



APC Holdings
KMG-Bernuth, Inc.
Luxembourg-Pamol, Inc.

September 27, 2005

Our Ref.: 050927-309
Via E-Mail and Hand Delivery

Mr. R. Lance Wormell
Special Review and Reregistration Division (MC 7508C)
Office of Pesticide Programs
U.S. Environmental Protection Agency
1801 South Bell Street
Arlington, VA 22202

Re: Response to EPA's Questions

Dear Mr. Wormell,

On behalf of the Methanearsonic Acid (MAA) Research Task Force, I am submitting responses to the twelve questions that you sent us on March 14, 2005. You will find three sets of attachments: A. Responses to Questions 1-5 on the behavior of organic arsenicals in soil after application; B. Responses to Questions 6-11 on the use of monosodium methanearsonate (MSMA) and disodium methanearsonate (DSMA); and C. Response to a follow-up question on the calculation of the margin of exposure (MOE) for dimethylarsinic acid.

We are confident that after reviewing the attached documents, you and others at EPA will appreciate that the responses are very substantive. The Task Force expended a great deal of time and effort to prepare responses that are scientifically sound and accurate, and in our view, provide EPA with the level of information that it needs to undertake comprehensively the reregistration process.

Please do not hesitate to contact me should you have any questions.

Sincerely,

Michal Eldan, Ph.D., Chair,
MAA Research Task Force (MAATF)
P.O.Box 33856
Washington, D.C., 20033-0856
Tel. (212) 495-9717

MAA RESEARCH TASK FORCE

MAATF

APC Holdings
KMG-Bernuth, Inc.
Luxembourg-Pamol, Inc.

Email: meldan@luxpam.com

Attachments

CC (via email only): Margaret J. Rice
G. Thomas Myers
Dirk V. Helder
Ana Lowit
Diana Locke
Alex Clem
Barbara D. Beck
Jennifer K. Saxe
MAA Research Task Force members

MAA RESEARCH TASK FORCE

■ P.O. Box 33856, Washington D.C. 20033-0856, PHONE: (800) 890-3301, FAX: (202) 557-3836, E-mail: meldan@luxpam.com ■



Response to Questions and Requests for Information for the MAA Research Task Force

March 14, 2005

A. Environmental Fate

Introduction

This document responds to Questions 1-5 of the twelve questions that the U.S. Environmental Protection Agency (EPA) asked the Methanearsonic Acid (MAA) Research Task Force (Task Force, MAATF). Gradient Corporation (Gradient) has reviewed the literature to obtain data about the behavior of MSMA in soil after its use. This literature review is presented in the report, "The Environmental Fate of Monosodium Methanearsonate (MSMA): A Review of Important Processes" (Gradient, 2005a). Data from that review, as well as additional data from sponsored studies and from an updated literature search was used to respond to EPA's questions 1-5.

The responses include a thorough coverage of the existing data, including numerous sources that appeared to address the questions, but very often could not be used upon closer scrutiny. In such cases, the information was included with an explanation why it is not relevant to the question.

There are some issues, common to all the responses, which should be borne in mind when reviewing the data. These issues are:

- the criteria used to decide what data to include in the responses to these questions,
- the differences between data from well-designed field experiments and data from laboratory experiments, and the superiority of the field studies for answering EPA's questions, and
- the limitations of analytical methods for identifying distinct arsenic compounds in soil, and the implications for answering these questions.

Criteria for Including Data in the Responses to Questions 1-5

Questions 1-5 include requests for available data that quantify the phenomena of environmental mobility and transformation of organic arsenic. In response, tables are provided that include the available relevant data that address each specific question. The entry for each relevant study includes the full bibliographical citation as well as a summary of the pertinent data from that study. The responses include summarized data from studies sponsored by the Task Force, as well as from studies that are published in the public literature. The data review was independent of the purpose of the studies or the conclusions drawn by the study authors. Some studies included in the tables were conducted for purposes other than quantifying the environmental mobility and transformation of organic arsenic compounds, but nevertheless contain data that help answer the questions posed by EPA. In such cases, we provided the relevant data in the response, and when appropriate, note that the authors did not make any relevant conclusions based on those data. In some other cases, studies in the literature purport to contain data that address the environmental mobility and transformation of organic arsenic compounds, but do not contain any reliable data that address these issues. In each such case, an entry for the study was included in the table, with a description of the circumstances that disqualify the data from addressing the question. In many cases, conclusions presented in the cited literature are not consistent with the underlying data, and as a result, the conclusions in the responses to questions 1-5 are not necessarily in agreement with the conclusions of the authors' whose data are cited. In all these cases we included explanations for our conclusions.

The Superiority of Data from Field vs. Laboratory Studies

The responses to questions 1-5 cite two different types of studies as evidence of the behavior of MSMA in the environment: field studies and laboratory studies. Of the two study types, field studies provide results that are a more reliable representation of the behavior of MSMA when it is used as an herbicide. Results of field studies are more reliable because critical factors that determine the mobility and potential for microbial transformation of MSMA, such as temperature, moisture levels, and microbial activity in soil, are representative of conditions where MSMA is used in practice. In contrast, laboratory studies cannot accurately recreate field conditions. Laboratory studies are usually designed specifically to *encourage* the measured behavior (*e.g.*, mobility or transformation), so that results are discernible during a study of limited duration. Thus, the quantitative information provided by the laboratory studies described in the responses below should generally be interpreted as describing extreme conditions (*e.g.*, maximum mobility or transformation) – in some cases so extreme as to be unattainable in the field – rather than typical expectations for MSMA in the field. For example, laboratory studies described in responses 1-5 include designs where soil was shaken continuously with excess water

immediately after MSMA was added, in order to assess mobility, or where soil containing MSMA was kept moist and aerated while incubated at elevated temperatures with degradable organic amendments to assess the potential for MSMA to be metabolized by microorganisms. While these studies may be useful for comparing soils to one another qualitatively (*i.e.*, soil A will retain more MSMA than soil B, or MSMA will be transformed less extensively in soil A than in soil B), they are of little value for predicting the quantitative behavior of MSMA in soils.

An example of the discrepancy between results of laboratory and those of field studies is presented in a study described by Hiltbold *et al.* (1974), which includes both a laboratory and field component, including the same soils in both contexts. In the laboratory component, the ability of sandy soils to bind MSMA was determined in a batch study, and the results indicated that MSMA would not appreciably bind to these soils (*i.e.*, the soil-water partition coefficient, K_D , ranged from 0.2 to 1.7 mL/g). However, in the field component of the study, MSMA was applied heavily to these same sandy soils for six years (*i.e.*, the highest rate was 40 kg/ha per year or 218 lb/acre per year) and *all* of the arsenic attributable to MSMA was detected in the top 30 cm of soil. Thus, even though the laboratory study was conducted according to reasonable protocols, the result did not accurately reflect the behavior of MSMA in the field. The result of the field study proved that MSMA was bound to the top 30 cm of sandy soils, although the laboratory study suggested otherwise.

The Detection of Distinct Arsenic Compounds in Soil

The analytical capabilities for detecting distinct arsenic compounds in soil are limited. The primary compounds of interest in soil after MSMA is applied as an herbicide are monomethyl arsonic acid (MAA), which is the product of MSMA dissociation in water, and dimethylarsinic acid (DMA) and (inorganic) arsenate, both of which may be formed as a result of the microbial metabolism of MAA. In order to unequivocally understand the fate of MSMA in soil, a study should include measurements of MAA, DMA, and inorganic arsenic directly on soil and in soil pore water after the application of MSMA as an herbicide.

The methods reported in the literature for the analysis of arsenic compounds in soil involve two parts: First, extraction of the arsenic compounds from soil, and second, chemical analysis of the extracts for the specific arsenic compounds. There are two types of extraction methods that are typically used for soil prior to the chemical analysis of arsenic compounds: a) Mild extraction methods (*i.e.*, extraction with water, with a weak acid or weak base such as a dilute aqueous solution of ammonium hydroxide, *etc.*) leave arsenic-containing molecules intact, so that they can be analyzed using analytical techniques specific to each compound. These methods do not extract arsenic compounds that are bound to soil strongly. Moreover, the state of the art does not enable confirmation that the extracted compounds are not modified during

extraction. b) Methods used for the extraction of total arsenic in soil (*i.e.*, extraction with concentrated acids and oxidizers, or "digestion" methods), remove all or virtually all the arsenic from soil, but also destroy the soil structure and the arsenic species and/or form. Our literature search did not identify any studies that distinguish between organic and inorganic forms of arsenic compounds that are bound strongly to the soil. Due to the analytical limitations described above, no study includes all the information that is needed to respond to the questions in full. As a result, the data described in the responses to questions 1-5 do not provide complete or definitive answers to the questions.

One suite of analytical methods that is capable of discriminating the form of arsenic bound to soil non-destructively is x-ray absorption spectrometry (XAS), including x-ray absorption near edge structure (XANES) and extended x-ray absorption fine structure (EXAFS) techniques. These methods require the use of a synchrotron light source, which is not a common instrument and requires special training to interpret the results. It is available only in a few laboratories and must be reserved for use months in advance of the analysis. Moreover, these methods are effective only for concentrations of arsenic in soil that are relatively high (*i.e.*, greater than 100 mg/kg, and ideally close to 1,000 mg/kg) compared to concentrations typically detected in areas where MSMA is used as an herbicide. The Task Force is in the process of conducting an XAS study of a soil where MSMA was spilled, the results of which are still being compiled. Preliminary results show that MAA is the form of arsenic bound in the soil both before and after extraction using EPA Method 1312 (Synthetic Precipitation Leaching Procedure, or SPLP).

Some of the studies addressing the transformation of MSMA to inorganic arsenic do not rely on the detection of arsenic compounds at all, but instead use secondary measures, such as tracking carbon from radiolabeled MSMA (*i.e.* ^{14}C -MSMA) and inferring that the concentration of inorganic arsenic is equivalent to the ^{14}C evolved. Although this is a standard scientific approach, it is not a direct measure of the species of interest (*i.e.*, inorganic arsenic) and thus could overestimate the amount of inorganic arsenic present in a system where active demethylation *and* methylation of arsenic compounds occur simultaneously. Specifically, ^{14}C evolved from radiolabeled MSMA signals the cleavage of the As-C bond, but provides no information about possible subsequent metabolism of inorganic arsenic to (unlabeled) MAA or DMA, which would reduce the final concentration of inorganic arsenic below the levels predicted by the ^{14}C evolution measurement. The results of these studies should therefore be regarded as worst case results.

These three issues should be borne in mind when reviewing the data described in the following responses to EPA's questions.

Question 1: What data are available to quantify organic/inorganic arsenic accumulation in soil over time due to repeated organic arsenic herbicide applications?

Response 1:

Gradient has reviewed the literature to obtain data showing the quantity of arsenic measured in soil where MSMA or DSMA use has occurred, in order to assess the behavior of MSMA in soil after its use. This literature review is presented in the report, "The Environmental Fate of Monosodium Methanearsonate (MSMA): A Review of Important Processes" (Gradient, 2005a). The data from that review, as well as additional relevant data for cacodylic acid (DMA) applied as an herbicide are summarized in Table 1. Note that although data are presented for the accumulation of arsenic compounds in soil after application of MSMA and DMA as herbicides, the use patterns, application rates, and the toxicity (see Response 4) of these two compounds differ and thus the data from studies of MSMA and DMA are neither interchangeable, nor additive. The data from controlled studies where organic arsenical herbicides were applied according to current product label directions, shows that the total arsenic in digestates of soil were only slightly increased after multiple applications. Most field studies were conducted for multiple years, with multiple herbicide applications each year, using application rates that exceeded (and sometimes vastly exceeded) those directed on the current product labels. Nevertheless, total arsenic concentrations measured in those studies generally ranged from negligible to less than 10 mg/kg in surface soil, with even lower concentrations at depth. These data suggest that organic arsenic herbicide use at current labeled rates, which are lower than the rates tested in most of the studies summarized in Table 1, would result in only slight increases in total soil arsenic, and those increases would be limited to surface soil.

Table 1
Studies Addressing Organic/Inorganic Arsenic Accumulation in Soil

Reference	Gradient's Summary of Findings Relevant for MSMA Use
Johnson, LR; Hiltbold, AE. 1969. "Arsenic content of soil and crops following use of methanearsonate herbicides." <i>Soil Sci. Soc. Amer. Proc.</i> 33:279-282.	MSMA and DSMA were applied four times per year to an Alabama sandy loam soil (containing 0% to 10% clay at various depth intervals) during a 4-year period. High application rates of 2.23, 4.47, and 8.86 kg/ha were used. At the end of the study period, soil samples collected from depths of 0 to 5 cm, 5 to 15 cm, and 15 to 30 cm in test and control plots were analyzed for total arsenic and the arsenic contribution from herbicides was calculated. Recovery of applied arsenic in the top 30 cm of soil was approximately 100%, 75% and 50% for the 2.23, 4.47, and 8.86 kg/ha treatments, respectively. The highest concentrations of arsenic in soil attributable to MSMA or DSMA found in the top 5 cm of soil, ranged from 3.3 to 12.7 mg/kg, and decreased with depth. Arsenic concentrations attributable to MSMA or DSMA ranged from 2.0 to 5.7 mg/kg at the 15 to 30 cm depth, after 4 years of application.
Hiltbold, AE; Hajek, BF; Buchanan, GA. 1974. "Distribution of arsenic in soil profiles after repeated applications of MSMA." <i>Weed Sci.</i> 22:272-275.	MSMA was applied to three Alabama soils (a loamy sand, a fine sandy loam, and a silt loam) in test plots in the field at relatively high rates of 10, 20, and 40 kg/ha per yr for six years. Soils were plowed annually to a depth of 23 cm. Soil cores 90 cm deep were divided in 15 cm increments and analyzed for total arsenic. The arsenic concentrations in the 0 to 15 cm depth samples, collected from treated soils, ranged from 7.6 to 31.5 mg/kg, while in control soil samples collected from 0 to 15 cm, arsenic concentrations ranged from 2.4 to 10.3 mg/kg. The arsenic content in soil deeper than the plowed layer (<i>i.e.</i> , the 15-30 cm increment) from treated plots did not differ from untreated plots.
Robinson, EL. 1975 "Arsenic in Soil with Five Annual Applications of MSMA." <i>Weed Sci.</i> 23(5): 341-345.	MSMA was applied to test plots in the field at rates of 4.4, 9, 13, 18, 22, 36, 72, 144, and 288 kg/ha per yr for 5 years. An increase in total arsenic was observed only when the application rate was greater than 36 kg/ha per yr. For treatments where elevated arsenic concentrations were detected, those elevated concentrations were limited to the top 30 cm of soil.

