

Health Consultation

CMC HEARTLAND PARTNERS LITE YARD SITE
MINNEAPOLIS, HENNEPIN COUNTY, MINNESOTA

APRIL 8, 1999

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Agency for Toxic Substances and Disease Registry

Division of Health Assessment and Consultation

Atlanta, Georgia 30333

Health Consultation: A Note of Explanation

An ATSDR health consultation is a verbal or written response from ATSDR to a specific request for information about health risks related to a specific site, a chemical release, or the presence of hazardous material. In order to prevent or mitigate exposures, a consultation may lead to specific actions, such as restricting use of or replacing water supplies; intensifying environmental sampling; restricting site access; or removing the contaminated material.

In addition, consultations may recommend additional public health actions, such as conducting health surveillance activities to evaluate exposure or trends in adverse health outcomes; conducting biological indicators of exposure studies to assess exposure; and providing health education for health care providers and community members. This concludes the health consultation process for this site, unless additional information is obtained by ATSDR which, in the Agency's opinion, indicates a need to revise or append the conclusions previously issued.

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HEALTH CONSULTATION

CMC HEARTLAND PARTNERS LITE YARD SITE
MINNEAPOLIS, HENNEPIN COUNTY, MINNESOTA

Prepared by:

Minnesota Department of Health
Under a Cooperative Agreement with the
Agency for Toxic Substances and Disease Registry

FOREWORD

This document summarizes potential public health concerns at a hazardous waste site in Minnesota. It is based on a formal site evaluation prepared by the Minnesota Department of Health (MDH). A number of steps are necessary to do such an evaluation:

- Evaluating exposure: MDH scientists begin by reviewing available information about environmental conditions at the site. The first task is to find out how much contamination is present, where it's found on the site, and how people might be exposed to it. Usually, MDH does not collect its own environmental sampling data. We rely on information provided by the Minnesota Pollution Control Agency (MPCA), U.S. Environmental Protection Agency (EPA), and other government agencies, businesses, and the general public.
- Evaluating health effects: If there is evidence that people are being exposed—or could be exposed—to hazardous substances, MDH scientists will take steps to determine whether that exposure could be harmful to human health. The report focuses on public health—the health impact on the community as a whole—and is based on existing scientific information.
- Developing recommendations: In the evaluation report, MDH outlines its conclusions regarding any potential health threat posed by a site, and offers recommendations for reducing or eliminating human exposure to contaminants. The role of MDH in dealing with hazardous waste sites is primarily advisory. For that reason, the evaluation report will typically recommend actions to be taken by other agencies—including EPA and MPCA. However, if there is an immediate health threat, MDH will issue a public health advisory warning people of the danger, and will work to resolve the problem.
- Soliciting community input: The evaluation process is interactive. MDH starts by soliciting and evaluating information from various government agencies, the organizations responsible for cleaning up the site, and the community surrounding the site. Any conclusions about the site are shared with the groups and organizations that provided the information. Once an evaluation report has been prepared, MDH seeks feedback from the public. *If you have questions or comments about this report, we encourage you to contact us.*

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Introduction

The Minnesota Department of Agriculture (MDA) requested technical assistance from the Minnesota Department of Health (MDH) on public health implications related to arsenic contamination at the CMC Heartland Partners (CMC) Lite Yard site (Site) in the City of Minneapolis, Hennepin County, Minnesota. In January of this year (1998) MDH completed a health consultation on a proposal by representatives of CMC Heartland (CMC) to use soil cleanup levels for arsenic which were used at the Anaconda Montana site by the United States Environmental Protection Agency (MDH 1998a). Subsequent to that discussion, CMC has proposed using an *in vitro* model to determine the bioavailability of the arsenic species found on-site. MDH stated in the January 1998 Health Consultation that "MDH would be willing to review bioavailability or toxicity studies based on site-specific compounds and mixtures from the CMC site." This document has been completed for the purpose of discussing the appropriateness of the use of the proposed model to determine the bioavailability of arsenic at this site.

Information reviewed for this document include communications between a consultant for CMC, James Smith, Jr. of Oak Creek Toxicology and Risk Assessment, and Carl Herbrandson of MDH, as well as numerous peer reviewed scientific papers and other reference materials. While this health consultation focuses on the bioavailability of compounds found on-site, the discussion has more general application in raising many issues which must be addressed prior to the use of an *in vitro* model to predict the bioavailability of a compound found in soil.

Site Background

The site is a 7.7 acre triangular piece of land in south Minneapolis, and is situated between 28th Street (South), Hiawatha Avenue (East), the city of Minneapolis Asphalt Plant (North), and railroad tracks and the Mattaini Warehouse (West) (see Figure #1). The site was previously used by a pesticide manufacturing company. There is a small building standing on the site which post-dates the use of the site for pesticide manufacturing or packaging. The site is currently rented and used by Bituminous Roadways. The site has partially restricted access with a chain link fence on the southern boundary and a broken snow fence along the railroad track boundary to the west/northwest.

The site is located within an industrial corridor which includes numerous railroad tracks and switching areas, warehouses, streets with high volumes of traffic, and retail commercial businesses. Two large retail and grocery shopping areas are within one-half mile of the site, to the south and southeast. The residential houses closest to the site are one block west and northwest of the site on Longfellow Avenue. This residential area is along the edge of the Phillips neighborhood which includes some high density housing and apartments to the west-northwest, within one-fourth mile of the site.

