arsenic concentration in soil causing health effects (mg/kg)
Best Estimate	**13**	**20,000**	**40**	**1**	**1625**
More Protective	13	50,000	60	0.32	139
Less Protective	13	20,000	20	2.37	7702

Scenario 3

Adult workers and residents are exposed to arsenic-contaminated soil in relatively inaccessible areas (under roads and buildings) or beneath accessible areas such as residential yards. Activities such as gardening, repair work in a crawl space, fence installation, road repair, utility repair, and home construction could result in exposure. These activities are expected to be relatively common in a residential area. Occasional exposure to this contaminated soil is expected.

Scenario 3	Body weight (kg)	Soil ingestion rate (mg soil/day)	Bioavailability (%)	Toxicity (mg arsenic/kg body weight)	Arsenic concentration in soil causing health effects (mg/kg)
Best Estimate	**70**	**2000**	**100**	**0.05**	**1750**
More Protective	70	2000	100	0.035	1225
Less Protective	70	100	100	0.071	49700

CALCULATION OF SOIL ARSENIC CONCENTRATIONS TO PROTECT PUBLIC HEALTH FOR SHORT-TERM EXPOSURE

The calculated soil arsenic concentrations in the above tables reflect the amount of arsenic that may cause health effects after a single day exposure. Since the goal of DOH is to ensure that health effects are prevented, a no-effect level will be determined to protect public health. A no-effect level is typically estimated by dividing the dose observed to cause health effects by a safety factor. There is little scientific information available to guide the selection of a safety factor for short-term exposure to arsenic in soil. The selection must be based on judgement of the margin of safety desired for protection from the potential adverse consequences of this type of event.

For the three scenarios a safety factor of 10, to derive a no-effect level from an effect level, was considered adequate to calculate soil arsenic concentrations protective of public health. This choice was based on consideration of documented variability in human sensitivity to the toxic effects of arsenic (Appendix B, Analysis of Acute Arsenic Toxicity) as well as consideration of likelihood of occurrence of the various scenarios. Therefore, using the best estimates from the preceding tables, protective concentrations for the three scenarios can be calculated as follows:

Scenario 1 (common child exposure, transient effect)

$$\frac{371\ mg\ arsenic\ per\ kg\ soil}{10} = 37\ mg\ arsenic\ per\ kg\ soil$$

Scenario 2 (atypical child exposure, fatality)

$$\frac{1625\ mg\ arsenic\ per\ kg\ soil}{10} = 162\ mg\ arsenic\ per\ kg\ soil$$

Scenario 3 (common adult exposure, transient effect)

$$\frac{1750\ mg\ arsenic\ per\ kg\ soil}{10} = 175\ mg\ arsenic\ per\ kg\ soil$$

OTHER FACTORS NOT CONSIDERED IN THIS EVALUATION

Other factors that could influence this evaluation were not incorporated into this evaluation. While the qualitative effects these factors would have on the analysis can be assessed, quantification of the effects is problematic.

- Toxicity factors were mostly derived from cases where people were exposed to arsenic for one day or less. However, it is possible that people could have multiple exposures to contaminated soil for several days during some projects. Multiple exposures to a specific concentration of arsenic in soil could result in health effects where a single exposure might not.
- Community protection measures, such as educational efforts and programs that encourage proper handling and disposal of contaminated soil, could help reduce exposure to a portion of the potentially exposed population.

CONCLUSIONS

The hazards of short-term ingestion of large amounts of arsenic-contaminated soil were evaluated. Such exposures may occur to contaminated soil that is located at the ground surface, as well as to soil located in relatively inaccessible areas (such as in crawl spaces under homes) or that has been excavated from beneath the ground surface or from under structures.

Best estimates of concentrations of arsenic in soil to protect the public from adverse health effects due to short-term exposure were estimated for three scenarios:

1. Relatively common child exposure to contaminated soil from accessible areas, resulting in transient adverse health effects (37 mg arsenic/kilogram soil),
2. Infrequent child exposure to deeply buried or relatively inaccessible, contaminated soil resulting in death (162 mg arsenic/kilogram soil), and
3. Relatively common adult resident or worker exposure to subsurface or relatively inaccessible soil resulting in transient adverse health effects (175 mg arsenic/kilogram soil).