Table 1
Studies Addressing Organic/Inorganic Arsenic Accumulation in Soil

Reference	Gradient's Summary of Findings Relevant for MSMA Use
Woolson, E; Aharonson, N; Iadevaia, R. 1982. "Application of the HPLC-Flameless Atomic absorption Method to the Study of Alkyl Arsenical Herbicide Metabolism in Soil." <i>J. Agric. Food Chem.</i> 30: 580-584.	This publication briefly describes field data for plots treated with large amounts of MSMA and DMA in "low" and "high" treatment level plots (eight annual applications at 11.2 and 22.4 kg/ha respectively, and seven annual applications of at 56 and 112 kg/ha, respectively). The application rates in this study far exceed the amount used according to current label rates. Data are poorly described in this study (presented only as a line plot, and total arsenic concentrations are not reported). The authors made no conclusions regarding the accumulation of total arsenic in soil as a result of MSMA application. The results of this study are not reliable for drawing conclusions regarding MSMA concentrations in soil after its use as an herbicide.
Akkari, KH; Frans, RE; Lavy, TL. 1986. "Factors Affecting Degradation of MSMA in Soil." <i>Weed Sci.</i> 34:781-787.	In a study that included both field and laboratory components, MSMA was applied to cotton, soybeans, sorghum, and rice, over four years. In the field, applications were made according to "their associated weed control practices" at a rate of 1.7 kg/ha. The number of applications made in this study is unclear. In aerobic soils, extractable DMA and arsenate concentrations did not change after MSMA application (data for extractable MAA were not presented by the authors). The total arsenic concentration during the first two months after application was elevated by 0.85 mg/kg, but thereafter, arsenic concentrations returned to original levels. In flooded soils, total arsenic, extractable MAA, DMA, and arsenate were comparable to natural background concentrations at all times during the study. Note that the authors calculated degradation rate constants for MSMA based on <i>extractable</i> MAA concentrations, thus some or all MSMA "degradation" is likely sorption. The authors concluded that "MSMA treatments contributed only a small fraction to total soil arsenic...under present recommended use patterns it is highly unlikely that MSMA will accumulate in the environment."
Mid-South Agricultural Research, Inc.; PTRL East, Inc. 1992. "Terrestrial Dissipation of MSMA in Cotton." Prepared for MAA (MSMA/DSMA) Research Task Force Three.	MSMA was applied twice to test plots in the field at a rate of 2 lb/acre over the course of one year. The maximum extractable MSMA concentration found in soil was 2.37 mg/kg and occurred after the first application. No MSMA residue was detected in soil deeper than 6 inches.

Table 1
Studies Addressing Organic/Inorganic Arsenic Accumulation in Soil

Reference	Gradient's Summary of Findings Relevant for MSMA Use
Pan-Agricultural Laboratories, Inc.; PTRL East, Inc. 1992. "Terrestrial dissipation of monosodium methanearsonate (MSMA) in California soil." Prepared for MSMA/DSMA Research Task Force Two, c/o Luxembourg Industries (Pamol), Ltd.	MSMA was applied three times to test plots in the field at a rate of 4.95 lb/ha at 3 week intervals. The maximum concentration of extractable MSMA in the top 0-6 inch layer of soil was 9.44 mg/kg, measured immediately after the third application, and in the 6-12 inch layer - 0.62 mg/kg, measured five days after the third application. Extractable DMA was detected at maximum concentrations of 0.24 mg/kg in the top 0-6 inch layer of soil at 91 days after the third application, and 0.06 mg/kg in the 6-12 inch layer of soil at 179 days after the third application. Extractable MSMA and DMA were undetectable at all depths by the end of the 365 day study. Over the course of the study, the average total arsenic concentration in the top six inch layer of treated plots was 12.61 mg/kg vs. 10.14 mg/kg in the control plot. There was no significant difference in total arsenic concentrations between treated and control plots in depths below six inches.
Plant Sciences, Inc. and PTRL East, Inc. Coody, PN; White, JW. 1993. "Terrestrial Dissipation of Cacodylate 3.25 in Bare Ground Simulating Product Use on Turf." Prepared for MAA Research Task Force Three Luxembourg Industries (Pamol), Ltd.	DMA was applied two times to low-iron test plots in the field at a rate of 24 lb/acre with a five-day interval between applications. The maximum extractable DMA and MAA concentrations in soil 0-6 inches deep after treatment were 32.75 and 1.65 mg/kg, respectively, and the maximum concentrations in 6-12 inch deep soil were 1.69 and 0.16 mg/kg, respectively. The total arsenic concentration was not increased in soil deeper than 12 inches.
Bednar, AJ; Garbarino, JR; Ranville, JF; and Wildeman, TR. 2002. "Presence of organoarsenicals used in cotton production in agricultural water and soil of the southern United States." <i>J. Agric. Food Chem.</i> 50:7340-7344.	Soil samples were taken from cotton fields where MSMA, DSMA, and/or DMA were reportedly used. Herbicide application rates, as well as application rates for other arsenic-containing materials (<i>e.g.</i> , fertilizers, inorganic arsenical pesticides) are unknown. The authors made no conclusions specifically addressing the accumulation of arsenic compounds in soil as a result of MSMA application. This was not a controlled study thus its results are not reliable for drawing conclusions regarding MSMA concentrations in soil after its use as an herbicide.

Table 1
Studies Addressing Organic/Inorganic Arsenic Accumulation in Soil

Reference	Gradient's Summary of Findings Relevant for MSMA Use
Dept. of Environmental Resources Management (DERM). 2002. "Environmental Quality Monitoring at Five Municipal Golf Courses in Miami-Dade County. Final Report."	Total arsenic was measured in soil at five municipal golf courses in South Florida, at pesticide mix/load areas where spills were documented or suspected, and in playing areas where MSMA was reportedly used. This was not a controlled study. Local background arsenic concentrations in soil were not measured for comparison. The sources of arsenic in the soils were unknown, and some or all of the arsenic concentrations measured were due to sources other than MSMA. MSMA application records were not included. Fertilizers containing arsenic were cataloged as being in use at the golf courses, but their contribution to soil arsenic concentrations was not quantified. The courses with the highest deep soil arsenic concentrations were former agricultural and landfill areas. The results of this study are not reliable for drawing conclusions regarding MSMA concentrations in soil after its use as an herbicide as also explained in the comments to the study that were submitted by the MAA Research Task Force in June 2005 (Gradient, 2004).
Florida Dept. of Environmental Protection (FDEP). 2002 "Environmental Risks from Use of Organic Arsenical Herbicides at South Florida Golf Courses." December 27. Downloaded from http://fdep.ifas.ufl.edu/msma.htm on February 20, 2004.	Total arsenic was measured in soil at former golf courses in South Florida. This was not a controlled study. MSMA application records were not included for most courses, and were incomplete where they were available. No record was reported describing alternative arsenic sources at the study sites, such as use of arsenic-containing fertilizers, use of older inorganic arsenical pesticides, or the historical use of the soil (<i>e.g.</i> , agriculture, landfill etc.). The results of this study are not reliable for drawing conclusions regarding MSMA concentrations in soil after its use as an herbicide, as explained in the comments to the study that were submitted by the MAA Research Task Force in June 2005 (Gradient, 2005b).
Feng, M; Schrlau, JE; Snyder, R; Snyder, GH; Chen, M; Cisar, JL; Cai, Y. 2005. "Arsenic Transport and Transformation Associated with MSMA Application on a Golf Course Green." <i>Ag. Food Chem.</i> 53(9): 3556-3562.	MSMA was applied three times to test plots in the field at a rate of 2.24 kg/ha. Prior to the first MSMA application, total arsenic concentrations ranged from 0.27 to 0.34 mg/kg. One week after the third MSMA application, concentrations were 0.45 to 0.69 mg/kg. The results of this study are not reliable for drawing conclusions regarding MSMA residue concentrations in soil after typical MSMA use, because even though MSMA is not normally used on golf course greens, the test plots simulated golf course greens that are engineered to allow rapid drainage and to promote leaching.

Question 2: What data are available to demonstrate how rapidly and to what extent MSMA and DSMA are converted to cacodylic acid (DMA) after applied?

Response 2:

Gradient has reviewed the literature to obtain data on the environmental fate of MSMA and summarized it a report titled "The Environmental Fate of Monosodium Methanearsonate (MSMA): A Review of Important Processes" (Gradient, 2005a). This review includes data on the rate and extent of MSMA conversion to DMA in soil where MSMA use has occurred. Data from that report, relevant to the conversion of MSMA to DMA are summarized in Table 2. The conclusion based on the reviewed literature is that MSMA is a stable compound that does not break down or undergo transformation spontaneously. The transformation of MSMA to DMA in soil is solely a biologically mediated process, and as such can occur only in the presence of soil microorganisms capable of methylating MAA when MSMA or MAA (resulting from dissociation of MSMA in water) is bioaccessible (*i.e.*, accessible to soil microorganisms for metabolism), during time periods beginning immediately after MSMA application until sorption to soil has occurred. The process of MSMA transformation can occur only in locations and at times that conditions favor microbial activity. Such conditions include adequate moisture, warm temperatures, and sufficient substrates for microbial activity. Soils that sustain the most favorable conditions are not common. Additionally, the occurrence and extent of these transformations depends on the specific microorganisms that are present in the soil. Thus, when MAA transformation to DMA occurs, it is incomplete, episodic, and variable among locations. This variability is borne out in the results of studies described in Table 2. The laboratory study conducted by PTRL East and submitted to EPA for MSMA re-registration (see Table 2) shows that about 32% of MSMA applied was converted to DMA. Because laboratory conditions were maintained to be favorable for microbial activity, and do not represent field conditions, this is likely a high-end estimate of the proportion of MSMA that could be transformed to DMA in field conditions.

Table 2
Studies Addressing MSMA/DSMA Transformation to DMA in Soil

Reference	Gradient's Summary of Findings Relevant for MSMA Use
Woolson, E; Aharonson, N; Iadevaia, R. 1982. "Application of the HPLC-Flameless Atomic absorption Method to the Study of Alkyl Arsenical Herbicide Metabolism in Soil." <i>J. Agric. Food Chem</i> 30: 580-584.	This publication briefly describes field data for plots treated with large amounts of MSMA in "low" and "high" treatment level plots (eight annual applications at 11.2 kg/ha and seven annual applications of at 56 kg/ha). The application rates in this study far exceed the amount used according to current label rates. The reported half-life from this study for MAA is 22 days, with DMA and arsenate detected as degradation products. Arsenic recovery rates from soil were highly variable, indicating that soil-bound residues (which could be MAA or other compounds) contribute to the apparent depletion of MAA from soil. Data are poorly described in this study (presented only as a line plot), and do not appear to support this half-life analysis. For example, about half of the applied MAA was <i>extractable</i> from soil and detectable at about 22 days after application for the "low" application rate plot. However, after about two more weeks, the extractable, detectable MAA concentration remained stable for the remainder of the study period described (26 weeks). Thus, the reported half-life was based only on an initial period of active demethylation and sorption to soil and thus, cannot be extrapolated to accurately estimate future metabolism of MAA. Furthermore, the authors present data for extractable, detectable MAA concentrations in their "high" application rate plot, beginning one year after MSMA application. During the 26 weeks (182 days) for which data are plotted, the extractable, detectable MAA concentration decreases, but is not halved, which shows that the 22 day half life estimate is incorrect. Finally, the authors note that MAA apparently forms "insoluble compounds which are not immediately subject to degradation." Based on Gradient's review of the literature (Gradient, 2005), it is likely that these "insoluble compounds," exhibiting low to no bioavailability, are MAA itself or other arsenic compounds sorbed to soil.

Table 2
Studies Addressing MSMA/DSMA Transformation to DMA in Soil

Reference	Gradient's Summary of Findings Relevant for MSMA Use
Akkari, KH; Frans, RE; Lavy, TL. 1986. "Factors Affecting Degradation of MSMA in Soil." <i>Weed Sci.</i> 34:781-787.	In a study that included both field and laboratory components, MSMA was applied to cotton, soybeans, sorghum, and rice, in the field for four years. Applications were made according to "their associated weed control practices" at a rate of 1.7 kg/ha, but the number of applications made is unclear. In the laboratory, MSMA was added to soil to achieve arsenic concentrations of 2 and 5 mg/kg. In aerobic soils, extractable DMA and arsenate concentrations did not change after MSMA application (MAA concentrations not presented). The total arsenic concentration during the first two months after application was elevated by 0.85 mg/kg, but thereafter, arsenic concentrations returned to original levels. In flooded soils, total arsenic, extractable MAA, DMA, and arsenate were comparable to natural background concentrations at all times during the study. Note that the authors calculated degradation rate constants for MSMA based on <i>extractable</i> MAA concentrations, thus some or all MSMA "degradation" is likely sorption. The authors concluded that "MSMA treatments contributed only a small fraction to total soil arsenic...under present recommended use patterns it is highly unlikely that MSMA will accumulate in the environment."
Mid-South Agricultural Research, Inc. and PTRL East, Inc. 1992. "Terrestrial Dissipation of MSMA in Cotton." Prepared for MAA (MSMA/DSMA) Research Task Force Three.	MSMA was applied twice to test plots in the field at a rate of 2 lb/acre over the course of one year. The maximum MSMA concentration was 2.37 mg/kg after the first application. The DMA concentration was 0.14 mg/kg, and was detectable in surface soil only.
Pan-Agricultural Laboratories, Inc.; PTRL East, Inc. 1992. "Terrestrial dissipation of monosodium methanearsonate (MSMA) in California soil." Prepared for MSMA/DSMA Research Task Force Two, c/o Luxembourg Industries (Pamol), Ltd.	MSMA was applied three times to test plots in the field at a rate of 4.95 lb/ha at 3 week intervals. The maximum concentration of extractable MSMA after treatment was 9.44 mg/kg in the top 0-6 inches layer of the soil, and 0.62 mg/kg in the 6-12 inch layer. DMA was only detected in the top 0-6 inches soil, with a maximum concentration of 0.24 mg/kg observed three months after the final MSMA application.

Table 2
Studies Addressing MSMA/DSMA Transformation to DMA in Soil

Reference	Gradient's Summary of Findings Relevant for MSMA Use
PTRL East, Inc.; Atkins, RH. 1994. "Aerobic aquatic metabolism of [¹⁴ C] MSMA." Prepared for MAA Research Task Force Three, c/o ISK Biosciences.	Saturated, aerated soil was cultured in the laboratory for 30 days with ¹⁴ C-MSMA added at a concentration of 5.9 mg/kg. A maximum of 5.1% of the ¹⁴ C was transformed to DMA (occurring on day one of the study), and DMA was detected only in the water phase, suggesting that transformation occurred only to the unbound, bioaccessible MSMA fraction (i.e., the fraction accessible to microbes for metabolism). No pattern of increasing or decreasing transformation to DMA was observed. This is a laboratory study and thus promotes metabolism and reflects a worst case scenario for the possible transformation of MSMA to DMA in the field, as explained in the introduction.
PTRL East, Inc.; Peel, D. 1996. "Aerobic soil metabolism of [14-C] MSMA." Prepared for MAA Research Task Force Three, c/o ISK Biosciences.	Sandy Loam was cultured in the laboratory for 12 months, with ¹⁴ C-MSMA added at a concentration of 6.1 mg/kg. ¹⁴ C disposition observed was 35.1% MAA, 31.9% DMA, 19.4% CO ₂ , 9.7% bound residues, (expressed as percent of ¹⁴ C-MSMA applied). This is a laboratory study and thus promotes metabolism and reflects a worst case scenario for the possible transformation of MSMA to DMA in the field, as explained in the introduction.
PTRL East, Inc.; Peel, D. 1996. "Anaerobic aquatic metabolism of [¹⁴ C] MSMA." Prepared for MAA Research Task Force Three, c/o ISK Biosciences.	Saturated, anaerobic soil was cultured in the laboratory for one year with ¹⁴ C-MSMA added at a concentration of 6.2 mg/kg. The maximum amount of ¹⁴ C-DMA detected was 3% of the applied ¹⁴ C, occurring after six months of incubation. This is a laboratory study and thus promotes metabolism and reflects a worst case scenario for the possible transformation of MSMA to DMA in the field, as explained in the introduction.
Kuhlmeier, PD. 1997. "Partitioning of Arsenic Species in Fine-Grained Soils." <i>J. Air & Waste Management Association</i> . 47: 481-490.	Unknown proportions of MSMA, DSMA, DMA, and TMAO were spilled at least 17 years prior to the study period at the Crystal Chemical Site in Houston, TX. MAA and DMA were both detected in soil (as were arsenate and arsenite). This demonstrates that some or all of the MAA and DMA in soil was stable at least for 17 years. The results of this study are not reliable for drawing conclusions regarding the quantity of MSMA transformed to DMA in soil after herbicide application. However, they indicate that organic arsenicals are stable, and are not completely transformed to inorganic, if at all, even after 17 years.