Two blocks to the south of the site, the Hiawatha Avenue overpass has been completed. Road construction to the north of this overpass impacts the east / northeast edge of the site. The

Minnesota Department of Transportation (DOT) has an easement to complete a corridor along Hiawatha Avenue. This may include the construction of a mass transit or bus corridor, as well as the roadway which is currently under construction. Contaminated soil in the area of the easement has been identified and will be treated according to appropriate federal and state regulations. It has been determined that dewatering is not necessary for construction to take place.

Across from 28th Street, directly to the south of the site, the Green Corporation is building a new headquarters. This project includes moving 21st Avenue South. It is unknown at this time if the construction will impact the CMC site or if the site may impact construction.

Chemicals of Concern

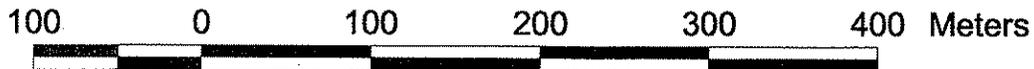
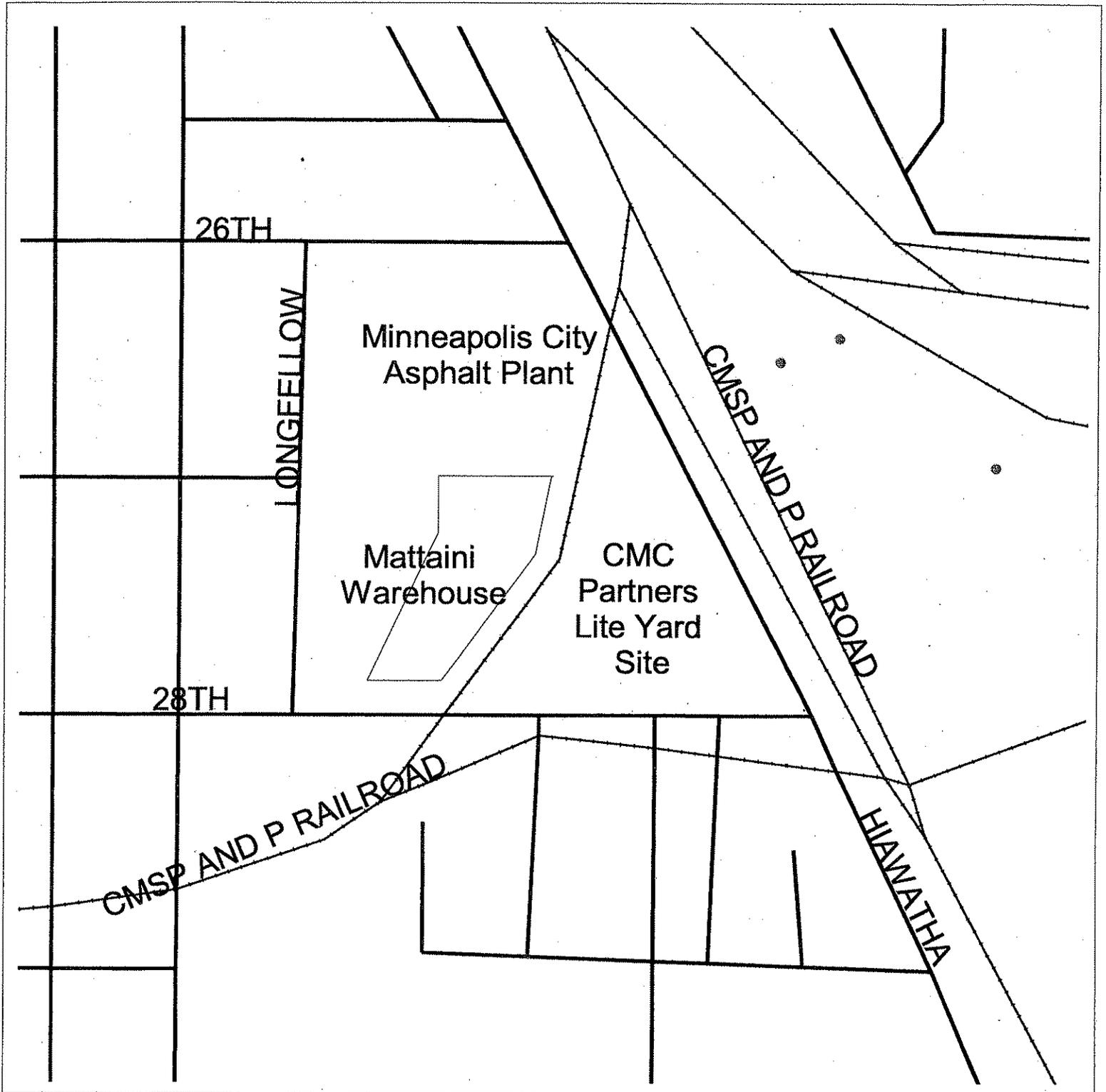
Arsenic (As), a metal found in many different compounds on-site, is the primary chemical of concern on the site due to its presence in soil and groundwater at very high concentrations (up to 18,000 mg/kg and 320,000 µg/L, respectively). MDH is currently concerned about acute exposures to these high levels of arsenic on-site. Workers involved in the cleanup, unsuspecting construction workers on the adjacent Hiawatha corridor, or other individuals could be accidentally exposed to high levels of arsenic in materials which are superficially covered on-site. Drinking water containing 60,000 ppb (60 mg/L) arsenic could be lethal. The minimum lethal dose of arsenic has been calculated to be about 1-3 mg/kg (mg arsenic / kg body weight). Therefore, ingestion of about 0.2 liters water containing 320,000 ppb arsenic or about 3 grams of soil containing 18,000 mg/kg arsenic (maximal concentrations found on the CMC site) could be lethal. Further discussion of arsenic toxicity is found in the January 1998 MDH Health Consultation (MDH 1998a), as well as an August 1998 memo from MDH to MDA (MDH 1998b).