To derive these best estimates, parameters were selected from ranges that reflect documented variability in humans with respect to sensitivity to the toxic effects of arsenic and documented variability in behaviors that lead to different amounts of exposure. Another agency, such as Ecology, may choose different values within the ranges depending on what combinations of sensitivities and behaviors are expected in a potentially exposed population, as well as other factors the agency deems appropriate to consider.

Further work is necessary to determine where in Washington arsenic-contaminated soil may be a hazard and what actions would be appropriate to ensure protection of public health. It will be important to involve a wide range of stakeholders to develop approaches to these problems.

APPENDIX A

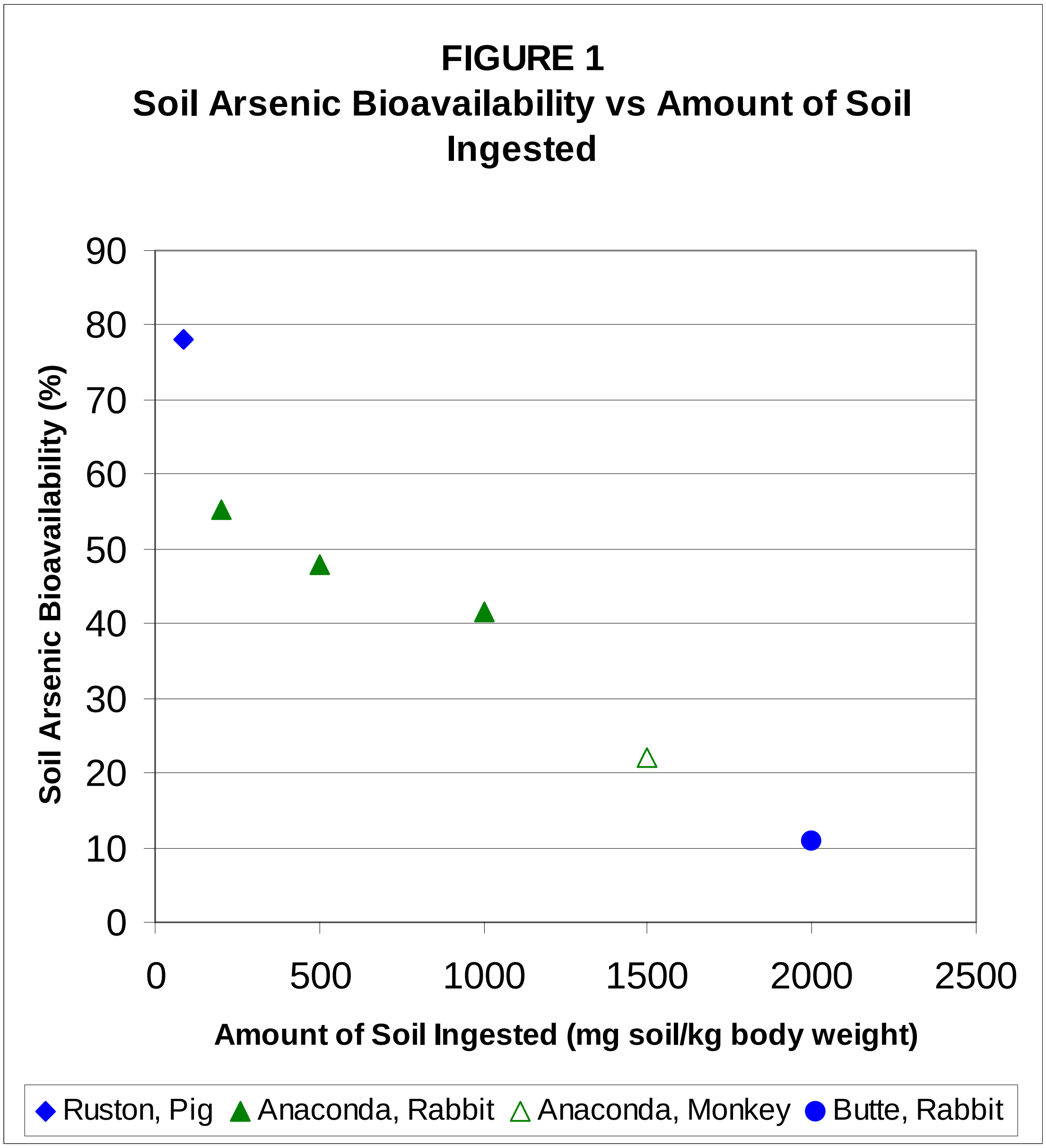
EVALUATION OF BIOAVAILABILITY STUDIES

Human and Animal Studies

In most studies of the absorption of ingested arsenic, humans or animals ingest arsenic and the amount of arsenic excreted in urine and feces is measured for five to ten days [26-31,33]. Frequently, a significant percentage of the original dose of arsenic is not recovered in either the urine or feces and appears to be retained in the body. A study in humans using radioactive arsenic supports this conceptual model.[27] The sum of the arsenic excreted in urine and retained by the body reflects the arsenic that was absorbed, while the arsenic in feces represents the unabsorbed fraction. An analysis of this type may slightly underestimate the absorbed fraction, since some absorbed arsenic may be excreted in the bile and appear in the feces.[39]

Studies in humans have found that arsenic, in the form of purified compounds such as arsenic trioxide, arsenic acid, and lead arsenate, is almost completely absorbed (94-99%) when ingested.[26-28] Essentially complete absorption was also observed in one study in monkeys (98%).[40] However, based on fecal excretion, significantly less absorption of purified arsenic compounds was observed in a different study in monkeys (75%) [30], as well as studies in swine (variable, but roughly estimated as 25-30%) [31] and rabbits (48-55%).