Table 2
Studies Addressing MSMA/DSMA Transformation to DMA in Soil

Reference	Gradient's Summary of Findings Relevant for MSMA Use
Bednar, AJ; Garbarino, JR; Ranville, JF; and Wildeman, TR. 2002. "Presence of organoarsenicals used in cotton production in agricultural water and soil of the southern United States." <i>J. Agric. Food Chem.</i> 50:7340-7344.	Soil samples were taken from cotton fields where MSMA, DSMA, and/or DMA were reportedly used. Herbicide application rates, as well as application rates for other possible arsenic-containing materials (such as fertilizers, inorganic arsenic pesticides) are unknown. The authors made no conclusions regarding MSMA transformation in soil, because the relative abundance of extractable MAA, DMA, and arsenate in samples was influenced by factors including natural background arsenic concentrations and arsenic sorption to soil. The results of this study are not reliable for drawing conclusions regarding the quantity of MSMA transformed to DMA in soil after application. This was not a controlled study.
Tu, C; Ma, LQ; Zhang, W; Cai, Y; Harris, WG. 2003. "Arsenic species and leachability in the fronds of the hyperaccumulator Chinese brake (<i>Pteris vittata L.</i>)" <i>Environmental Pollution.</i> 124:223-230.	Water was used to extract arsenic compounds from soil that was artificially contaminated with 50 mg/kg arsenic as MAA. A soil subsample was extracted one week after MAA was added to soil, and another subsample was extracted 18 weeks later, after brake ferns were grown in the soil for 18 weeks. The water extraction of the first week removed 10% to 11% of the total arsenic as MAA and about 1% as DMA; the remainder was not detected. In the corresponding week-nineteen soil sample, the water extraction removed 8% to 9% of the total arsenic as arsenate and 1% to 2% as MAA; the remainder was not detected. The species of arsenic bound to soil, not removed in the water extraction, is unknown because it was not analyzed. This is a laboratory study and thus promotes metabolism and reflects a worst case scenario for the possible transformation of MSMA to DMA in the field, as explained in the introduction.

Table 2
Studies Addressing MSMA/DSMA Transformation to DMA in Soil

Reference	Gradient's Summary of Findings Relevant for MSMA Use
<p>Feng, M; Schrlau, JE; Snyder, R; Snyder, GH; Chen, M; Cisar, JL; Cai, Y. 2005. "Arsenic Transport and Transformation Associated with MSMA Application on a Golf Course Green." <i>Ag. Food Chem.</i> 53(9): 3556-3562.</p>	<p>MSMA was applied three times to test plots in the field at a rate of 2.24 kg/ha. DMA was detected in water collected in underground lysimeters beneath treated plots at levels exceeding MAA concentrations. In the three sandy substrates tested, the cumulative mass of DMA detected in subsurface water was 7.4, 13.3 and 25.8 mg/m². The results of this study are not reliable for drawing conclusions regarding the quantity of MSMA transformed to DMA in soil after typical MSMA application, because even though MSMA is not normally used on golf course greens, the test plots simulated golf course greens (designed of 30 cm of soil and 10 cm of coarse drainage material engineered to allow rapid drainage and to promote leaching). The percolated water percolated was collected in stainless steel pans for one to two weeks before removal and analysis. The study's results showing MSMA transformation to DMA and arsenate are likely due to experimental artifact. Soil microorganisms are known to readily, and tenaciously attach to stainless steel, forming an active biofilm capable of metabolizing chemicals, even when substrates are present in only trace amounts.¹ A study (summarized above) illustrates that MAA transformation to DMA appears to occur only in soil pore water or free water contacting soil, and not to compounds bound to soil particles (PTRL East, Inc.; Atkins, RH. 1994) undermining the interpretation of the authors of Feng <i>et al.</i> (2005) that MSMA transformation occurred in the soil. It is likely that MSMA transformation to DMA and arsenate was enhanced in this study by extended sample holding times in buried stainless steel pots.</p>

¹ VanHaecke, E; Remon, JP; Moors, M; Raes, F; DeRudder, D; VanPeteghem, A. 1990. Kinetics of *Pseudomonas aeruginosa* adhesion to 304 and 316-L stainless steel: Role of cell surface hydrophobicity. *App. Environ. Microbiol.* 56:788-795; Stanley, P. 1983. Factors affecting the irreversible attachment of *Pseudomonas aeruginosa* to stainless steel. *Can. J. Microbiol.* 29:1493-1499; Pedersen, K. 1990. Biofilm development on stainless steel and PVC surfaces in drinking water. *Wat. Res.* 24:239-243.

Question 3: *What data are available to demonstrate how rapidly and to what extent DMA, MSMA, and DSMA are converted to inorganic arsenic after applied?*

Response 3:

Gradient has reviewed the literature to obtain data addressing the environmental fate of MSMA, including the rate and extent of MSMA conversion to inorganic arsenic in soil where MSMA use has occurred (Gradient, 2005a). The data from that report, relevant to the rate and extent of MSMA and DMA conversion to inorganic arsenic in soil are summarized in Table 3. The conclusion based on the reviewed literature is that MSMA and DMA are stable compounds that do not break down or undergo transformation spontaneously. The transformation of MSMA and DMA to inorganic arsenic in soil is solely a biologically mediated process, and as such can occur only in the presence of soil microorganisms capable of demethylating organic arsenical compounds, during time periods when MAA or DMA (resulting from the dissociation in water of MSMA, DSMA, or cacodylic acid) is bioaccessible (*i.e.*, accessible to soil microorganisms for metabolism). This time period lasts from immediately after the herbicide application until sorption to soil has occurred. This process can occur only in locations and at times that conditions favor microbial activity. Such conditions include adequate moisture, warm temperatures, and sufficient substrates for microbial activity. Soils that sustain the most favorable conditions are not common. Additionally, the occurrence and extent of these transformations depends on the specific microorganisms that are present in the soil. Because of these required conditions, MAA and DMA transformation to inorganic arsenic, when it occurs, is incomplete, episodic, and variable among locations. This variability is borne out in the results of studies described in Table 3.

The laboratory study conducted by PTRL East and submitted to EPA for MSMA re-registration (see Table 3) shows that about 19% of the radiolabeled carbon from ^{14}C -MSMA applied was evolved during the course of the study. Because laboratory conditions were maintained to be favorable for microbial activity, this is likely a high-end estimate of the proportion of MSMA that could be transformed to inorganic arsenic in field soils. Note also that the evolved $^{14}\text{CO}_2$ represents the aggregate total of ^{14}C evolved from *both* the MAA and the DMA formed in soil after MSMA application, thus, when evaluating the potential accumulation of inorganic arsenic in soil due to MSMA use, a separate assessment of DMA mineralization based on studies where DMA was directly added to soil, is not necessary, *i.e.*, the amounts of MAA and DMA (due to the application of MSMA) that may be transformed to inorganic arsenic are not additive. Furthermore, the aerobic and anaerobic aquatic metabolism studies for MSMA, submitted to EPA for MSMA re-registration (see Table 3), showed negligible ^{14}C evolution in saturated soils incubated with MSMA, providing evidence that inorganic arsenic formation from MAA does not always occur in all soils.

Table 3
Studies Addressing MSMA, DSMA and DMA Transformation to Inorganic Arsenic in Soil

Reference	Gradient's Summary of Findings Relevant for MSMA Use
<p>Von Endt, DW; Kearney, PC; Kaufman, DD. 1968. "Degradation of MSMA by Soil Microorganisms." <i>Ag. Food Chem.</i> 16(1): 17-20</p>	<p>Four soils were incubated in the laboratory with 10 and 100 mg/kg of ¹⁴C-MSMA. Between 1.7% and 10% of radiolabeled carbon from ¹⁴C-MSMA was evolved over 60 days, with most degradation occurring immediately after initial application of MSMA to soil. The extent of ¹⁴CO₂ evolution increased with increasing organic matter content in soil. This is a laboratory study and thus promotes microbial metabolism and reflects a worst case scenario for the possible transformation of MSMA to arsenate in the field, as explained in the introduction.</p>
<p>Dickens, R; Hiltbold, AE. 1967. "Movement and Persistence of Methanearsonates in Soil." <i>Weeds</i> 15:299-304.</p>	<p>Soil samples were amended in the laboratory, with ¹⁴C-DSMA to achieve a concentration of 210 mg/kg MAA (a high concentration relative to labeled application rates), and incubated at 30 °C for 30 days. In clay loam, silt loam, and clay soils, the ¹⁴CO₂ evolution totaled 0.7%, 1.8%, and 5.5% of the ¹⁴C-DSMA applied, with ¹⁴CO₂ evolution decreasing with decreasing soil organic matter content. ¹⁴CO₂ evolution rates decreased dramatically after the first observation, 10 days after ¹⁴C-DSMA addition to soil. In contrast, in a loamy sand soil (87% sand, 5% clay), about 2% of the ¹⁴C-DSMA applied evolved as ¹⁴CO₂ and 16% evolved when the soil was amended with 0.5% weight finely ground ryegrass (provided as an organic carbon-rich amendment). The evolution rate increased sometime after the measurement made, 20 days after ¹⁴C-DSMA addition to soil. The results suggest that the presence of decomposing organic matter and clay both influence the degree to which As-C bond cleavage occurs in soil. Increased organic matter decomposition resulted in a greater extent of As-C cleavage. In the low-clay (5%) soil, MAA applied at the high rate described in this study (210 mg/kg) apparently remained soluble and thus bioaccessible to soil microorganisms, resulting in As-C bond cleavage that continued to occur for a longer period of time than in soils containing more clay (<i>i.e.</i>, 19% to 45% clay) This is a laboratory study and thus promotes microbial metabolism and reflects a worst case scenario for the possible transformation of MSMA to arsenate in the field, as explained in the introduction.</p>

Table 3
Studies Addressing MSMA, DSMA and DMA Transformation to Inorganic Arsenic in Soil

Reference	Gradient's Summary of Findings Relevant for MSMA Use
Woolson, EA; Kearney, PC. 1973. "Persistence and Reactions of ¹⁴ C-Cacodylic Acid in Soils." <i>Environ Sci and Tech.</i> 7: 47-50.	In the laboratory, three soils containing 1, 10, or 100 mg/kg ¹⁴ C-DMA were moistened and incubated for 32 weeks. Total arsenic and ¹⁴ C were measured in soil and in soil extracts. The authors measured ¹⁴ CO ₂ evolution in only one soil type, to which 10,000 mg/kg DMA had been added, and found that after incubating these samples for 98 days, 2% of the applied ¹⁴ C evolved as ¹⁴ CO ₂ in unacclimated soil (<i>i.e.</i> , soil where microbes were not accustomed to contact with DMA), and 13% of the applied ¹⁴ C evolved as ¹⁴ CO ₂ in acclimated soil (<i>i.e.</i> , soil where microbes were accustomed to contact with DMA and thus could have activated metabolic pathways to metabolize it). In other samples where measurements of ¹⁴ CO ₂ were not attempted, the authors qualitatively suggest that ¹⁴ CO ₂ and arsenate were formed, because of the difference between arsenic and ¹⁴ C concentrations detected. The results of this study are not reliable for drawing conclusions regarding the quantity of DMA or MSMA transformed to arsenate in soil after application, because the DMA concentration studied is many orders of magnitude higher than in soils where DMA is used as an herbicide.
Abdelghani A; Anderson A; Englande, AJ; Mason, JW; Dekernion, P. 1977. "Demethylation of MSMA by Soil Microorganisms." In Hemphill DD (ed) <i>Trace Substances in Environmental Health-Part XI.</i> University of Missouri, Columbia, 419-426.	MSMA was added in the laboratory to soil using solutions of 11, 22, and 43 mg/L of ¹⁴ C-MSMA. Soil was submerged under water while humidified compressed air was bubbled into each flask to continuously flush ¹⁴ CO ₂ produced. Three stages of ¹⁴ CO ₂ evolution were noted: a lag stage (no appreciable evolution), an active stage (¹⁴ CO ₂ evolved) and a plateau (no appreciable evolution). The active stage lasted from 4.5 to 7.5 days depending on the initial MSMA concentration. The plateau may be attributable to the sorption of MSMA to the soil matrix, where it becomes inaccessible to microorganisms, as suggested by the authors' note that sorption of MSMA added to soil was not complete at the outset of the study. This is a laboratory study conducted under conditions substantially different than field conditions, and thus is not reliable for predicting the transformation of MSMA to arsenate in the field.