There are no known wells for drinking water in the area of the site. Residences in the area of the site are connected to the Minneapolis municipal water system. The nearest known well, about 1 mile west-southwest of the site, supplies water to a cooling tower at Abbott-Northwestern Hospital. Issues concerning groundwater migration and exposure to groundwater will be discussed in a separate health consultation.

MDH is also concerned about chronic exposures associated with this site. While the site was an operating pesticide facility, it is probable that wind blew materials from the site on to neighboring soil. An area south of the site has been sampled for remnants of any potential plume. Arsenic concentrations found in soil drop off steeply within a block of the site, but MDH has not yet reviewed all of the available data. Furthermore, no soil sampling has been conducted in the residential neighborhood which begins 1 block northwest of the site. Therefore, it is possible that there are low level chronic exposures to arsenic in soil off-site.

Currently, contamination on the site is supposed to be covered by 1 foot of dirt (Class 5 gravel). Constant activity is occurring on the site due to its use as a staging area for an asphalt plant. This activity may make the cap ineffective and chronically expose workers on the site to arsenic.

Figure # 1



Furthermore, workers on the site in the future may be exposed to arsenic at levels that are determined by cleanup standards. For this reason, determination of protective standards is important.

The estimated volume of soil found on-site contaminated at greater than 250 mg/kg arsenic is 28,480 cubic yards (yds³); the estimated volume contaminated at greater than 3,000 mg/kg arsenic is 9,620 yds³ (Peer 1997a).

Arsenic at the CMC site is not found in one specific compound but is a mixture of weathered arsenic pesticide products. Initial speciation showed a large portion (of a single core sample) to be calcium arsenate, which was assumed to be an end product manufactured or packaged at the site, and iron oxide arsenate, which may have been a raw material, by-product of production, or a product of weathering. It is expected that ingestion of similar amounts of arsenic, in either form would result in different uptake by a laboratory animal or a human. This difference would be a result of a difference in bioavailability of these compounds. CMC, through their consultant James Smith, suggested that since the bioavailability of arsenic compounds on the site may be less than the bioavailability of aqueous sodium arsenate (the basis of the Minnesota Pollution Control Agency soil reference value) that the cleanup requirement be adjusted proportionally. MPCA has developed health-based soil reference values as draft guidance for maximum concentrations of hazardous compounds in soil which may be expected to have negligible effect on the health of sensitive individuals under reasonable maximal exposure conditions.

Background on Bioavailability

Bioavailability is the measure of the fraction of a compound which enters an organism relative to the total amount of the compound to which the organism has been exposed. When ingestion is the route of exposure, bioavailability is the ratio of the total amount absorbed from the gastrointestinal (GI) tract to the dose ingested. Regardless of its toxicity, if an ingested compound is encapsulated and not bioavailable there is no internal dose and the compound cannot cause adverse health effects. On the other hand, if 100 % of a dose is absorbed in the GI tract then the internal dose to the individual is 100 %.

The bioavailability of chemicals is species dependent due to physiological differences between species. For some compounds there can be large inter-individual variability which can be a result of age or development, diet, time since last meal, nutritional status, gender, hormonal state, health status, level of stress, co-administration of drugs, or genetic differences. Furthermore, temporal differences in bioavailability may be found in individuals as a result of many of these same factors.

Generally, it is not ethical to measure the bioavailability of toxic compounds to humans. Therefore, the human bioavailability of toxic compounds is typically inferred from animal models. Validation of animal bioavailability models is problematic due to the lack of controlled human data. Available human data is generally limited to occupational exposures, accidental or intentional poisonings, low dose studies, and occasionally, studies conducted prior to the

discovery of a mechanistic or symptomatic linkage of the compound or dose to an adverse effect. Toxicokinetics of a compound may be altered under chronic or acute exposure conditions. For some compounds there are known exposures of human populations to background concentrations which may provide information about the bioavailability or uptake kinetics of a compound. However, the data are often ecological and individual exposure concentrations must be inferred. Furthermore, compounds which are found contaminating sites may be chemically bound or attached to matrix material differently than naturally occurring chemicals, or they may be different species of the same compound or element. This is especially true for metals. For arsenic it is expected that arsenate found in mined ores and slag may be less bioavailable than arsenates found in water.