[29] In the swine study, a large portion of the administered arsenic "disappeared," and could not be found in the urine, feces, or tissues of the animals. Based on this finding, it is difficult to support the use of this study in evaluating bioavailability. In another swine study [32], estimated absorption was variable from animal to animal (49 to greater than 100%). Since absorption of arsenic in most of the animal studies was significantly less than absorption in humans, it is questionable whether any of the animal studies are appropriate for use in estimating bioavailability in humans.

Arsenic in soil may be in the form of mixtures of a number of arsenical compounds bound to soil particles and it has been suggested that arsenic in contaminated soil may not be as bioavailable as the purified compounds used in the human studies. Studies have been conducted to measure the bioavailability of arsenic from soil, based on the hypothesis that bioavailability may vary depending on the specific contaminated soil sample. Mean bioavailability of arsenic from soil, relative to the bioavailability of purified compounds, has been reported as 20% in monkeys [30], 48% in rabbits [29], 78% in immature swine [32], and 8.3% in dogs.[41] While these results could be interpreted as supporting the hypothesis, the differences in bioavailability reported in the studies may instead reflect differences in animal models and study conditions and not actual differences among soils. For example, different amounts of contaminated soil were fed to the animals in four different studies. A trend is observed when bioavailability is compared to the amount of soil ingested. See Figure 1.



The trend demonstrated in Figure 1 is consistent for soil at a single hazardous waste site, since the four data points in the middle of the curve all represent bioavailability results from the Anaconda, Montana site (three points from a study in rabbits, one from a study in monkeys).[29,30] The data point at the far left of the curve is from a study on soil at the Ruston, Washington smelter site,[32] and the data point at the far right is from a study on soil at a site in Butte, Montana.[33]

For reference, a 13 kilogram child who ingested 1 gram of soil would receive a soil dose of 77 milligrams of soil per kilogram of body weight, or less than the left-most point on the above graph. A 13 kilogram child who ingested 20 grams of soil would receive a soil dose of 1538 milligrams of soil per kilogram of body weight.