Table 3
Studies Addressing MSMA, DSMA and DMA Transformation to Inorganic Arsenic in Soil

Reference	Gradient's Summary of Findings Relevant for MSMA Use
<p>Woolson, E; Aharonson, N; Iadevaia, R. 1982. "Application of the HPLC-Flameless Atomic absorption Method to the Study of Alkyl Arsenical Herbicide Metabolism in Soil." <i>J. Agric. Food Chem</i> 30: 580-584.</p>	<p>In the laboratory, ¹⁴C-DMA was added to soil to achieve 10 mg/kg total arsenic. In moist soils (at least 77% of field capacity) incubated for 60 days, as much as 45% of the applied ¹⁴C was detected as ¹⁴CO₂. The authors briefly describe field data for plots treated with large amounts of MSMA and DMA in "low" and "high" treatment level plots (eight annual applications at 11.2 and 22.4 kg/ha, respectively, and seven annual applications of at 56 and 112 kg/ha respectively). The reported half-lives from this study for MAA and DMA are 22 and 20 days, with arsenate detected as a degradation product. Arsenic recovery rates from soil were highly variable, indicating that soil-bound residues (which could be MAA, DMA or other compounds) contribute to the apparent depletion of MAA and DMA from soil. Data are poorly described in this study (presented only as a line plot), and do not appear to support this half-life analysis. For example, about half of the applied MAA was extractable from soil and detectable at about 22 days after application for the "low" application rate plot. However, after about two more weeks, the extractable, detectable MAA concentration remained stable for the remainder of the study period described (26 weeks). Thus, the reported half-life was based only on an initial period of active demethylation and sorption to soil, and thus, cannot be extrapolated to accurately estimate future metabolism of MAA. Furthermore, the authors present data for extractable, detectable MAA concentrations in their "high" application rate plot, beginning one year after MSMA application. During the 26 weeks (182 days) for which data are plotted, the extractable, detectable MAA concentration decreases, but is not halved, which shows that the 22-day half-life estimate is incorrect. Finally, the authors note that MAA and DMA apparently form "insoluble compounds which are not immediately subject to degradation." Based on Gradient's review of the literature, it is likely that these "insoluble compounds," exhibiting low to no bioavailability, are arsenic compounds sorbed to soil.</p>

Table 3
Studies Addressing MSMA, DSMA and DMA Transformation to Inorganic Arsenic in Soil

Reference	Gradient's Summary of Findings Relevant for MSMA Use
Akkari, KH; Frans, RE; Lavy, TL. 1986. "Factors Affecting Degradation of MSMA in Soil." <i>Weed Sci.</i> 34:781-787.	In a study that included both field and laboratory components, MSMA was applied to cotton, soybeans, sorghum, and rice, over four years. Applications were made according to "their associated weed control practices" at a rate of 1.7 kg/ha, but the number of applications made is unclear. In the laboratory, MSMA was added to soil to achieve arsenic concentrations of 2 and 5 mg/kg. In aerobic soils, extractable arsenate and DMA concentrations did not change after MSMA application. The total arsenic concentration during the first two months after application was elevated by 0.85 mg/kg, but thereafter, arsenic concentrations returned to original levels. In flooded soils, total arsenic, extractable MAA, DMA, and arsenate were comparable to natural background concentrations at all times during the study. Note that the authors calculated degradation rate constants for MSMA based on <i>extractable</i> MAA concentrations, thus some or all MSMA "degradation" is likely sorption. The authors concluded that "MSMA treatments contributed only a small fraction to total soil arsenic...under present recommended use patterns it is highly unlikely that MSMA will accumulate in the environment.
PTRL East, Inc.; Atkins, RH; Kesterson, A. 1992. "Aerobic soil metabolism of [¹⁴ C] cacodylic acid." Prepared for Luxembourg Industries (PAMOL), Ltd.	Moist sandy loam was cultured in the laboratory at 25 °C with ¹⁴ C-DMA added at a concentration of 12.3 mg/kg. ¹⁴ C disposition did not follow a trend over the course of the 366-day experiment. ¹⁴ CO ₂ accounted for 0.2% or less of the applied ¹⁴ C at all sampling intervals. Up to 9.9% of the applied ¹⁴ C was bound to soil and could not be extracted for chemical analysis. In extracts, ¹⁴ C-DMA predominated, with ¹⁴ C-MAA and lower quantities of unknown ¹⁴ C-compounds detectable in some samples. This is a laboratory study and thus promotes metabolism and reflects a worst case scenario for the possible demethylation of MSMA in the field, as explained in the introduction.
PTRL East, Inc.; Atkins, RH. 1993. "Aerobic aquatic metabolism of [¹⁴ C] Cacodylic Acid." Prepared for Luxembourg-Pamol, Inc.	Saturated, aerated soil was cultured in the laboratory for 30 days at 25 °C with ¹⁴ C-DMA added at a concentration of 12.2 mg/kg, and 0.2% of the applied ¹⁴ C was evolved as ¹⁴ CO ₂ indicating a low level of transformation to arsenate. This is a laboratory study and thus promotes metabolism and reflects a worst case scenario for the possible demethylation of MSMA in the field, as explained in the introduction.

Table 3
Studies Addressing MSMA, DSMA and DMA Transformation to Inorganic Arsenic in Soil

Reference	Gradient's Summary of Findings Relevant for MSMA Use
<p>PTRL East, Inc.; Atkins, RH. 1994. "Aerobic aquatic metabolism of [¹⁴C] MSMA." Prepared for MAA Research Task Force Three, c/o ISK Biosciences.</p>	<p>Saturated, aerated soil was cultured in the laboratory for 30 days at 25 °C with ¹⁴C-MSMA added at a concentration of 5.9 mg/kg. Less than 2% of the applied ¹⁴C was evolved as ¹⁴CO₂ indicating a low level of transformation to arsenate. This is a laboratory study and thus promotes metabolism and reflects a worst case scenario for the possible demethylation of MSMA in the field, as explained in the introduction.</p>
<p>PTRL East, Inc.; Peel, D. 1996. "Aerobic soil metabolism of [¹⁴C] MSMA." Prepared for MAA Research Task Force Three, c/o ISK Biosciences.</p>	<p>Moist sandy loam was cultured in the laboratory at 25 °C with ¹⁴C-MSMA added at a concentration of 6.1 mg/kg. ¹⁴C disposition observed was (expressed as percent of ¹⁴C-MSMA applied): 19.4% CO₂, 31.9% DMA, 9.7% bound residues, 35.1% MAA. This is a laboratory study and thus promotes metabolism and reflects a worst case scenario for the possible demethylation of MSMA in the field, as explained in the introduction.</p>
<p>PTRL East, Inc.; Peel, D. 1996. "Anaerobic aquatic metabolism of [¹⁴C] MSMA." Prepared for MAA Research Task Force Three, c/o ISK Biosciences.</p>	<p>Saturated, anaerobic soil was cultured in the laboratory for one year at 25 °C with ¹⁴C-MSMA added at a concentration of 6.2 mg/kg. Of the applied ¹⁴C, 0.1% was evolved as ¹⁴CO₂ indicating a low level of transformation to arsenate. This is a laboratory study and thus promotes metabolism and reflects a worst case scenario for the possible demethylation of MSMA and DMA in the field.</p>
<p>Gao S; Burau, RG. 1997. "Environmental Factors Affecting Rates of Arsenic Evolution from and Mineralization of Arsenicals in Soil." <i>J. Environ. Qual.</i> 26: 753-763.</p>	<p>Sacramento silty clay was amended in the laboratory, with 100 mg/kg of arsenic as MAA. MSMA application rates, according to labeled instructions, would result in total arsenic concentrations several orders of magnitude lower than the concentration used in this study. In a second part of the study, DMA was added to soil to achieve total arsenic concentrations between 10 and 100 mg/kg. Soils were incubated for 70 days at varied moisture levels and temperatures, and with cellulose amendments. The greatest extent of apparent demethylation occurred in soil containing 100 mg/kg arsenic (added as DMA) and 550 mL of water per kg of soil. In soils containing low levels of DMA, apparent demethylation to inorganic arsenic was greater at higher temperatures, higher water content, and lower cellulose content. This is a laboratory study conducted under conditions substantially different from field conditions, and thus is not reliable for predicting the transformation of MSMA in the field.</p>

Table 3
Studies Addressing MSMA, DSMA and DMA Transformation to Inorganic Arsenic in Soil

Reference	Gradient's Summary of Findings Relevant for MSMA Use
Kuhlmeier, PD. 1997. "Partitioning of Arsenic Species in Fine-Grained Soils." <i>J. Air & Waste Management Association</i> . 47: 481-490.	Unknown proportions of MSMA, DSMA, DMA, and TMAO were spilled at least 17 years prior to the study period at the Crystal Chemical Site in Houston, TX. MAA and DMA were detected in soil (as were arsenate and arsenite). This demonstrates that some or all of the MAA and DMA in soil was stable at least for 17 years. The results of this study are not reliable for drawing conclusions regarding the quantity of MSMA and DMA transformed to arsenate in soil after herbicide application. However, they indicate that organic arsenicals are stable, and are not completely transformed to inorganic arsenic, if at all, even after 17 years.
Bednar, AJ; Garbarino, JR; Ranville, JF; Wildeman, TR. 2002. "Presence of organoarsenicals used in cotton production in agricultural water and soil of the southern United States." <i>J. Agric. Food Chem.</i> 50 :7340-7344.	Soil samples were taken from cotton fields where MSMA, DMA, and/or DMA were reportedly used. Herbicide application rates, as well as application rates for other arsenic-containing materials (<i>e.g.</i> , fertilizers, inorganic arsenical pesticides) are unknown. The authors made no conclusions regarding MSMA and/or DMA transformation in soil, because the relative abundance of extractable MAA, DMA, and arsenate in samples was influenced by factors including natural background arsenic concentrations and arsenic sorption to soil. This was not a controlled study, and its results are not reliable for drawing conclusions regarding the quantity of MSMA or DMA transformed to inorganic arsenic in soil after application.

Table 3
Studies Addressing MSMA, DSMA and DMA Transformation to Inorganic Arsenic in Soil

Reference	Gradient's Summary of Findings Relevant for MSMA Use
<p>Tu, C; Ma, LQ; Zhang, W; Cai, Y; Harris, WG. 2003. "Arsenic species and leachability in the fronds of the hyperaccumulator Chinese brake (<i>Pteris vittata</i> L.)." <i>Environmental Pollution</i>. 124:223-230.</p>	<p>Water was used to extract arsenic compounds from soil that was artificially contaminated with 50 mg/kg arsenic as MAA. The water soluble arsenic that was transformed to arsenate totaled less than 10% of the arsenic added to soil. A soil subsample was extracted one week after MAA was added to soil, and another subsample was extracted 18 weeks later, after brake ferns were grown in the soil for 18 weeks. The first water extraction (one week after MAA or DMA application) removed 10% to 11% of the total arsenic as MAA and about 1% as DMA; the remainder was not detected. In the corresponding week-nineteen soil sample, the water extraction removed 8% to 9% of the total arsenic as arsenate and 1% to 2% as MAA; the remainder was not detected. The species of arsenic bound to soil, not removed in the water extraction, is unknown because it was not analyzed. This is a laboratory study and thus promotes metabolism and reflects a worst case scenario for the possible transformation of MSMA to arsenate in the field.</p>

Table 3
Studies Addressing MSMA, DSMA and DMA Transformation to Inorganic Arsenic in Soil

Reference	Gradient's Summary of Findings Relevant for MSMA Use
<p>Feng, M; Schrlau, JE; Snyder, R; Snyder, GH; Chen, M; Cisar, JL; Cai, Y. 2005. "Arsenic Transport and Transformation Associated with MSMA Application on a Golf Course Green." <i>Ag. Food Chem.</i> 53(9): 3556-3562.</p>	<p>MSMA was applied three times to test plots in the field at a rate of 2.24 kg/ha. Arsenate was detected in water collected in underground lysimeters beneath treated plots at levels exceeding MAA concentrations. In the three sandy substrates tested, the cumulative mass of arsenate detected in subsurface water was 14.1, 19.5 and 19.7 mg/m². The study's results showing MSMA transformation are likely due to experimental artifact. Tests were conducted within buried wooden sidewalls containing a stainless steel pot underlying 30 cm of soil and 10 cm of coarse drainage material to simulate a golf course green. Water percolated through soil was allowed to collect in the stainless steel pans for one to two weeks before removal and analysis. Some soil microorganisms (<i>Pseudomonas</i>) have a superior ability to demethylate MSMA, while others (<i>Aeromonas</i> and <i>Enterobacter</i>) do not demethylate MSMA at all.² <i>Pseudomonas</i> are known to readily, and tenaciously attach to stainless steel (the material used to collect percolate water in this study), forming an active biofilm capable of metabolizing chemicals, even when substrates are present in only trace amounts.³ A study (summarized above) illustrates that MAA transformation to DMA appears to occur only in soil pore water or free water contacting soil, and not to compounds bound to soil particles (PTRL East, Inc.; Atkins, RH. 1994) undermining the interpretation of Feng <i>et al.</i> (2005) that MSMA transformation occurred in the soil. It is likely that MSMA transformation was enhanced in this study by extended sample holding times in buried stainless steel pots.</p>

² Shariatpanahi, M; Anderson, AC; Abdelghani, A. 1981. Microbial demethylation of monosodium methanearsonate. In *Trace Substances in Environmental Health-Part X* (Ed: D.D. Hemphill), University of Missouri, Columbia, pp. 383-387.

³ VanHaecke, E; Remon, JP; Moors, M; Raes, F; DeRudder, D; VanPeteghem, A. 1990. Kinetics of *Pseudomonas aeruginosa* adhesion to 304 and 316-L stainless steel: Role of cell surface hydrophobicity. *App. Environ. Microbiol.* 56:788-795; Stanley, P. 1983. Factors affecting the irreversible attachment of *Pseudomonas aeruginosa* to stainless steel. *Can. J. Microbiol.* 29:1493-1499; Pedersen, K. 1990. Biofilm development on stainless steel and PVC surfaces in drinking water. *Wat. Res.* 24:239-243.

Table 3
Studies Addressing MSMA, DSMA and DMA Transformation to Inorganic Arsenic in Soil

Reference	Gradient's Summary of Findings Relevant for MSMA Use
Sarkar, D; Datta, R; Sharma, S. 2005. "Fate and bioavailability of arsenic in organo-arsenical pesticide-applied soils. Part-I. Incubation study." <i>Chemosphere</i> 60: 188-195.	In the laboratory, two Florida soils were amended with DMA to achieve concentrations of 45, 225, and 450 mg/kg. Soil partitioning and bioavailability of DMA were evaluated in soil subsamples using several different chemical extractants. Soils were extracted immediately after DMA addition and after four months of aging. The authors inferred the generation of inorganic arsenic based on the observation that in the month four sampling event, a larger portion of the total arsenic detected in extracts was present in the extractants representing the operationally-defined "iron- and aluminum-bound phase" and the "calcium- and magnesium-bound phase" compared to the results of the sampling event that occurred immediately after DMA addition. This conclusion is flawed, because there was no measurement of the arsenic form in soil and no reason to believe that DMA was not the species measured in the extractants. Changes to the portions of total arsenic in each extractant were more likely due to slow equilibration between soluble DMA and soil. The conclusions of this study regarding the transformation of DMA are not supported by the data generated in the study, and its results are not reliable for drawing conclusions regarding the quantity of DMA transformed to inorganic arsenic in soil after application.

Question 4: *As estimated in the draft environmental fate chapter, at the maximum use rates - assuming no redistribution, transformation, or recycling - the regulatory total arsenic limit in soil (43 ppm) theoretically would be exceeded in approximately 30 years for cotton and approximately 3 years for citrus.*

- a. What dispersal or dissipative pathways into other environmental compartments may prevent this from happening?*
- b. Should the soil become saturated (i.e., unable retain organic arsenic herbicides or their by-products), what effect will this have on the environmental fate and redistribution of arsenic species?*
- c. Should the soil become saturated, to what extent is there increased potential for offsite movement into drinking water sources and increased potential for human exposure through contact?*

Response 4:

This question refers to the text in the draft environmental fate chapter that addresses the regulatory total arsenic limit in soil, as follows,

"Currently, the Agency has a limit of 43 parts per million of total arsenic in soil as the concentration beyond which remediation is necessary (for example, at Superfund sites impacted by various sources of arsenic and currently on The American University campus in Washington, DC, where World War I chemical warfare agents containing the poisonous gas lewisite (ClCHCHAsCl₂) were tested and disposed)."

The text quoted above from the draft environmental fate chapter appears to adopt the view that the residential EPA Region III Risk-Based Concentration (RBC) in soil for arsenic, adjusted from an excess cancer risk of 10⁻⁶ (corresponding to 0.4 mg/kg) to an excess cancer risk of 10⁻⁴ (corresponding to 43 mg/kg) applies as a ceiling concentration of arsenic in soil above which remediation is necessary.⁴

The regulatory soil arsenic "limit" of 43 mg/kg, described in the draft environmental fate chapter, is calculated based on an excess cancer risk of 10⁻⁴ for a specific set of conservative assumptions that regarding the manner in which a resident is exposed to soil. Some of these assumptions, which are described in EPA's RBC Technical Background Information (US EPA, 2003), are not supported by recent scientific literature and lead to an exaggeration of risk.