Human Arsenic Bioavailability

Solubility of arsenic compounds in acid appears to be a good, but rough, measure of the relative bioavailability of different arsenic compounds. Therefore, the relative bioavailability of sodium arsenate is expected to approximate the bioavailability of arsenic acid or arsenic found in groundwater. On the other hand, other arsenic species, such as smelter byproducts including arsenic oxides, arsenic iron oxides, silicates, and sulfates, or pesticides lead arsenate, calcium arsenate and Paris Green (copper acetoarsenite) may be expected to have reduced bioavailability. While animal studies may provide a basis for proposing reduced bioavailability to humans, without confirmatory studies in humans any quantitative reduction in regulatory criteria or levels of concern may be problematic.

Human bioavailability studies

Excessive exposure to environmental arsenic is usually either from groundwater containing high natural concentrations of arsenic or arsenic from contaminated soil, dust, or products related to mining, smelting, or pesticide activities. Some human ingestion experiments have been conducted with volunteers as well. Fecal excretion of ^{74}As by six male volunteers following ingestion of a single gelatin capsule containing arsenic acid (AsH_3O_4) was 6.1 % (± 2.8 S.D.) (Pomroy et al. 1980). It was not determined if fecal excretion was due to the lack of uptake by the gastrointestinal (GI) tract or to biliary excretions.

An interesting study on arsenic retention was reported by Bettley and O'Shea in 1975 (Bettley & O'Shea 1975). They looked at the blood concentration, fecal excretion, and urinary excretion of arsenic following the ingestion of Liquor Arsenicalis by four patients with arsenical keratoses and superficial carcinomas and three patients with no history of arsenic ingestion but with other diagnosed skin conditions who were controls. Blood arsenic levels, monitored over a ten day period following dose administration on one day (split dose), were found to be significantly higher in controls. Urinary excretion of arsenic (pooled 24 hour urine), but not urinary arsenic concentration, was also significantly greater for controls. The total fecal excretion by test subjects ranged between 0.3 % and 3.5 % of the total dose, with no apparent difference between the previously exposed and affected group and the control group. Given the low level of fecal excretion by all subjects, it is not surprising that there was no significant difference between the

groups for this route of excretion. If this study had been conducted with an arsenic compound which is less bioavailable it may have been possible to discern differences in bioavailability of arsenic compounds to previously exposed, affected individuals, and previously unexposed individuals using fecal excretion as a measure. The results of this study demonstrate that while uptake may be similar between previously unexposed individuals and those who have been exposed and are victims of an arsenic related disease, the retention of arsenic by the latter group is greater (i.e. less proportional urinary excretion in previously exposed individuals). The study implies that human populations may have different toxicokinetic responses to environmental arsenic which depend on previous exposure to arsenic or potential susceptibility to arsenic toxicity.

A study by Fairhall and Neal in 1938 (Fairhall & Neal 1938) demonstrated that about 100 % of the ingested arsenic from lead arsenate (ingested with food) is absorbed. Two volunteers ingested 10 mg of lead arsenic per day for 6 days while on a special diet of milk, graham crackers, and apples. Less than 1 % of the ingested arsenic was excreted in feces. These data are in direct contrast to the excretion of 85.5 ± 11.5 % of the lead in feces. Urinary excretion over 12 days of monitoring was 96 % and 77 % of ingested arsenic for the two individuals, accounting for about 86 % of the ingested dose. Lead arsenate is generally considered to be less soluble than calcium arsenate (Shepard 1951). Furthermore calcium arsenate has been shown to be more toxic or bioavailable to rats and dogs than arsenic trioxide or lead arsenate (Finner & Calvery 1939; Gaines 1969; Morris & Wallace 1938).

Apple growers have historically used the pesticide lead arsenate. It has been favored over Paris Green and calcium arsenate since it causes less plant damage. This is presumed to be due to lead arsenate's decreased water solubility relative to the other pesticides (Shepard 1951). A study, by Webster in 1941 (Webster 1941), of apple growers ingesting apples sprayed with lead arsenate demonstrated that not all ingested arsenic is bioavailable. This study showed greater fecal excretion (13.3 % of total ingested arsenic) than urinary excretion (11.6 % of total ingested arsenic) of arsenic. Measured arsenic recovery by these two excretion routes was about 25 %. In contrast to the low arsenic fecal excretion, 58 % percent of the ingested lead was recovered in the feces suggesting relatively higher uptake and retention of arsenic.

Data necessary to calculate mass balance is not available from the Webster study due to study design. The period of sample ingestion and the period of specimen collection were the same 10 - 12 days, and prior exposure to lead arsenate from apples is presumed. It is probable that the life style of the subjects included a continuous diet which contained significant amounts of lead arsenate. Therefore, the study may contain data approximating steady-state with regard to lead arsenate toxicokinetics. The number of apples ingested were determined by the test subjects and represented average seasonal maximal consumption. It is possible that some of the low arsenic recovery may be attributed to excessive retention of arsenic in these individuals who had been chronically exposed to arsenic.

While the Fairhall and Neal experiment shows no human fecal excretion of arsenic ingested as lead arsenate, Webster has shown significant fecal excretion. A comparison of these studies

suggests that either the exposure matrix may significantly affect uptake or prior exposure to arsenic may affect uptake and / or retention. However, study design restricts the utility of the Webster study.