Studies in animals suggest that arsenic in soil is less bioavailable than purified arsenic compounds. However, due to uncertainties and limitations of the studies, these findings could be due to the animal model, experimental conditions, and protocols, and not actual decreases in bioavailability. The data appear to be highly uncertain and can be explained by other hypotheses. It remains to be demonstrated that the results of these animal studies accurately and reliably reflect bioavailability in humans.

In Vitro Leaching/Solubility Tests

A study to investigate leaching of lead and arsenic from contaminated soil, as a surrogate measure of bioavailability, was published in 1996.[42] An *in vitro* system designed to mimic the actions of the human stomach and intestines on solubilizing arsenic from contaminated soil was constructed. Soil samples weighing 0.4 g were placed in 40 milliliters (ml) of solution similar to gastric juice (at either pH 1.3 or pH 2.5) and incubated for 1 hour. The solution was then neutralized to pH 7 and the samples allowed to incubate for 3 more hours to simulate passage through the small intestine. Arsenic concentrations were measured in samples withdrawn at specific time points. Bioavailability was estimated by comparing the amount of arsenic in solution in the final aliquot with the total amount added to the reaction vessel. At the end of the experiment, approximately 44 - 50% of the soil-bound arsenic was in solution when the simulated gastric juice was pH 1.3, and approximately 30 - 32% solubilized when the gastric juice was pH 2.5.

There are four potential problems with using this system as a model for human bioavailability. First, the volume of artificial gastrointestinal solutions used versus the amount of soil added was significantly less than would be expected in a human who swallowed soil. The total daily volume of liquid that is excreted and resorbed by the adult human gastrointestinal tract is typically 8.5 liters [43], or 212 times the volume used in this extraction procedure. The authors provided no evidence to clarify whether the arsenic that remained bound to the soil was simply not extractable or whether it had reached an equilibrium between the soil and liquid phases. Increasing the volume of extraction solution might result in greater release of arsenic from the soil.

Second, the concentration of sodium chloride in the test system was significantly below physiological concentrations. In a study published in 1939,[44] the solubility of lead arsenate in different fluids was measured. Although lead arsenate was poorly soluble in water, solubility was significantly greater when placed in saliva, gastric juice, serum, or isotonic sodium chloride. The *in vitro* system could underpredict solubility of soil-bound arsenical compounds due to the low ionic strength of the solutions.

Third, during the course of the test, 2 ml aliquots were removed for analysis at 5 time points and replaced with 2 ml of fresh solution. When the final aliquot was removed and analyzed to estimate bioavailability, the reaction vessel would still contain 40 ml of solution, but only 81.35% of the original material. Thus, bioavailability would be underestimated when the authors compared the arsenic concentration in this aliquot to the original amount added. There is no indication that the authors corrected for this reduction in material.

Fourth, it is believed that many factors not modeled by the *in vitro* system could play a role in the solubility of substances in the gastrointestinal tract.[45] For example, when the pH of the artificial gastric fluid was raised from 2.5 to 7, it was observed that arsenic solubility decreased by 25-29%, possibly due to precipitation reactions. The formation of precipitates may be less likely *in vivo* due to the presence of small organic molecules that would tend to keep the arsenic in solution.

In conclusion, since the extraction test appears to ignore a number of potentially significant features of human digestive system physiology, the results of the test may not accurately model bioavailability in humans.

APPENDIX B

ANALYSIS OF ACUTE ARSENIC TOXICITY

Several authors have published estimates of the amount of arsenic that has been observed to cause illness after short-term ingestion (from one dose to week-long exposures).[25,35-37] Information in four reports will be summarized and discussed below.

1. *Mizuta et al.*[36]

In 1956, more than 400 people in Japan developed health effects from the ingestion of soy sauce contaminated with arsenic. Arsenic concentration in the soy sauce was stated to be 0.1 milligrams per milliliter, and people were thought to ingest approximately 30 ml of soy sauce per day. Affected individuals reported health effects beginning the day after exposure. Observable health effects included edema of the face, enlarged liver, conjunctivitis, anemia, gastrointestinal illness, and abnormal electrocardiograms. The dose was estimated to be approximately 0.05 mg/kg/day of arsenic, assuming a typical Japanese body weight of 60 kilograms.