⁴ An excess cancer risk of 10⁻⁶ is the low end of the range of risks where US EPA uses its discretion to decide if remediation is necessary. An excess cancer risk of 10⁻⁴ is the high end of that range. (US EPA, 1990; US EPA, 2002)

Gradient has calculated an alternative target level for arsenic, using assumptions that are more scientifically supportable, and are based on a more recent scientific evidence.

One of the assumptions EPA used to develop the RBC is that arsenic in soil is 100% bioavailable. However, a large number of *in vitro* and animal *in vivo* studies indicate that only a fraction of soil arsenic is bioavailable. Using a wide range of soil types and arsenic concentrations, these studies collectively show that the bioavailability of arsenic in soil generally ranges between 3% and 40% (Groen *et al.*, 1994; Rodriguez *et al.*, 1999; Roberts *et al.* 2002). Additionally, there is regulatory precedent for using a bioavailability for arsenic less than 100%. Just recently, the Florida Department of Environmental Protection (FDEP) has determined that a default bioavailability for arsenic of 33% should be used to derive the Department's Soil Cleanup Target Levels for arsenic (FDEP, 2004) based on the results of an *in vivo* study in which between 11% and 25% of the arsenic in soil was bioavailable to primates in five soil samples (Roberts *et al.*, 2002). Based on the available information, for our example calculation (Table 4-1) we adopted the FDEP bioavailability value of 33% as a plausible, conservative estimate for arsenic in soil.

Table 4-1
Alternative Assumptions in Derivation of Risk-Based Limits for Arsenic in Soil

Inputs	EPA Default Parameters	Alternative Conservative Parameters
Adult weight	70 kg	70 kg
Child weight	15 kg	15 kg
Exposure duration adult	24 years	24 years
Exposure duration child	6 years	6 years
Exposure frequency	350 day	350 days
Averaging time	70 years	70 years
Adult soil ingestion rate	100 mg	50 mg
Child ingestion rate	200 mg	100 mg
Bioavailability	100%	33%
Cancer slope factor	1.5	1.5

Soil ingestion rates used to calculate the residential RBCs are also overestimated. The default soil ingestion rates of 200 mg/day for children and 100 mg/day for adults are based on older studies with questionable underlying methodologies. More recent studies indicate that the 95th percentile soil ingestion rate is 100 mg/day for children (Stanek and Calabrese 2000; Stanek *et al.*, 2001) and 50 mg/day for adults (Stanek *et al.* 1997). For example, in children, estimates of the 95th percentile soil ingestion rate from Stanek and Calabrese (2000) range from 106 to 133 mg/day, depending on the time period over which the estimate applies; and the 95th percentile soil ingestion rate from Stanek *et al.* (2001) is 91 mg/day. These more recent studies are authored by the same researchers that EPA cites for their higher estimates of soil ingestion rates

in risk assessment guidance (e.g., US EPA 1996). The results of these newer studies by the same authors should supersede the older results.

Table 4-1 provides a comparison between EPA default parameters used to calculate RBCs for arsenic and alternative values that we believe are more appropriate, while still conservative and health protective, based on current scientific understanding of these issues.

Gradient re-calculated the residential RBC in soil for arsenic, using the alternative values for arsenic bioavailability and soil ingestion rates in Table 4-1 and a target risk of 10^{-4} , while leaving all other parameters equal to EPA generic default values. The calculation yields a revised value of 258 mg/kg.⁵ This value better reflects the current understanding of arsenic bioavailability and soil ingestion patterns among children and adults. Using EPA's assumption that 30 years are needed to reach a level of 43 mg/kg arsenic in soil following regular use of MSMA and assuming that this estimate can be scaled linearly, then 258 mg/kg of arsenic will be reached after ca. 180 years. These calculations use an inorganic arsenic-specific toxicity factor (i.e., the cancer slope factor in Table 4-1). Thus, the results are relevant to inorganic arsenic. However, it is inappropriate to consider inorganic arsenic and MSMA toxicologically equivalent, or to assume that MSMA is completely transformed in the environment to inorganic arsenic.

In the case of inorganic arsenic (As_i^V and As_i^{III}), most of the compound in the blood penetrates the cells and undergoes oxidative methylation followed by reduction (Lerman *et al.*, 1983; Georis *et al.*, 1990). Metabolism of inorganic arsenic is relatively efficient in humans, with most ingested inorganic arsenic methylated to DMA^V . Typically, urinary arsenic in exposed humans consists of 10-20% inorganic arsenic, 10-20% MMA, and 60-80% DMA (Vahter, 1994), indicating extensive inorganic arsenic metabolism through the above sequence of events.

In contrast, in the case of the organic arsenicals, in humans and most other mammals, most of the compounds are excreted from the blood through the urine, and only a very small portion is metabolized (Buchet *et al.*, 1981; Vahter and Marafante, 1983; Marafante *et al.*, 1987; Jaghabir *et al.*, 1991). The mechanisms by which MMA^V and DMA^V are rapidly excreted unchanged are relatively well characterized. Both species are poorly taken up into cells (Styblo

⁵ Calculations used to obtain this result, shown below, follow guidance from USEPA (2003) with the exceptions noted in Table 4-1. If US EPA default parameters were used, the result of the calculation below would be 43 mg/kg.

$$\text{Lifetime Soil Ingestion} = \frac{50 \frac{\text{mg}}{\text{d}} \times 24 \text{ yr}}{70 \text{ kg}} + \frac{100 \frac{\text{mg}}{\text{d}} \times 6 \text{ yr}}{15 \text{ kg}} = 57 \frac{\text{mg} \cdot \text{yr}}{\text{kg} \cdot \text{d}}$$

$$\text{Concentration} = \frac{10^{-4} \times 70 \text{ yr} \times 365 \frac{\text{d}}{\text{yr}}}{10^{-6} \frac{\text{kg}}{\text{mg}} \times 350 \frac{\text{d}}{\text{yr}} \times 0.33 \times 1.5 \left(\frac{\text{mg}}{\text{kg} \cdot \text{d}} \right)^{-1} \times 57 \frac{\text{mg} \cdot \text{yr}}{\text{kg} \cdot \text{d}}} = 258 \frac{\text{mg}}{\text{kg}}$$

et al., 1999; Styblo *et al.*, 2000; Shiobara *et al.*, 2001). Furthermore, MMA^V has a low affinity for the enzyme that reduces it to the trivalent species (Zakharyan *et al.*, 1999).

The difference between the metabolism of organic compounds and that of inorganic is important because highly toxic trivalent organic arsenic compounds (*i.e.*, MAA^{III} and DMA^{III}) are generated intracellularly as metabolic intermediates during the process (*e.g.*, Cohen *et al.*, 2002; Vega *et al.*, 2001; Kitchin *et al.*, 2003). Organic arsenic compounds are not well metabolized and do not produce any significant amounts of the toxic trivalent intermediates, which are, incidentally, very unstable in the environment.

Thus, it is inappropriate to consider inorganic arsenic and MSMA toxicologically equivalent, or to assume that MSMA is completely transformed in the environment to inorganic arsenic. Considering that no more than 20% of MSMA is ever transformed to inorganic arsenic, then it will be at least 900 years before the level of inorganic arsenic in soil would be 258 mg/kg. This idea is also expressed in EPA's draft environmental fate chapter for MSMA, as follows:

"Furthermore, it must be remembered that total arsenic is only a crude measure of potential toxicity. Ideally and logically, toxicity should be based on the specific kinds and proportions of arsenic moieties. Whenever arsenic concentrations are elevated above local background, to speciate is common sense." (*Transformation by Microbes* Section).

For example, MSMA has unique chemical and toxicological properties that make it much less toxic than inorganic arsenic (see, for example, Section 5.3 of Gradient, 2005a).

To the extent that MSMA is converted to inorganic arsenic in soil, the calculations listed in Table 4-2 are useful. If transformation of MSMA to inorganic arsenic in soil occurs, it occurs to varying extents in different soils, depending on local conditions. The studies cited in the response to Question 3 suggest that the fraction of applied MSMA that could be transformed would not exceed 20%. Thus, MSMA application may contribute to total arsenic in soil, but arsenic in the form of MAA and DMA could be present at substantially higher concentrations than the regulatory limit of 43 mg/kg (or 258 mg/kg) without posing an unacceptable risk.

The following exercise shows an example risk calculation for MSMA and its potential metabolites (*i.e.*, DMA and arsenate) in the specific case of golf course soil. The calculation demonstrates the difference in risk given equal concentrations of MAA, DMA, or inorganic arsenic in soil.

Example Risk Calculation (from Gradient 2005a)

We calculated the incidental exposures to arsenic compounds in soil at golf courses, for two scenarios: (1) an adult golf course groundskeeper who spends a 30-year career at a golf course, and (2) a resident living for six years as a child and 24 additional years as an adult on land formerly used as a golf course. These scenarios, particularly the residential scenario, are commonly used in standard human health risk assessment performed for and by EPA and U.S. states. Exposure due to contact with soil from the playing areas of golf courses, where agrochemicals, including MSMA, may have been routinely applied, was evaluated by calculating ingestion and dermal absorption exposures of compounds from soil. Exposure *via* inhalation is shown in Appendix B of Gradient 2005a to be negligible relative to ingestion and dermal absorption *via* soil and thus was not included in the exposure calculations.

To estimate the reasonable worst-case concentration of arsenic compounds (expressed as total arsenic) in surface soil at Florida golf courses, data from two reports were reviewed, and the most conservative data from those reports were used (DERM, 2002; FDEP, 2002). These two reports include data that are not reflective of arsenic concentrations or arsenic speciation due solely from MSMA use, and thus are exaggerated, because other arsenic containing products were used at the golf courses investigated, application rates of MSMA and other arsenic-containing agrochemical were not fully documented at these golf courses, and background arsenic concentrations were not subtracted from arsenic levels measured in soil. For that reason, the data from these reports are not appropriate for regulatory use or decision making regarding MSMA (See Gradient, 2004; 2005b). However, because the data are exaggerated, they are appropriate for use in this conservative, illustrative calculation.

In these two reports, total arsenic measurements in soil from eight different golf courses in Florida were described. The total arsenic measurements in soil represent an aggregate sum of arsenic atoms in all compounds containing arsenic, originating from all arsenic sources in soil. Gradient used total arsenic concentrations measured at the Plantation Golf Club in the illustrative exposure calculations, representing the maximum average value reported for any of the eight golf courses included in these reports (DERM, 2002; FDEP, 2002). Nevertheless, this value is not an estimate of exposure to arsenic compounds due to the use of MSMA, because natural background arsenic and arsenic contributions from other human sources, such as the historic use of inorganic arsenical pesticides (*e.g.*, lead arsenate) and arsenic-containing fertilizers, are combined with any total arsenic contributed to soil by MSMA. Furthermore, any exposure to arsenic-containing compounds that result from MSMA use occurs in locations where other potential arsenic sources may also exist, so in the absence of MSMA-specific concentration data in soil, it is appropriate to estimate the total dose of arsenic-containing compounds from all sources in soil as a conservative (overestimate) of the health implications due to MSMA use. Because we consider all arsenic sources in this calculation, health implications are assessed as if

all arsenic in soil was all MAA, all DMA, or all inorganic arsenic, when in reality, a mixture of these compounds would exist. This approach is superior to using labeled application rates to estimate the concentration of arsenic compounds in soil due to MSMA use, because it is an actual experimental value rather than a theoretical calculated one, which would require making assumptions regarding soil properties (*e.g.*, bulk density) and the depth of soil through which MSMA migrates.

This calculation considers the three most common arsenic-containing compounds that may theoretically be present in soil following the use of MSMA: MAA, DMA, and inorganic arsenic. The results are shown in Table 4-2, while the details of the calculations are presented in Appendix A.

In summary, total arsenic concentrations at a "worst-case" golf course (*i.e.*, highest average arsenic concentration in surface soil) where MSMA was reportedly used for many years, are low relative to results of human epidemiological studies with inorganic arsenic and to mammalian no-effects levels demonstrated in laboratory studies with MAA and DMA. The predominant fate of MAA from MSMA in soil – binding to surface soil with the possibility of some biologically-mediated transformation of a portion of MAA to DMA and/or inorganic arsenic – suggests that a combination of MAA, DMA, and inorganic arsenic might result in surface soil from the use of MSMA rather than 100% MAA, DMA, or inorganic arsenic, as was assumed for these illustrative calculations. However, because conservatively estimated doses of all three of these arsenic compounds are less than levels likely to be of human health concern, then any mixture of the three compounds that combine to form the same total arsenic concentration will also not constitute a human health concern. Thus, the calculations and comparisons in this Section indicate that the combination of MAA and some DMA and/or inorganic arsenic in soil due to long-term use of MSMA is not a human health concern.

**Table 4-2
Comparison of Estimated Intake with No Adverse Effects Levels
Assuming Soil Contains 100% MAA, DMA, or Inorganic Arsenic**

Scenario	Compound	Endpoint	Estimated Arsenic Intake from Soil [mg/(kg d)]	NOAEL [mg/(kg d)]	Comparison between Intake and NOAEL
Resident	MAA	Cancer	Not relevant – not a carcinogen	Not a carcinogen	Not relevant – not a carcinogen
		Non-cancer	2.0×10^{-5}	2	Intake 100,000-fold less than NOAEL
	DMA	Cancer	8.7×10^{-6}	1.6 ^[a]	Intake 180,000-fold less than NOAEL
		Non-cancer	2.0×10^{-5}	0.14	Intake 7,000-fold less than NOAEL
	Inorganic Arsenic	Cancer	8.1×10^{-6}	N/A ^[b]	Risk is 1.2×10^{-5} ; <i>i.e.</i> , in acceptable range ^[a]
		Non-cancer	1.9×10^{-5}	0.0008	Intake 42-fold less than NOAEL
Groundskeeper	MAA	Cancer	Not relevant – not a carcinogen	Not a carcinogen	Not relevant – not a carcinogen
		Non-cancer	1.3×10^{-5}	2	Intake 150,000-fold less than NOAEL
	DMA	Cancer	5.7×10^{-6}	1.6 ^[a]	Intake 280,000-fold less than NOAEL
		Non-cancer	1.3×10^{-5}	0.14	Intake 11,000-fold less than NOAEL
	Inorganic Arsenic	Cancer	5.2×10^{-6}	N/A ^[a]	Risk: 7.8×10^{-6} ; <i>i.e.</i> , in acceptable range ^[a]
		Non-cancer	1.2×10^{-5}	0.0008	Intake 67-fold less than NOAEL

Notes:

N/A indicates that this value is not applicable for the compound.

[a] The drinking water margin of exposure (MOE) calculation presented later in this submission adopts NOAELs of 0.73 and 0.79 mg/(kg d), which are conservatively based on the endpoint of pre-neoplastic changes in the rat bladder, which occurred at a lower concentration (3.2 mg/(kg d)) than did bladder tumors (8 mg/(kg d)) (Life Science Research, 1989). The calculation in this document is reproduced from Gradient (2005a) and relies on a slightly different approach for establishing a NOAEL. If the minimum NOAEL value from the MOE calculation were substituted here, the exposure for the resident would be 84,000-fold less than the NOAEL, and the exposure for the groundskeeper would be 128,000-fold less than the NOAEL.