Bioavailability inferred from EPA Exposure Assessment Model

Walker and Griffin (Walker & Griffin 1998) used the EPA Exposure Assessment Model to predict urinary arsenic concentrations in children near the Anaconda Montana smelter site. The model used arsenic bioavailability fractions of 18.3 % from soil and 25.8 % from dust. These values are from a bioavailability study in cynomolgus monkeys which tested soil from this site (Freeman et al. 1995). The EPA model slightly underpredicted the speciated urinary arsenic concentrations measured in this potentially at-risk population. There were two sets of data for soil arsenic concentrations and dust arsenic concentrations available for use in the model. One set was data from the yards and houses of all children (364) from which urinary arsenic was measured. The other set was data from the yards and houses of a subset of 26 homes included in the previous study. The results of the second study, in the subset of residences, showed the concentration of arsenic in dust and soil to be 39 % of the arsenic concentration measured by the larger study. The Walker and Griffin paper used the environmental sampling data from the larger study. This apparent data discrepancy could translate into a bioavailability of arsenic from a smelter site which is 2 - 3 times greater than the fraction applied to this model. For this exposure assessment model to be calibrated for use with smelter waste, actual bioavailability and soil / dust concentration data needs to be better defined.

Models of Arsenic Bioavailability

Two different types of models have been proposed as arsenic bioavailability models. *In vivo* models have been investigated in laboratory animals including rat, hamster, rabbit, monkey, and swine. *In vitro* models are also being developed to simulate the human GI tract and take advantage of the apparent limiting factor of arsenic bioavailability, solubility, to predict a proportion of arsenic which is accessible to an animal, and which could potentially be absorbed (i.e. bioavailable).

Human bioavailability of dissolved arsenic in drinking water is presumed to be 100 %. There are limited data on the absolute bioavailability of other forms of arsenic to humans. It is reasonable, though, to propose that animal species which have GI tracts physiologically similar to humans and which have similar kinetic characteristics in arsenic uptake and metabolism may demonstrate similar relative bioavailability to different arsenic compounds as humans. Therefore, a validated *in vivo* model could be of use in determining a reasonable measure of the absolute bioavailability of arsenic compounds in humans.

Validation of an *in vivo* model is difficult given the lack of human arsenic bioavailability data. While there are data on dissolved arsenic bioavailability (Pomroy et al. 1980) in humans, there are few data on nonsolubilized phase bioavailability. Furthermore, there is some evidence that the inter-individual variability in uptake is significant (77 % coefficient of variability (CV)) (Bettley & O'Shea 1975).

Animal models

Rodents have been investigated for use as bioavailability models, but their use may be problematic. Rabbit data show the average urine arsenic recovery from sodium arsenate administered by gavage is 47 % and the average recovery of arsenic from smelter contaminated soil is 24 % (0.2 and 0.5 g soil /kg groups) and 17 % (1.0 g/kg group) (Freeman et al. 1993). This projects a 36 - 51 % relative bioavailability of arsenic from smelter contaminated soil. But rabbits may be poor models due to their modified colon, their diet, and the array of different flora in their GI tracts. Furthermore, it has been noted that rabbits accumulate some arsenic in erythrocytes (Ducoff et al. 1948; Lanz et al. 1950).

Arsenic has also been shown to bind even more avidly to rat erythrocytes (Hunter et al. 1942; Peoples 1975). This trait provides a mechanism whereby absorbed arsenic can be sequestered in rats rendering it less toxic. Therefore, rats are also poor human kinetic models.

Monkey and swine, have been proposed as *in vivo* models due to physiological similarities with humans. However, similarities in anatomy, physiology, or function do not necessarily equate to a good animal model. Humans, as well as most animals, methylate arsenic (Vahter 1994) as a means of detoxifying it and increasing excretion. New world monkeys (marmoset and tamarin) and chimpanzees do not methylate arsenic (Vahter et al. 1995; Vahter & Marafante 1985; Zakharyan et al. 1996). New world monkeys and chimpanzees may have developed other, as yet unknown methods for decreasing the toxicity of ingested arsenic. Possible methods by which toxic effects may be decreased include the evolutionary incorporation of mechanisms which decrease uptake, increase clearance of non-methylated arsenic, or decrease the toxicity of arsenic to susceptible organs and tissues. The potential toxicokinetic or toxicodynamic difference between humans and new world monkeys make new world monkeys a poor model for arsenic bioavailability studies.

On the other hand, some old world monkeys, such as rhesus monkeys which methylate mercury, may make good human models due to their close taxonomic relationship and similarities in GI tracts. Swine, especially immature swine, may also make good human models since their diet is similar to humans, and size and growth needs of immature swine may approximate children.

The bioavailability of arsenic from a smelter site has been measured using cynomolgus monkeys (Freeman et al. 1995). Cynomolgus monkeys are old world monkeys. However, MDH has been unable to locate any published information on their ability to methylate arsenic. Test animals (n=3) were serially dosed with sodium arsenate, arsenic containing soil, and arsenic containing house dust. Urine and feces were collected for 5 days following administration. About 100 % of the applied doses were recovered (94.4 %, 101 % and 95.4 % respectively). Bioavailability, calculated from urine recovery values, was 67.6 %, 19.2 %, and 13.8 % respectively. Bioavailable arsenic was presumed to be primarily from metal arsenic silicates and iron arsenic sulfates.

The growth needs of the immature animal to a large extent determine the uptake of metals - including non-essential metals. Developing organisms take up more essential and non-essential

metals. Increased uptake of non-essential metals has been demonstrated in children with lead (Hammond 1982). Lead uptake has been shown to be via a calcium transport mechanism (Sobel et al. 1938). Deficiencies in iron, calcium, protein and zinc have all been related to increased lead uptake or blood levels (Mahaffey 1981; Mahaffey & Michaelson 1980).