Urinary arsenic was reported for 5 patients. An inconsistency in this study was the finding that urinary arsenic output appeared too high for the estimated intake 5 to 10 days after exposure ceased. This could be due to an underestimate of the intake for these 5 patients, or for the entire population. Alternatively, these patients could have consumed seafood with significant levels of arsenic prior to the test.

2. *Franzblau and Lilis*[35]

In September 1987, a couple began to visit a vacant house once or twice a week prior to its purchase. During these visits the wife would drink one or two glasses of water. "Immediately after consumption of well water at the house began, she noted the onset of occasional nausea, diarrhea, and abdominal cramps. These symptoms worsened, and, in addition, she started experiencing occasional vomiting, paresthesias in the lower extremities and right hand (burning and tingling), and a sensation of swelling and irritation of the eyes and sinuses." (page 386)

The husband also consumed water during visits to the house and reported symptoms including abdominal cramps, nausea, headache, nasal congestion, and diarrhea.

The concentration of inorganic arsenic in the water supply was measured on eight occasions and ranged from 9,000 to 10,900 μg/liter. Assuming the wife weighed 70 kilograms and drank 1 to 2 glasses (0.25 to 0.5 liters) containing 10,000 μg/liter, her dose was approximately 0.036 to 0.071 mg arsenic/kilogram body weight.

3. Armstrong et al.[37]

Eight members of a family of nine became ill over the course of approximately one week while drinking arsenic-contaminated well water. Two individuals died and the remaining six affected people had numerous signs consistent with arsenic toxicity.

Arsenic concentration in the well water was 108 mg/liter. Information was gathered on approximate daily consumption of water. Estimated arsenic doses calculated by the authors ranged from 26 to 166 mg/day. Assuming a body weight of 70 kilograms (likely an overestimate, most family members were less than 18 years of age), these doses, adjusted for body weight, become 0.37 to 2.37 mg/kg/day.

Of interest is the finding that output of arsenic in the urine was significantly less than the estimated intake.

4. Pharmacotherapeutics[25]

Arsenical compounds were once used as medicines to treat a variety of conditions. The doses of arsenic causing toxic effects are discussed in this reference book, primarily as they relate to medicinal use.

The following information was used to calculate arsenic doses based on statements in the book:

Compound	Formula	Molecular Weight	Percent Arsenic (by weight)
Potassium metaarsenite	$KAsO_2$	146.02	(51.3% arsenic)
Arsenic trioxide	As_2O_3	197.84	(75.7% arsenic)
Sodium orthoarsenate (mono-H)	$Na_2HAsO_4 \bullet 7H_2O$	312.01	(24.0% arsenic)
"Exsiccated" sodium arsenate	Na_2HAsO_4	185.94	(40.3% arsenic)

1 milligram = 1/60 grain

1 minim = 0.06 milliliter

In addition, the following assumptions were used to calculate arsenic doses from statements in the book:

For the calculations below, it was assumed that "sodium arsenate" refers to the "exsiccated" form (40.3% arsenic) and **not** the hydrated form (24.0% arsenic). If it was assumed that the hydrated form were used, the resulting calculations would suggest that arsenic had greater toxicity.

Fowler's solution is typically referred to as a solution containing 1% potassium arsenite, thus containing 0.513% arsenic. However, the book, "Pharmacotherapeutics" suggests that it is a 1% solution of arsenic trioxide with potassium bicarbonate added, resulting in a solution that contains 0.757% arsenic. In the calculations below, it will be assumed that Fowler's solution contained 0.757% arsenic, and **not** 0.513%. If it were assumed that Fowler's solution contained 0.513% arsenic, the resulting calculations would suggest that arsenic had greater toxicity.