[b] Inorganic arsenic is considered by EPA to be a non-threshold carcinogen, so a cancer slope factor (CSF) is used to evaluate risk rather than a NOAEL. EPA's CSF for inorganic arsenic is $1.5 \text{ (mg/(kg d))}^{-1}$ which, when multiplied by the arsenic intake, results in the incremental cancer risk listed in the "Comparison" column. EPA's acceptable risk range is 10^{-6} to 10^{-4} .

Finally, there are Superfund sites where arsenic concentrations exceeding 43 mg/kg in soil were allowed to remain. Examples of cleanup levels for inorganic arsenic in soil described in Records of Decision (RODs) that exceed 43 mg/kg include (see also Valberg *et al.*, 1997):

- National Zinc Site, Oklahoma – 60 mg/kg arsenic cleanup level for residential and recreational areas, 600 mg/kg for commercial and industrial areas
- Crystal Chemical, Texas – 300 mg/kg arsenic cleanup level based primarily on human health effects for residential and commercial/industrial uses
- Old Works East Anaconda Development Area Site, Montana – 500 mg/kg arsenic cleanup level for occupational use, and 1,000 mg/kg for recreational use
- Selma Treating, California – 50 mg/kg arsenic cleanup level for workers
- Cape Fear Wood Preserving, North Carolina – 94 mg/kg arsenic cleanup level for workers

This demonstrates that, in contrast with the statement from the draft environmental fate chapter, remediation of soils where the total arsenic content exceeds 43 mg/kg is not necessarily required by EPA. The 60 mg/kg *residential* cleanup goal at the National Zinc Site, and the 300 mg/kg arsenic cleanup level based primarily on human health effects for residential and commercial/industrial uses at Crystal Chemical, Texas, particularly provides evidence that the 43 mg/kg value is not seen by EPA as a limit "beyond which remediation is necessary."

In conclusion, EPA recognizes that a range of arsenic concentrations in soil does not pose unacceptable health risks, and that range extends to values well above 43 mg/kg. The range of acceptable values adopted at different sites is based in part on differences in the way that exposure is considered at those sites. The exposure parameters on which the 43 mg/kg value is based include three values (i.e., bioavailability, children's soil ingestion, and adults' soil ingestion) that are outdated, and result in an overestimation of risk. Updating these parameters results in an inorganic arsenic limit of 258 mg/kg in soil. When one considers that this value applies to inorganic arsenic and not MAA or DMA, which are both less toxic than inorganic arsenic, then an "arsenic from MSMA" limit would exceed 258 mg/kg, because arsenic in soil due to MSMA use would consist of a mixture of MAA, DMA, and inorganic arsenic. When the herbicide MSMA reaches soil, only a fraction of the applied mass is expected to be transformed to DMA and/or inorganic arsenic (see Response 2 and 3 and Gradient, 2005a). Thus applying a regulatory arsenic limit of 43 mg/kg, or even the updated, less conservative limit of 258 mg/kg

for MSMA is inappropriate, because the value is based on toxicological data for inorganic arsenic and applies only if 100% of the arsenic in soil is inorganic.

Response 4a, 4b, and 4c:

Subparts (a), (b), and (c) of Question 4 concern the possibility that arsenic compounds present in soil due to the use of MSMA may become mobile and be transported into other environmental compartments.

Question 4a asks whether arsenic from MSMA might be transported from soil to other environmental compartments to prevent the regulatory limit from being exceeded. The discussion above, addressing the appropriateness of the 43 mg/kg limit, bears directly on the response to this question. Specifically, no dispersion of arsenic from soil is necessary to avoid exceeding an appropriate risk-based arsenic limit in soil. For example, the question states that 30 years would be required for the total arsenic concentration in soil to exceed 43 mg/kg at the application rate for cotton. The updated and more appropriate inorganic arsenic limit of 258 mg/kg, calculated above, is six times greater, so the duration needed to exceed that limit likely would be approximately six times longer (*i.e.*, about 180 years). (Citrus is no longer a labeled use for MSMA, so that application rate is not relevant.) Furthermore, far more years of MSMA application than 180 would be required before unacceptable health risks would result due to the mixture of MAA, DMA, and inorganic arsenic that most likely occurs in soil after MSMA application. Thus, it is unnecessary to consider potential arsenic sinks (*e.g.*, leaching to deeper soils or groundwater, or volatilization) in addition to surface soil. Typically, MSMA is bound strongly to soil particles in the top layer of the soil and expected to remain predominantly in the top six to twelve inches of soil. Only in soil containing a very low clay and organic matter content, MSMA may leach from the surface to deeper layers (Gradient, 2005a).

Questions 4b and 4c concern the possibility that soils may become saturated with MSMA or its metabolites. Soils contain a finite capacity for binding sorbates such as MAA, DMA, and arsenate (collectively "MSMA and its metabolites"). The capacity varies widely among soils, and the concentration corresponding to "saturated" cannot be generalized. If a soil's sorption capacity were exceeded, then water from precipitation or irrigation would advectively carry any added MSMA into deeper soil, until reaching soil unsaturated with respect to arsenic binding sites. When unsaturated soil was encountered, MSMA and its metabolites would bind to those deeper soils.

If surface soils were to become saturated with MSMA and its metabolites, those compounds would travel to deeper soils where sorption will retain the compounds. In conditions where groundwater is sufficiently shallow and soil sufficiently lacking in sorption capacity then

MSMA and its possible metabolites may migrate to groundwater. In such conditions, arsenic compounds are diluted in groundwater, and may also equilibrate with arsenic binding sites in the saturated zone, thus exiting groundwater. It should be emphasized though, that the binding propensity of MSMA is relatively high, thus, if conditions are such that MSMA cannot be bound to the soil, *any* plant protection chemical, including other pesticides and fertilizers, are also likely to migrate to groundwater. It is anticipated, based on combination of the clay content of U.S. soils (Figure 1) and the depth to groundwater, that saturation of soil would not occur to the extent that migration to groundwater would result due to the regular use of MSMA, except potentially in some areas of South Florida, where geographical conditions represents a unique combination of an extremely shallow water table (typically less than 10 feet) and very low-clay soil (Figure 1) making that region unusually susceptible to saturation of soil sorption sites due to any substances applied to soil. However, even in South Florida, where MSMA has been in use, this situation has not been demonstrated to occur. Other areas of the country are unlikely to experience migration of MSMA and its metabolites to groundwater at detectable levels.

Question 4c concerns the possibility for increased human exposure potential through contact with soils saturated with MSMA and/or its metabolites. The fact that a soil is saturated with MSMA will not increase the level of exposure. First, as discussed previously, MSMA and its metabolites are soluble in water, and in saturated soil, they would leach to the deeper layers and bind there, thus there would be no "excess" MSMA or its metabolites available for exposure in a saturated soil.⁶ Second, bioavailability⁷ of chemicals in soil is dependent on a number of factors, many of which are independent of the saturation limit, including chemical form, solubility, particle size of the ingested soil, soil type, and nutritional status of the individual (*e.g.*, Ruby *et al.*, 1993). Roberts *et al.* (2002) calculated the oral bioavailability of arsenic in soil as 25% or less based on primates' ingestion of five Florida soils that had been treated with inorganic compounds of arsenic. The alternative "regulatory limit" applicable to inorganic arsenic calculated earlier in this response (*i.e.*, 258 mg/kg) is based on a 33% oral bioavailability value, which is likely operable even in soils saturated with MSMA and its metabolites, given the likelihood that some of the soils used in the Roberts *et al.* (2002) study were saturated or nearly saturated with arsenic, based on the arsenic concentrations in soil and the soils' origins (*i.e.*, Florida, where low clay soils are common). Furthermore, the dermal bioavailability of MAA and DMA as well as that of inorganic arsenic (around 3%) is much lower than the oral bioavailability (see Section A.2 in Appendix A). Dermal absorption of MSMA and its metabolites from saturated soil are insignificant relative to ingestion, because MAA, DMA, and arsenate are all anions at circumneutral pH, and charged species are poorly absorbed through skin unless there is

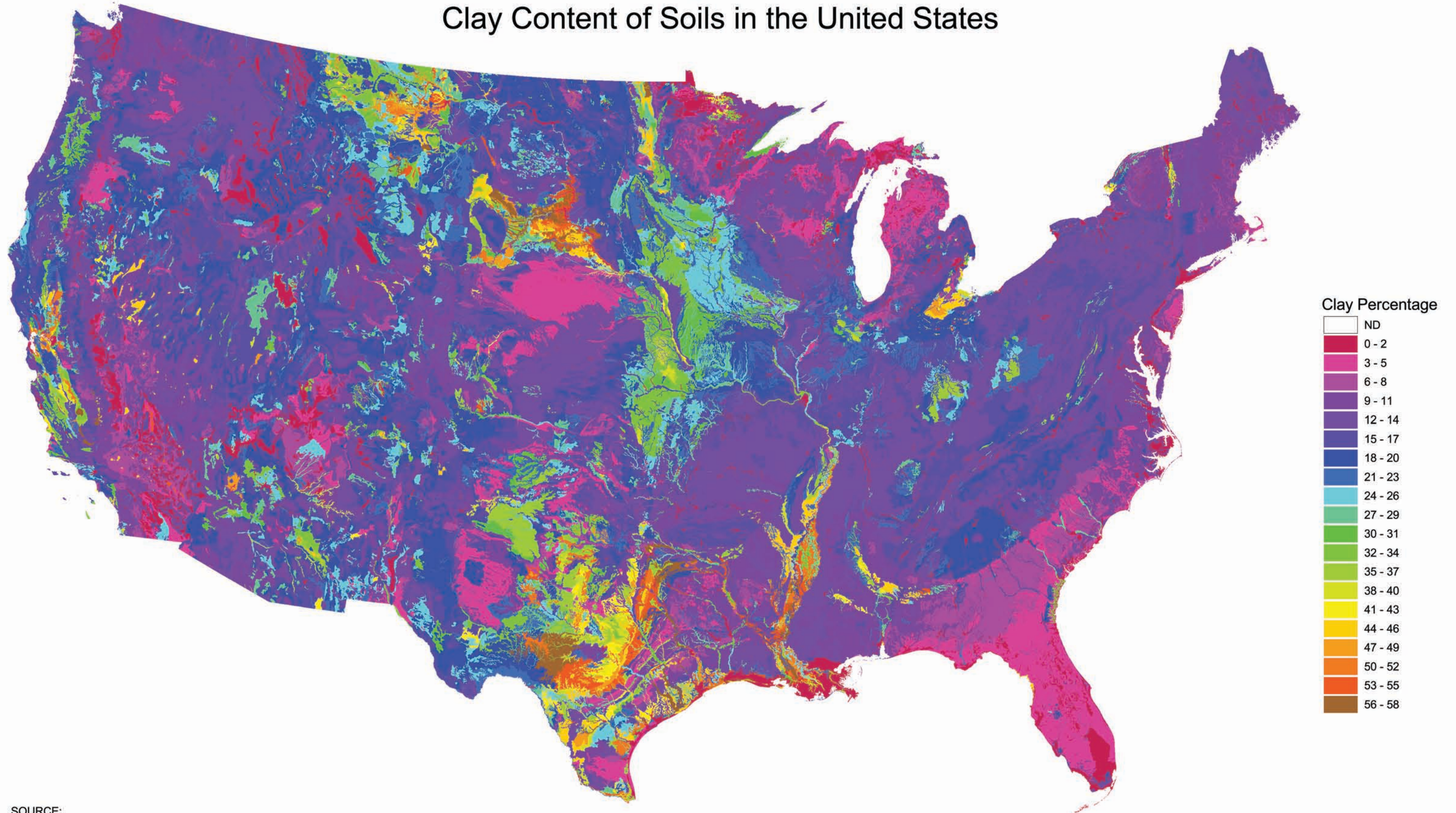
⁶ When assessing risk, exposure to a chemical in soil is characterized by the concentration of that chemical in the soil that comes into contact with humans, and saturation is not considered (*e.g.*, US EPA 1996; 2003). Whether a soil is saturated or not, the measured concentration of MSMA and its possible metabolites in soil describe the amount of exposure that can occur.

⁷ When assessing risk, the human exposure to a chemical that would be predicted using the chemical's concentration in soil can be modified by considering bioavailability.

an active transport mechanism to aid its absorption (*e.g.*, Drexler *et al.*, 2003). In summary, saturation of soil with organic compounds of arsenic will not change the low bioavailability of these compounds. The amount that may enter the bloodstream will be mostly excreted unmetabolized through urine.

In conclusion, MSMA binds to soils strongly compared to many other pesticides. In soils where MSMA does not bind well, it is likely that most other plant protection chemicals would also leach into groundwater, thus such areas are not appropriate for agriculture.

Figure 1
Clay Content of Soils in the United States



SOURCE:
United States Department of Agriculture - Natural Resources Conservation Service,
Data Resources, http://www.ftw.nrcs.usda.gov/soils_data.html

- Question 5:**
- a What data are available for estimating the partitioning of arsenic species between soil and water?*
 - b How would the MAATF select effective soil to water sorption coefficients in various soils/sediments in order to estimate potential drinking water exposure concentrations due to runoff/erosion and leaching?*

Response 5a:

The literature review presented in Gradient’s report, "The Environmental Fate of Monosodium Methanearsonate (MSMA): A Review of Important Processes" (Gradient, 2005a) contains data allowing the estimation of soil partitioning of arsenic species in soil where MSMA use has occurred. The data relevant to this question from the studies reviewed in that report, as well as additional studies from a more recent literature search, addressing the partitioning of arsenic species between soil and water, are summarized in Table 5-1.

**Table 5-1
Studies Addressing Partitioning of Arsenic Species between Soil and Water**

Reference	Gradient's Summary of Findings Relevant for MSMA Use
Ehman, PJ. 1965 "Effect of arsenical build-up in the soil on subsequent growth and residue content of crops." <i>Proc. S. Weed Conf.</i> 18:685-687.	This study showed that when DSMA was added in the laboratory to the top of one-foot-thick soil samples, the addition of 60 inches of rain extracted 9% of the MAA ⁸ from sandy soils, and 6% of the MAA from clay soils.

⁸ Like with MSMA, MAA is formed from the addition of moisture to DSMA.