Nutritional status may affect the bioavailability of arsenic. Arsenate may be taken up by some cells via phosphate specific transport proteins (Luecke & Quioco 1990) and this uptake may be potentiated by increased need for phosphate or decreased phosphate availability. Calcium consumption has been shown to decrease the uptake of phosphate in the gut due to the formation of insoluble calcium phosphate (Guyton 1991).

Immature swine are currently being developed as a potential animal model for human uptake of arsenic (and lead). EPA Region 10 has published data which may demonstrate that swine absorb a larger fraction of arsenic from environmental media than other test animals (EPA 1996). However, these data have not been peer reviewed. EPA Region 8 is currently involved in arsenic bioavailability studies using immature swine. However, they have encountered mass balance difficulties.

In vitro models

In vitro models are being developed to help predict the bioavailability of arsenic and lead (Davis et al. 1992; Davis et al. 1995; Ruby et al. 1993; Ruby et al. 1996). The *in vitro* models for arsenic and lead are mechanistically based models which presume that the uptake of these metals is primarily dependent on their solubility in the GI tract. Lead and arsenic solubility in these physical/chemical models of the GI tract is equated to the bioaccessibility of these metals. Bioaccessibility is assumed to be the maximum concentration of chemical which is available to be absorbed by the GI tract. Therefore, bioaccessibility may be a conservative measure of bioavailability.

Initial studies comparing *in vitro* bioaccessibility to the bioavailability of arsenic from smelter contaminated soil have demonstrated the feasibility of the *in vitro* assay. However calibration and validation of the models has not occurred. Much of the problem with calibration and validation is related to the lack of a validated animal model of human arsenic bioavailability discussed above.

The Solubility/Bioavailability Research Consortium is sponsoring *in vitro* model development for lead and arsenic. Phase I *in vitro* experimental results from the Solubility/Bioavailability Research Consortium (PTI 1997) included 4 lead arsenate samples from the Anaconda smelter site. While the *in vitro* assay data from Anaconda (smelter) soil has been shown to have an arsenic bioaccessibility of 31 to 50 % (Ruby et al. 1996), the arsenic bioaccessibility from the lead arsenate samples was 112.5 % (mean; 9.4 SD). Much of the work on bioaccessibility and *in vitro* models was reviewed by a Toxicology Excellence for Risk Assessment panel (<http://tera.org/news/april27s.htn>) in April 1998.

PBPK model

James Smith Jr. suggested for CMC that similarities between animal and human pharmacokinetics

are demonstrated by a physiologically based pharmacokinetic (PBPK) model described by Mann et al. (Mann et al. 1996a; Mann et al. 1996b). This PBPK model of arsenic in humans is not currently designed to model arsenic bioavailability. The model demonstrates that the same mechanisms probably exist for the metabolism and, to a more limited extent, the excretion of arsenic in humans and rabbits/hamsters. But in their present form, the model does not suggest relative arsenic uptake factors. To demonstrate similar kinetic mechanisms it is necessary to use fitting parameters determined from animal data and show that the human data and model outputs approximate each other. In the Mann et al. human model (Mann et al. 1996b), tissue affinity constants were obtained from constants fit using the animal model (Mann et al. 1996a). Therefore, interspecies similarity has only been demonstrated in relative arsenic tissue affinity and in the relationships between model compartments. The value of this model at this point of development is that it presents a structure for hypothesis testing. As the rate constants are refined and confidence in them increases it may become possible to use models like the Mann et al. model to extrapolate between animal and human exposures to arsenic. Until then the applicability of this model to bioavailability is limited.

Discussion

The contaminant of concern at the CMC site is arsenic. Current interest is focused specifically on the bioavailability of a major constituent of the arsenic contamination at CMC, calcium arsenate. However, since there are other arsenic species on-site a general discussion of environmental arsenic bioavailability is in order.

The toxicity of arsenical species varies considerably. The relative toxicity of different arsenic compounds probably correlates with their relative bioavailability. Unfortunately, the reported toxicities of similar compounds to similar animal species varies greatly. This variability does not appear to be limited to expected inter-laboratory differences in quantified measures of toxicity (typically LD₅₀'s). Done and Peart (Done & Peart 1971) propose that the large variability in experimental results may be due to improper methods which include dosing animals with dissolved arsenical compounds. Since the bioavailability of arsenic appears to be primarily a function of GI tract solubility, dissolved test compounds may be expected to be 100 % bioavailable. The solubility of many arsenic compounds is limited; therefore, some investigators heated test compounds (Harrison et al. 1958) possibly changing chemical structures. Other non-solubilized solutions could contain nonhomogeneous mixtures of small particulates in a water.

No studies have been identified which directly characterize the bioavailability of calcium arsenate. Calcium arsenate is more soluble than lead arsenate; therefore, the Fairhall and Neal study of lead arsenate may provide an appropriate lower bound reference. While the study is old, it appears to be a well conducted study. Identified shortcomings include the lack of a detailed method section containing a description of the dosing regime. If the lead arsenate, which was taken with food, was dissolved prior to ingestion, arsenic uptake would be expected to approximate 100 %. It is unlikely that the pesticide was dissolved given the statement in the paper that, "this unexpected finding (100 % absorption), in view of the low solubility of lead arsenate in water, is direct

evidence that the ingested lead arsenate was broken down in passing through the gastrointestinal tract."