The following excerpts were taken from the specified pages of "Pharmacotherapeutics."[25]

page 601:

"From 1/24 to 1/20 grain (2.5 to 3 mgm) of arsenic trioxide or sodium arsenate, or 5 to 6 minims (0.3 to 0.4 cc.) of the official 1 percent (Fowler) solution of potassium arsenite will ordinarily be well borne by an adult not previously habituated of the drug; but symptoms of *intolerance* - irritation of all the mucous membranes - have been induced by a much smaller quantity; as 3 minims of Fowler's solution in one of our cases."

This suggests that 3 minims of Fowler's solution, or 1.36 mg of arsenic (0.18 ml x 10 mg/ml x 0.757), can cause health effects. Assuming body weight was 70 kg, the dose was 0.02 mg/kg.

page 601:

"An initial dose of 1/10 grain (6 mgm) of sodium arsenate or 10 minims of Fowler solution will commonly excite distress; indeed some persons cannot readily acquire tolerance to this quantity, even by gradual approach."

This suggests that 6 milligrams of sodium arsenate, or 2.42 mg of arsenic (6 mg x .403) commonly caused health effects. Further, 10 minims of Fowler's, or 4.54 mg of arsenic (0.6 ml x 10 mg/ml x 0.757) commonly caused health effects and could not be tolerated with a gradual buildup in dose. Assuming body weight was 70 kg, the respective doses were 0.035 mg/kg and 0.065 mg/kg.

page 601:

"In an instance related to us, 3 cc. (45 minims) of Fowler solution, equivalent at most to 30 mgm. (gr. 1/2) of potassium arsenite, proved fatal to an adult."

This suggests that 45 minims of Fowler's, or 22.71 mg of arsenic (3 ml x 10 mg/ml x 0.757) was fatal to an adult. Assuming body weight was 70 kg, the fatal dose was 0.32 mg/kg.

page 606:

"In the absence of habituation, full doses (1/60 to 1/12 grain; 1 to 5 mgm.) excite salivation, nausea, vomiting, epigastric pain, diarrhea, or constipation and, if continued, chronic intoxication. Larger doses (1/6 to 1/3 grain; 0.01 to 0.02 Gm) produce dryness and burning of the tongue, mouth and throat and perhaps epigastric cramp."

Assume this refers to arsenic trioxide. This suggests that the first set of health effects occurs at doses of 0.757 to 3.78 mg of arsenic (1 mg or 5 mg x 0.757), and the second set at doses of 7.57 to 15.14 mg of arsenic (10 mg or 20 mg x 0.757). Assuming body weight was 70 kg, the dose range for these effects was 0.01 to 0.22 mg/kg. If the compound was sodium arsenate, the corresponding dose range of arsenic would have been 0.006 mg/kg to 0.12 mg/kg.

Summary of Information From this Reference

Single doses of inorganic arsenicals used as drugs ranging from 0.035 to 0.065 mg arsenic/kg body were commonly found to cause adverse health effects. In some individuals, single doses caused adverse health effects at even lower doses that ranged from 0.01 to 0.02 mg arsenic/kg body weight. A dose of 0.32 mg arsenic/kg body weight was reported to cause death in an individual. All doses assume that body weight was 70 kg.

Summary of Information on Acute Arsenic Toxicity

The dosage data for medicinal arsenicals may be the best human exposure estimates available, given the widespread use of the drugs, consistent formulations, and standard treatment regimens. Data in the other studies appear to be reliable.

There are some potential data gaps and unexplained inconsistencies in the reviewed studies. In all cases, body weights can only be estimated. Although these publications provided estimates of the amounts of arsenic ingested, none listed the body weights of affected individuals, an important consideration when extrapolating exposure information to other individuals. Urinary outputs do not match up well with estimated inputs in the Mizuta and Armstrong studies.

However, taken together, these publications consistently suggest a small range of doses that produce nonfatal adverse health effects from short-term (often a single) exposure:

Pharmacotherapeutics:[25]	0.035 - 0.065 mg/kg (or sometimes lower)
Mizuta:[36]	0.05 mg/kg
Franzblau:[35]	0.036 - 0.071 mg/kg

Fatal doses reported in these references [25,37] ranged from 0.32-2.37 mg/kg.

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