Table 5-1
Studies Addressing Partitioning of Arsenic Species between Soil and Water

Reference	Gradient's Summary of Findings Relevant for MSMA Use
Dickens, R; Hiltbold, AE. 1967. "Movement and Persistence of Methanearsonates in Soil." <i>Weeds</i> 15:299-304.	<p>This laboratory study addressed DSMA sorption to four Alabama soils, to sand, silt, and clay fractions of one soil, and to four clay minerals. In column studies, two soils were packed in separate nine-inch deep columns. DSMA was added at a rate equivalent to 100 lb/acre (a rate much higher than the labeled rate), allowed to equilibrate for 1.5 days and leached with the equivalent of 20 inches of rainfall (approximately seven pore volumes). No arsenic was detected in leachate from the column containing clay loam. Almost 50% of the arsenic attributed to DSMA was detected in the top one inch of the clay loam column, and no arsenic was detected deeper than six inches at the conclusion of the experiment. Arsenic attributed to DSMA eluted from the column containing loamy sand within one pore volume, with a maximum concentration of about 8 mg/L occurring in the second pore volume eluted, and rapidly decreasing thereafter to 0.7 mg/L in the last (approximately seventh) pore volume. No data on the final arsenic concentrations in the loamy sand column were provided. In batch studies, soil, soil fractions, and clays were shaken five hours in a 1:25 solid:solution ratio mixture containing DSMA solutions of 6.5 mg arsenic/L (for soils) or 5.0 mg arsenic/L (for soil fractions and clay). The sand, silt, and clay fractions of soil retained 12%, 11%, and 100% of the arsenic applied, respectively. The clay minerals montmorillonite, vermiculite, kaolinite, and limonite retained 12%, 26%, 76%, and 100% of the arsenic applied, respectively. The loamy sand, clay loam, silt loam, and clay retained 8%, 27%, 34% and 50% of the arsenic applied, respectively. This corresponds to arsenic concentrations in soil at saturation (under the study conditions) of 12.5 mg/kg, 44.1 mg/kg, 55.8 mg/kg, and 81.5 mg/kg, respectively. As a point of reference, the soil containing 44.1 mg/kg arsenic in the batch study is the same soil that retained 100% of the DSMA applied (at 100 lb/acre) in the top six inches in the column study. The soil containing 12.5 mg/kg arsenic in the batch study is the same soil through which arsenic leached (nine-inches) in the column study. These results show that batch laboratory studies are not reliable, because even when arsenic mobility is low in column- and field studies, a batch laboratory study with the same soil indicates a relatively low arsenic binding capacity.</p>

**Table 5-1
Studies Addressing Partitioning of Arsenic Species between Soil and Water**

Reference	Gradient's Summary of Findings Relevant for MSMA Use
Hiltbold, AE; Hajek, BF; Buchanan, GA. 1974. "Distribution of arsenic in soil profiles after repeated applications of MSMA." <i>Weed Sci.</i> 22:272-275.	Batch and column sorption studies on several horizons of three Alabama soils (a loamy sand, a fine sandy loam, and a silt loam) were conducted in the laboratory. In batch studies, soil samples were shaken overnight at a 1:1 soil:solution ratio with MSMA solution containing 50 mg/L total arsenic. Resulting K_D values were lowest in the fine sandy loam horizons (0.4, 1.1, and 8.7 mL/g – listed in order from the shallow soil layer to deeper soil layers), followed by the loamy sand horizons (0.2, 1.7, and 21.6 mL/g), followed by the silt loam (5.4, 38.4, and 63.6 mL/g). In column studies conducted using some of the same soil horizons, K_D values were lower, ranging from 0.3 to 8.9 mL/g. The authors concluded that their column studies did not allow sufficient equilibration time, and therefore their batch studies better represented MSMA behavior in the field. As a point of reference, in field studies (summarized in Table 1) arsenic attributable to MSMA application was not detected deeper than 30 cm in any of these soils in plots where arsenic was applied at high application rates (<i>i.e.</i> , up to 40 kg/ha per year or 218 lb/acre per year) for six years
Wauchope, RD. 1975. "Fixation of arsenical herbicides, phosphates and arsenate in alluvial soils." <i>J. Environ. Qual.</i> 4(3):355-358.	Using 16 Mississippi River alluvial floodplain soils, soil-solution slurries were prepared with a 1:20 soil:solution ratio containing either 2.5×10^{-3} M and 2.5×10^{-4} M MAA and shaken. Sorption increased with clay content, iron and aluminum oxide content. MAA sorption decreased as sand content increased in soils: 100 grams soil with 68.5% sand sorbed 116 mg MAA, whereas 100 grams soil with 3.6% sand sorbed 296 mg MAA. Arsenate sorption was similar to that of MAA. DMA sorption was less than that of MAA and arsenate, but was greater than that of phosphate.
Ricerca, Inc. 1988. "Adsorption and Desorption of Monosodium Methanearsonate to Soils." Document number 1702-87-0100-EF-000.	In a batch equilibrium laboratory study conducted with four soils, soil-solution slurries were prepared with a 1:10 soil:solution ratio and solutions containing between 1.0 and 18.6 mg/L MSMA and shaken. Soil sorbed between 5% and 81% of the applied MSMA mass. Sorption K_D values ranged from 0.5 to 39.1 mL/g, indicating that arsenic mobility depends heavily on soil characteristics.
Blumhorst, MR. 1989. "Adsorption/Desorption Studies – Batch Equilibrium for Cacodylic Acid" Laboratory Project No. 127-003. EPL Bioanalytical Services, Inc. Decatur, IL. December.	In a batch equilibrium laboratory study conducted with four soils, soil-solution slurries were prepared with a 1:5 soil:solution ratio and solutions containing between 0.44 and 88 mg/L cacodylic acid (DMA) and shaken. Sorption K_D values ranged from 6.5 to 28.8 mL/g indicating that arsenic mobility depends heavily on soil characteristics.

Table 5-1
Studies Addressing Partitioning of Arsenic Species between Soil and Water

Reference	Gradient's Summary of Findings Relevant for MSMA Use
Onken, BM; Adriano, DC. 1997. "Arsenic availability in soil with time under saturated and subsaturated conditions." <i>Soil Sci. Soc. Am. J.</i> 61:746-752.	This laboratory study showed that 94% of sodium arsenate sorbed to a sandy soil one hour after application.
Sarkar, D; Datta, R; Sharma, S. 2005. "Fate and bioavailability of arsenic in organo-arsenical pesticide-applied soils. Part-I. Incubation study." <i>Chemosphere</i> 60: 188-195.	In the laboratory, two Florida soils were amended with DMA to achieve concentrations of 45, 225, and 450 mg/kg. Soil partitioning and bioavailability of DMA were evaluated in soil subsamples using several different chemical extractants. Soils were extracted immediately after DMA addition and after four months of aging. In the low-iron- and aluminum-content soil containing 45 mg/kg DMA, 88% of the total arsenic was soluble in water immediately after DMA addition, decreasing to 70% after four months. In the higher iron- and aluminum-content soil containing 45 mg/kg DMA, 81% of the total arsenic was soluble in water immediately after DMA addition, decreasing to 25% after four months. Data were not presented for soils containing 225 and 450 mg/kg DMA but the authors reported that the results were similar with those rates.

Response 5b:

Ideally, soil- or sediment-water partition coefficients (K_D) would be selected by measuring the value of K_D in well-designed field experiments conducted in the specific soil of interest. It is recognized however that field experiments are costly and time consuming, and that measurement of K_D in every soil of interest is not possible. Moreover, few data exist to calculate field K_D values for arsenic compounds. If the goal of selecting a value for K_D is to model the general behavior of MSMA in soil, for example, then a reasonable worst-case value should be selected for K_D (*i.e.*, a K_D value determined in a soil where MSMA use would result in greater mobility than in most soils). An example of a rational selection process for a K_D value for MAA that could be used in conservative modeling follows.

The draft environmental fate chapter for DSMA/MSMA reviewed K_D values published in the literature and reported a range from 2.5 to 110 mL/g with a median of 40 mL/g in one study (not cited) and a range from 17 to 95 mL/g, with a median of 28 mL/g in another study (Wauchope, 1975). Hiltbold *et al.* (1974) reported a range of K_D values from 0.2 to 63.3 mL/g, summarized in Table 5-1. However, the study best suited to provide reliable soil-water partition coefficients for MSMA (as MAA) was performed by Ricerca (1988). This study was performed using EPA Pesticide Assessment Guidelines (*i.e.*, Guideline 163-1) with Good Laboratory Practices (GLP). Ricerca (1988) determined equilibrium soil-water partition coefficients (K_D) in batch laboratory studies using four soil samples, representing the following soil types: a Florida sand, a California sandy loam, a Tennessee silty loam, and an Ohio silty clay. The soil characteristics and K_D values for these soils are presented in Table 5-2.

Table 5-2
Soil Characteristics and Results of Ricerca (1988) MSMA Study

Soil origin	Sand (%)	Silt (%)	Clay (%)	Textural class	pH	CEC¹ (meq/kg)	OM² (%)	K_D (mL/g)
Florida	95.2	0.4	4.4	Sand	7.4	2.8	0.4	0.5
California	61.2	21.6	17.2	Sandy loam	5.8	13.0	3.1	39.1
Tennessee	12.8	72.0	15.2	Silt loam	7.3	8.7	0.7	11.4
Ohio	11.2	45.6	43.2	Silty clay	5.9	8.6	2.7	18.7

¹ CEC - Cation exchange capacity

² OM – Organic matter

The organic arsenical compounds are used as herbicides, and as such, they are applied at locations where plant material grows successfully. This fact provides some information about the types of soil where MSMA is (and is not) applied. Soils where plants are sustained contain organic matter in the root zone due to the presence of dead and decaying plant matter and plant

root exudates. Sandy soils consist mainly of large mineral particles, between which exist large pores. As a result of the large pore space in sandy soil, much less water can be stored in sandy soil than in clayey soil. A significant number of pores in sandy soils are large enough to drain within a day of precipitation or irrigation events, and this portion of water is lost before plants can use it (Haman and Izuno, 2003). Pure sand such as the Florida soil in Table 5-2 will not support plant growth, because nutrients and water are poorly retained in such a soil. For these reasons, the K_D value for the Florida sand is irrelevant for conditions where MSMA would be applied. Moreover, if for some reason one wanted to safely use arsenical herbicides in such a soil, it would be possible through the use of best management practices such as the co-application of iron or iron-rich clay with the herbicide.

A more appropriate value for K_D for MSMA is 11.4 mL/g, which is the second lowest value in Table 5-2, determined for the Tennessee silt loam. This value should be considered a reasonable worst-case K_D value for MSMA, consistent with the review of partition coefficients presented in the draft environmental fate chapter, because 11.4 mL/g is between the minimum and median values presented in the chapter.

Notably, the study described by Hiltbold *et al.* (1974), in which K_D values were determined in the laboratory (see Table 5-1), included also analyses of arsenic concentrations in field soils after six years of heavy MSMA application (*i.e.*, up to 40 kg/ha per year or 218 lb/acre per year for six years). The field portion of this study, summarized in Table 1, showed that *all* arsenic attributable to MSMA was detectable in the top 30 cm of soil. This is notable because the K_D values for these soils are extremely low, ranging from 0.2 to 1.7 mL/g in the top 30 cm. This result provides strong evidence that laboratory-derived K_D values are likely to overestimate the mobility of MSMA in field soils. This further indicates that the lowest laboratory-derived values for K_D ought not to be extrapolated to field conditions, where aging processes such as mineral precipitation may occur, reducing the mobility of arsenic compounds below what is suggested on the basis of batch laboratory partitioning studies. Thus, Hiltbold *et al.* (1974) provides additional support for the use of 11.4 mL/g as a reasonable worst-case value for K_D for modeling the behavior of MSMA in the field.

In conclusion, an example of a rational selection process for a soil-water partition coefficient (K_D) for MAA was presented and is summarized below. This type of selection process is valid for DMA and arsenate as well. Data from the literature (*e.g.*, Wauchope, 1975) suggest that a representative value for K_D for arsenate would be greater than or similar to that of MAA, and for DMA the value would be similar or slightly lower.

A wide range of K_D has been determined for MAA in the laboratory. Generally, pure sands yield the lowest values for K_D , with some such soils producing values less than one (*i.e.*, implying high MAA mobility). Clayey soils generally yield the highest values, around 100 mL/g.

The presence of clay minerals and iron in soil are associated with higher binding capacity for arsenic compounds (Wauchope, 1975; Wauchope and McDowell, 1984). Evidence is lacking that organic matter in soil plays an important role in binding arsenic compounds, but it is likely that in soils deficient in clay minerals, some types of organic matter would contribute to the soils' MAA retention capacity (and thus K_D). Pure sand soils (which yield the lowest K_D values) do not support plant growth well due to a lack of nutrient and water-holding capacity, and thus it is unlikely that MSMA or DSMA – herbicides – would be used in pure sands. Laboratory-derived K_D values for sand are inappropriate for use in modeling the behavior of MSMA in field soils. Therefore, the lowest non-sand K_D , a value of 11.4 mL/g should be considered a reasonable worst-case K_D value for MSMA. Moreover, laboratory-derived K_D values tend to overestimate the mobility of MAA in the field (*e.g.*, Hiltbold *et al.*, 1974), so the use of 11.4 mL/g in models to predict the environmental behavior of MAA would be conservative.

References

- Buchet, JP; Lauwerys, R; Roels, H. 1981. "Urinary Excretion of Inorganic Arsenic and its Metabolites After Repeated Ingestion of Sodium Metaarsenite by Volunteers." *Int. Arch. Occup. Environ. Health* 48 :111(8)
- Cohen, SM; Arnold, LL; Cano, M; Lu, X; Le, XC. 2002. "The presence of dimethylarsinous acid (DMAIII) in the urine of rats treated with dimethylarsinic acid (DMA)." Presented at the 41st Annual Meeting of the Society of Toxicology, held March 17-21, 2002 in Nashville, Tennessee. 9p.
- Dept. of Environmental Resources Management (DERM). 2002. "Environmental Quality Monitoring at Five Municipal Golf Courses in Miami-Dade County. Final Report."
- Drexler, J; Fisher, N; Henningsen, G; Lanno, R; McGeer, J; Sappington, K. 2003. "Issue Paper on the Bioavailability and Bioaccumulation of Metals. Draft." Submitted to U.S. Environmental Protection Agency Risk Assessment Forum. Washington, DC. August.
- Florida Dept. of Environmental Protection (FDEP). 2002 "Environmental Risks from Use of Organic Arsenical Herbicides at South Florida Golf Courses." December 27. Downloaded from <http://fdep.ifas.ufl.edu/msma.htm> on February 20, 2004.
- Florida Dept. of Environmental Protection (FDEP). 2004. "Draft Technical Report: Development of Cleanup Target Levels (CTLs) for Chapter 62-777, F.A.C." Center for Environmental & Human Toxicology. July 12.
- Georis, B; Cardenas, A; Buchet, JP; Lauwerys, R. 1990. "Inorganic arsenic methylation by rat tissue slices." *Toxicology* 63 (1) :73-84.
- Gradient Corporation (Gradient). 2004. Comments on the Report, "Environmental Quality Monitoring at Five Municipal Golf Courses in Miami-Dade County" Focusing on Organic Arsenical Herbicides. Prepared for the MAA Research Task Force. February 25.
- Gradient Corporation (Gradient). 2005a. "The Environmental Fate of Monosodium Methanearsonate (MSMA): A Review of Important Processes" Prepared for the MAA Research Task Force. February 28.
- Gradient Corporation (Gradient). 2005b. Comments on the report "Environmental Risks from Use of Organic Arsenical Herbicides at South Florida Golf Courses" Prepared by the Florida Department of Environmental Protection (FDEP). Letter from E.L. Butler and B.D. Beck, Gradient Corporation to Michal Eldan, MAA Research Task Force. March 30.
- Groen, K; Vaessen, HAMG; Kliet, JJG; de Boer, JL; van Ooik, T; Timmerman, A; Vlug, RF. 1994. "Bioavailability of inorganic arsenic from bog ore-containing soil in the dog." *Environ. Health Perspect.* 102(2):182-184.
- Haman, DZ; Izuno, FT. 2003. "Soil Plant Water Relationships." University of Florida, IFAS Extension. Publication #CIR1085.