The Fairhall and Neal (Fairhall & Neal 1938) study shows about 100 % bioavailability of arsenic from lead arsenate. Another study conducted with different individuals and protocols showed less than 100 % absorption of arsenic from lead arsenate for unknown reasons, possibly including environmental matrix effects (Webster 1941). The Fairhall and Neal study is important because it demonstrates the potential for 100 % arsenate absorption following exposure to an insoluble pesticide, and cannot be discounted by the Webster study which was designed to investigate the conditions of a small specific cohort.

As discussed in the previous section, rodents are not good models for arsenic bioavailability. Cynomolgus monkeys have been used in some experiments. Data from these animals suggest lower bioavailability of arsenic from sodium arsenate to cynomolgus monkeys than to humans. All proposed animal models, unlike humans, have been shown to absorb less than 100 % of arsenic from compounds such as sodium arsenate. In fact monkeys and rabbits absorb about 68 % and 50 - 65 % arsenic from sodium arsenate, respectively (assuming minimal biliary excretion of As, which may not be a reasonable assumption).

As expected, the bioavailability of arsenic from soil (smelter origin) to cynomolgus monkeys is less than sodium arsenate bioavailability. A serial dosing regime was used with the monkeys tested in the bioavailability studies. This allowed for the use of each test subject as its own control. However, and unfortunately, it has been demonstrated in some human studies that previous exposure may alter the toxicokinetics for humans exposed to arsenic (Bettley & O'Shea 1975; Webster 1941). Cynomolgus monkeys may turn out to be a functional human adult model, but given the extent of the published data (one study with 2 treatment groups and controls), the number of test animals (3 females), and the data variability (percent CV = 41 % soil absolute bioavailability) it is clear that this has yet to be demonstrated.

The monkeys used in the above studies were all adult monkeys. Adult animals are not subject to the growth needs of younger animals. Any immature animal may make a better model for human children than a good mature animal-to-adult model. Immature rabbits have been used in experiments, but as noted above, their use in arsenic models is problematic. Immature swine may be a good model for children, but at this point there are recovery problems which limit any mass balance analysis. Analysis of dermal excretion and accumulation in endogenous keratinous substrates may account for some of the loss, but until a thorough accounting is completed the utility of this model is limited as well.

Laboratory studies are beneficial for determination of the etiology of a specific toxic response because of experimental control over test animal genetics, environmental exposures, laboratory diets, and other experimental conditions. Paradoxically, while this may be a positive attribute for toxicity studies, it is not helpful in determining the presence of other important variables or 'drivers' as well as covariate dependence relationship and mechanisms. It is possible that animal bioavailability studies overlook specific factors which could be significant. There are indications

that not all uptake factors have been identified. Radioactive tracer studies with arsenic have shown large inter-individual variability in excretion and tissue distribution in many species (Ducoff et al. 1948; Hunter et al. 1942). Further investigation of uptake mechanisms may be necessary to identify other potentially significant variables.

Setting aside MDH's concern about the lack of a good animal model for the time being, let's assume that MDH accepts the use of a non-adult animal model. Since the MPCA cleanup number was calculated from an applied dose and not an internal dose, an appropriate comparative dose form for relative toxicity is sodium arsenate in water. The maximum (concentration dependent) relative bioavailability of arsenic from soil at a smelter site to prepubescent rabbits was 51% (Freeman et al. 1993 described above). Arsenic bioavailability from contaminated soil from a different smelter site was even greater in immature swine with 78 % relative bioavailability (EPA 1996). Soil from the CMC site would be expected to have higher arsenic bioavailability than either of these sites. But if arsenic bioavailability from CMC soil is assumed to be similar to smelter contaminated soil, the absolute best site-specific cleanup number which could be expected would be either 1/2 or 3/4 times the default.

Pentavalent arsenic ions (arsenate), is taken up by phosphate transport proteins. The absorption of phosphate in the digestive system is 100 % unless there is calcium present. In the presence of calcium, calcium phosphate is formed. Calcium phosphate is insoluble in the GI tract. The Fairhall and Neal data showing about 100 % absorption of arsenate, from lead arsenate, in 2 individuals on an apple, graham cracker, and milk diet. The simultaneous ingestion of large amounts of calcium and lead arsenate could create conditions in the GI tract where calcium and lead bind to available phosphate. The decrease in concentrations of free phosphate in the GI tract, as well as systemically, over 13 days (lead arsenate was administered over the last 10 days), could have led to a significant increase in the uptake of arsenate. While it is doubtful that there are individuals who are on an apple, graham cracker and milk diet, a child's diet may increase arsenate bioavailability. Furthermore, a similar potentiation mechanism may be involved in the uptake of calcium arsenate. Calcium arsenate has greater water solubility than calcium phosphate or lead phosphate.

Model development

Prior to the acceptance of an *in vitro* model for determining a conservative estimate of the bioavailability of arsenic from site-specific soil two issues must be addressed: is there a good animal (*in vivo*) model of the bioavailability of arsenic to humans from soil (discussed above); and, has an *in vitro* model of bioaccessibility been validated for use as a conservative predictor of bioavailability over a broad range of substrate solubility?

Phase I data from the Solubility / Bioavailability Research Consortium demonstrates that an *in vitro* model estimates the bioaccessibility of lead arsenate to be 100 %. This data point may provide support for the use of the *in vitro* model, but MDH advises caution. The bioaccessibility of lead arsenate in *in vitro* models may be equivalent to human data demonstrating about 100 % bioavailability. However, in contrast to *in vitro* experimental data with other arsenicals, we have

seen no definitive human data suggesting quantifiable bioavailability of arsenic compounds significantly below 100 %. *In vitro* arsenic models have not been calibrated or validated to date.

The measure of health risk (calculated from the EPA Oral Slope Factor) for arsenic has been determined from an applied dose in drinking water and not an internal dose. Any adjustments to the cleanup numbers can be calculated by a comparison of the bioavailability of arsenic from the site with the bioavailability of the arsenic in drinking water or sodium arsenate and not strictly from an absolute bioavailability of arsenic from site samples. Furthermore, potential animal models (immature swine and cynomolgus monkeys) have only been tested at the low end of the regression, where low bioavailability may be expected, and not with more soluble arsenic compounds and pesticides. Since first approximations of arsenic bioavailability are presumed to correlate with arsenic species solubility, this correlation needs to be thoroughly described. A non-linear relationship between bioavailability and solubility (under physiological conditions) within any experimental range could signify more than one mechanism of uptake for a compound, or regulation of an uptake mechanism.

The bioavailability of compounds to a proposed animal model must correlate with the bioavailability of the same compounds to humans. The correlation should be demonstrated to exist with compounds that have low solubility as well as high solubility. Furthermore, if the correlation between human and animal bioavailability becomes non-linear as solubility changes the range needs to be defined and quantitatively, as well as qualitatively, described.

Arsenic bioavailability at the CMC site

This review of literature on arsenic species toxicity and bioavailability suggests that the bioavailabilities of poorly soluble arsenic trioxide, lead arsenate, and calcium arsenate are high in humans. MDH expects that any reduced bioavailability at this site will primarily be a function of the extent of aging and mineralization of arsenic on the site. There may be some matrix effects at the site which could reduce the potential bioavailability of arsenic at the CMC site to somewhat less than 100 %, and leaching may have removed a quantity of some more water soluble arsenic species.

To this point, discussion has focused on the uncertainties in determining a single site-specific bioavailability for the CMC site. Experimental uncertainty also accompanies the choice of test particle size, and sample heterogeneity, while risk uncertainties extend to exposure scenarios and toxic sensitivity. There is expected to be great variability in exposure, uptake, and even toxic sensitivity in the human population. It is well known that there are large differences in the bioavailability of metals to different individuals. This has been clearly demonstrated in the cases of lead, iron, zinc, and other metals. Furthermore, it has been shown that the same individual can have different rates of absorption of trace elements given different nutritional conditions or needs. There is evidence that there is variability in human and animal uptake or retention of arsenic. It has also been demonstrated that individuals with a history of arsenic exposure and afflicted with arsenical carcinoma, may retain up to 50 % more arsenic than unexposed individuals. This may suggest the existence of a segment of the population which is sensitive to arsenic.

Given the papers and reports reviewed and preliminary speciation data suggesting that about 50% of the arsenic on-site is calcium arsenate, MDH is not convinced that data from an *in vitro* study with soil from the site will demonstrate a relative bioaccessibility (used as a conservative measure of bioavailability) which is significantly less than, say, 80 %. Therefore, it is doubtful that such work will make a material difference for cleanup at the CMC site.

Conclusions

1. This health consultation is restricted to a discussion of the bioavailability of arsenic on this site and a discussion of potential methods to determine a site-specific bioavailability for arsenic.
2. Extremely high concentrations of arsenic have been found in soil and groundwater at this site.
3. A temporary dirt cap covers contaminated soils. Daily, large earth-moving equipment move piles of dirt and recycled asphalt around the surface of the cap.
4. While the CMC site does not currently pose a public health hazard (assuming maintenance of the cap), the potential in the future for people to be exposed to contaminants from this site is of concern to MDH. Furthermore, in the past this site may have been a public health hazard; however, there is no known documentation or data describing historic conditions on this site. Workers on-site need to be protected now and in the future from potential exposures to arsenic at levels of acute and chronic concern.
5. At this time available data for arsenic in soil at the property boundary as well as south of the site imply that off-site exposures to arsenic associated with this site is not a public health hazard. However, data are not available on soil concentrations in a residential area located about 50 + (plus) meters northwest of the site.
6. There are no known groundwater receptors in the area.
7. *In vivo* models of arsenic bioavailability to humans have not been validated.
8. *In vitro* models of arsenic bioaccessibility have not been validated.
9. Upon review of the primary literature, MDH cannot, at this point, accept a bioavailability factor which is less than the current default (100 %).

Recommendations

- MDH recommends the use of the default bioavailability factor (100 %) for cleanup of this arsenic contaminated site.
- MDH recommends sampling of soil and determination of the magnitude and extent of arsenic contamination in a residential area located about 50+ meters northwest of the site.
- MDH recommends that measures be taken to assure that on-site workers are not exposed to high levels of arsenic found on-site.

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