Jaghabir, MW; Abdelghani, AA; Anderson, AC. 1991. "Absorption, distribution and elimination of arsenic in New Zealand white rabbits (*Oryctolagus cuniculus*) following multiple oral doses of monosodium methane arsonate." *Environ. Toxicol. Water Qual.* 6 (1) :113-119.

Kitchin, KT; Ahmad, S. 2003. "Oxidative stress as a possible mode of action for arsenic carcinogenesis." *Toxicol. Lett.* 137 (1-2) :3-13.

Lerman, SA; Clarkson, TW; Gerson, RJ. 1983. "Arsenic Uptake and Metabolism by Liver Cells is Dependent on Arsenic Oxidation State." *Chem. Biol. Interact.* 45 :401(6)

Life Science Research Israel. 1989. "Cacodylic Acid – Combined Chronic Feeding and Oncogenicity Study in the Rat." LSRI Project No. PAL/010/CAC. October 30.

Marafante, E; Vahter, M; Norin, H; Enval, J; Sandstrom, M; Christakopoulos, A; Rhyage, R. 1987. "Biotransformation of dimethylarsinic acid in mouse, hamster and man." *J. Appl. Toxicol.* 7 (2) :111-117.

Ricerca, Inc. (Ricerca). 1988. "Adsorption and Desorption of Monosodium Methanearsonate to Soils." Document number 1702-87-0100-EF-000.

Roberts, SM; Weimar, WR; Vinson, JRT; Munson, JW; Bergeron, RJ. 2002. "Measurement of arsenic bioavailability in soil using a primate model." *Toxicol. Sci.* 67 (2):303-310.

Rodriguez, RR; Basta, NT; Casteel, SW; Pace, LW. 1999. "An *in vitro* gastrointestinal method to estimate bioavailable arsenic in contaminated soils and solid media." *Environ. Science Technol.* 33(4):642-649.

Ruby, MV; Davis, A; Link, TE; Schoof, R; Chaney, RL; Freeman, GB; Bergstrom, P. 1993. "Development of an *in vitro* screening test to evaluate the *in vivo* bioaccessibility of ingested mine waste lead." *Environ. Sci. Technol.* 27:2870-2877.

Shiobara, Y; Ogra, Y; Suzuki, KT. 2001. "Animal species difference in the uptake of dimethylarsinous acid (DMA (III)) by red blood cells." *Chem. Res. Toxicol.* 14 (10) :1446-1452.

Stanek, EJ; Calabrese, EJ; Barnes, R; Pellow, P. 1997. "Soil ingestion in adults—Results of a second pilot study." *Ecotoxicol Environ Saf* 36:249–57.

Stanek, EJ; Calabrese, EJ. 2000. "Daily Soil Ingestion Estimates for Children at a Superfund Site." *Risk Analysis* 20(5):627-635.

Stanek, EJ; Calabrese, EJ; Zorn, M. 2001. "Soil ingestion distributions for Monte Carlo risk assessment in children." *Hum. Ecol. Risk Assess.* 7 (2):357-368.

Styblo, M; Del Razo, LM; LeCluyse, EL; Hamilton, GA; Wang, C; Cullen, WR; Thomas, DJ. 1999. "Metabolism of arsenic in primary cultures of human and rat hepatocytes." *Chem. Res. Toxicol.* 12 (7) :560-565.

Styblo, M; Del Razo, LM; Vega, L; Germolec, DR; LeCluyse, EL; Hamilton, GA; Reed, W; Wang, C; Cullen, WR; Thomas, DJ. 2000. "Comparative toxicity of trivalent and pentavalent inorganic and methylated arsenicals in rat and human cells." *Arch. Toxicol.* 74 :289-299.

US EPA. 1990. "National Oil and Hazardous Substances Pollution Contingency Plan; Final Rule." *Fed. Reg.* 55(46):8666-8865. March 8

US EPA. 1996. "Soil Screening Guidance: Technical Background Document." Second Edition. EPA/540/R95/128. Office of Solid Waste and Emergency Response. Washington, DC. May.

US EPA. 2003. "Technical Background Information. Development of Risk Based Concentrations." Internet content accessed 9/9/2005: <http://www.epa.gov/reg3hwmd/risk/human/info/tech.htm> Edited 4/16/2003

Wauchope, RD. 1975. "Fixation of arsenical herbicides, phosphates and arsenate in alluvial soils." *J. Environ. Qual.* 4(3):355-358.

Wauchope, RD; McDowell, LL. 1984. Adsorption of phosphate, arsenate, methanearsonate, and cacodylate by lake and stream sediments: Comparisons with soils. *J. Environ. Qual.* 13:499-504.

Vahter, M. 1994. "Species differences in the metabolism of arsenic compounds." *Appl. Organomet. Chem.* 8 :175-182.

Valberg, PA; Beck, BD; Bowers, TS; Keating, JL; Bergstrom, PD, and Boardman, PD. 1997. "Issues in setting health-based cleanup levels for arsenic in soil." *Regul. Toxicol. Pharmacol.* 26:219-229.

Vega, L; Styblo, M; Patterson, R; Cullen, W; Wang, C; Germolec, D. 2001. "Differential effects of trivalent and pentavalent arsenicals on cell proliferation and cytokine secretion in normal epidermal keratinocytes." *Toxicol. Appl. Pharmacol.* 172 :225-232.

Zakharyan, RA; Ayala-Fierro, F; Cullen, WR; Carter, DM; Aposhian, HV. 1999. "Enzymatic methylation of arsenic compounds: VII. Monomethylarsonous acid (MMA3) is the substrate for MMA methyltransferase of rabbit liver and human hepatocytes." *Toxicol. Appl. Pharmacol.* 158:9-15.

Appendix A

A.1 Calculation of Intake from Ingestion of Soil Containing Arsenic Compounds

The intake of chemicals in soil due to ingestion of soil is calculated as follows:

$$Intake \left(\frac{mg}{kg \cdot day} \right) = \frac{EPC \times FS \times IR \times EF \times ED \times 10^{-6} \frac{kg}{mg}}{BW \times AT} \times B$$

Where the acronyms represent the following parameters, which are further explained in detail:

EPC	=	Exposure Point Concentration of the specific chemical in soil (mg/kg),
FS	=	Fraction of Daily Ingested Soil from the Chemical Source Area ("Fraction of Source"; unitless),
IR	=	Ingestion Rate (mg/day),
EF	=	Exposure Frequency (days/year),
ED	=	Exposure Duration (years),
10 ⁻⁶	=	Units conversion factor from kg to mg
BW	=	Body Weight (kg),
AT	=	Averaging Time (days), and
B	=	Relative Bioavailability of the chemical in soil (unitless)

The parameter values that are used to quantify exposure to arsenic compounds from the soil ingestion pathway are described below.

Total Arsenic Concentration in Soil (EPC)

As described in Section 5.3 of Gradient (2005), two studies (DERM, 2002; FDEP, 2002) collectively reported total arsenic measurements from eight different golf courses in South Florida. The measurements Gradient used to conservatively represent the *EPC* the playing area in this exposure calculation were taken at the Plantation Golf Club, and they represent the maximum average concentrations measured among all eight sites. The playing area *EPC* used was 34.4 mg/kg total arsenic in soil.⁹ Typically, reasonable maximum exposure scenarios incorporate the use of a 95th percentile upper confidence limit on the mean (95 UCLM) as the *EPC*. In this case, the average concentration is appropriate to use because we chose the maximum average value among the golf courses in two studies,

⁹ This concentration is the average of 15 total arsenic measurements reported for samples collected in the upper two feet of soil during 1998 and 2002.

and because the data presented by FDEP (2002) are incomplete, leading to the inability to calculate a reliable 95 UCLM.

Fraction of Source (FS)

The fraction of source is portion of soil that has been treated with MSMA to which an individual is exposed. For the current illustrative calculation, we make the conservative assumption that 100% of the soil to which a resident is exposed at home has been treated with MSMA, and that none of the resident's daily soil exposure occurs away from home (*e.g.*, at school, work, or local playgrounds). For the golf course groundskeeper, we assigned *FS* equal to 0.5 (50%), because groundskeepers work in roughs and other areas of the golf course where MSMA and other arsenic-containing agrochemicals are not used.

Ingestion Rate (IR)

The ingestion rate is the total amount of soil ingested by the resident or groundskeeper per day. The IR used in this illustrative exposure equation is 50 mg/day for the adult resident and 100 mg/day for the child resident and the groundskeeper, as recommended by US EPA (1997).

Exposure Frequency (EF)

The exposure frequency is the number of days in a year during which the resident or groundskeeper is exposed to soil treated with MSMA. The exposure frequency of 350 days/year assigned in this calculation for a resident assumes that a resident spends two weeks of the year away from their home. The exposure frequency of 250 days/year for a groundskeeper accounts for time spent working five days a week during each year of exposure, with two weeks taken off from work.

Exposure Duration (ED)

The exposure duration is the number of years over which the resident or groundskeeper is exposed to soil treated with MSMA. For both adult exposure scenarios a value of 30 years was chosen for *ED*, which is conservative, given that most individuals live or work in one location for a period less than 30 years (US EPA, 1997). The exposure duration of the resident was chosen to be six years as a child and 24 years as an adult at the same (former golf course) residence.

Body Weight (BW)

In accordance with US EPA (1997, 2001), a body weight of 70 kg was assigned for both the adult resident and the groundskeeper, and a body weight of 16.6 kg was assigned for the child resident.

Averaging Time (AT)

For cancer risk, exposures are averaged over a lifetime. For non-cancer effects, exposures are averaged over a time period equal to the exposure duration. To be consistent with the life expectancy used by IRIS (US EPA, 1997) to calculate cancer slope factors and unit risks, we use 70 years (which equates to 25,550 days) as the averaging time for both the resident and the groundskeeper.

Bioavailability (B)

Bioavailability of total arsenic is defined as the fraction of the amount ingested that is absorbed into the bloodstream, relative to absorption of total arsenic from water. For example, chemicals that are tightly bound to soil may not dissolve in the gastrointestinal tract and are therefore not available for absorption into the bloodstream. The value of *B* assigned in this exposure calculation is 0.33, implying that 33% of the total arsenic ingested in soil is absorbed. This value is based on the FDEP's draft regulatory implementation of Roberts *et al.* (2002), where primates ingested arsenic-containing Florida soils and observed that arsenic bioavailability less than 25% in all samples.

A.2 Calculation of Intake from Dermal Contact with Soil Containing Arsenic Compounds

The intake of chemicals in soil due to dermal contact with soil is calculated as follows:

$$\text{Intake} \left(\frac{\text{mg}}{\text{kg} \cdot \text{day}} \right) = \frac{\text{EPC} \times \text{SA} \times \text{AF} \times \text{DA} \times \text{EF} \times \text{ED} \times 10^{-6} \frac{\text{kg}}{\text{mg}}}{\text{BW} \times \text{AT}}$$

Where the acronyms represent the following definitions, which are further explained in detail:

EPC	=	Exposure Point Concentration of the chemical in soil (mg/kg),
SA	=	Skin Surface Area exposed per day (cm ² /day),
AF	=	Soil to skin Adherence Factor (mg/cm ²),
DA	=	Dermal Absorption fraction (unitless),
EF	=	Exposure Frequency (days/year),
ED	=	Exposure Duration (years),

10^{-6}	=	Units conversion factor from kg to mg,
BW	=	Body Weight (kg), and
AT	=	Averaging Time (days)

The parameter values that are used to quantify exposure to arsenic compounds from the dermal absorption pathway are described below.

Skin Surface Area (SA)

This parameter represents the surface area of skin that is assumed to be available for exposure to arsenic compounds in soil. We assume that the residents are wearing shoes, shorts and a short-sleeved shirt, and therefore the surface areas assumed to be available for dermal exposure include the head, forearms, hands, and lower legs. The value for *SA* used in these calculations is 5,700 cm² for adult residents and 2,000 cm² for child residents (US EPA, 2001). For the groundskeeper, we assume that he is wearing shoes, pants, and a short-sleeved shirt, and therefore the surface areas assumed to be available for dermal exposure include the face, hands and forearms. The value for *SA* used in these calculations is 3,300 cm² for groundskeepers (US EPA, 2001).

Soil to Skin Adherence Factor (AF)

The *AF* represents the amount of soil that adheres to the skin per unit surface area (US EPA, 2001). Adherence factors vary depending on the properties of the soil, the part of the body exposed, and the type of activity in which the individual is engaged. The *AF* value used in this illustrative calculation is the EPA-recommended *AF* value of 0.07 mg/cm² for adult residents and 0.20 mg/cm² for child residents and groundskeepers (US EPA, 2001).

Dermal Absorption Fraction (DA)

The dermal absorption fraction accounts for the fact that only a certain fraction of a compound that comes into contact with an individual's skin is absorbed into the body. The values for *DA* used to quantify the fraction of arsenic compounds that are dermally absorbed are 3% for elemental arsenic (US EPA, 2001) and 3.5% for MAA and DMA. This value (3.5%) for DMA dermal absorption was used by EPA as a surrogate for MAA data (US EPA, 2000), and was also used for MAA and DMA here.

The exposure parameters described above are summarized in Table A-1.

Table A-1
Parameters Used to Conservatively Illustrate Exposure to Arsenic Compounds in Soil

Exposure Variable		Child Resident	Adult Resident	Grounds-keeper
Exposure Point Concentration (mg/kg)	<i>EPC</i>	34.4	34.4	34.4
Relative Bioavailability	<i>B</i>	0.33	0.33	0.33
Fraction from Source (%)	<i>FS</i>	1	1	0.5
Soil Ingestion Rate (mg/day)	<i>IR</i>	100 ^[a]	50 ^[a]	100
Exposure Frequency (days/year)	<i>EF</i>	350	350	250
Exposure Duration (years)	<i>ED</i>	6 ^[b]	24 ^[b]	30
Body Weight (kg)	<i>BW</i>	16.6 ^[a]	70 ^[a]	70
Averaging Time (days)				
Cancer	<i>ATc</i>	25,550	25,550	25,550
Non-cancer	<i>ATnc</i>	2,190 ^[b]	8,760 ^[b]	10,950
Skin Surface Area exposed per day (cm ² /day)	<i>SA</i>	2,000 ^[a]	5,700 ^[a]	3,300
Soil to Skin Adherence Factor (mg/cm ²)	<i>AF</i>	0.20 ^[a]	0.07 ^[a]	0.20
Dermal Absorption Fractions (unitless)				
Inorganic Arsenic	<i>DA_{As}</i>	0.03	0.03	0.03
MAA	<i>DA_{MAA}</i>	0.035	0.035	0.035
DMA	<i>DA_{DMA}</i>	0.035	0.035	0.035

Notes:

^[a]Exposure duration-weighted averages for the parameters *IR*, *BW*, *SA*, and *AF* in the combined child/adult exposure scenario were used for the calculation. Those values are 60 mg/day, 59 kg, 4,960 cm²/day, and 0.10 mg/cm², respectively.

^[b]The sum of the child and adult values for *ED* and *ATnc* were used for the calculation. Those values are 30 years and 10,950 days, respectively.

A.3 Exposure Calculation Summary

The exposure parameters listed in Table A-1 were substituted into the equations listed in Section A.1 for ingestion exposure and Section A.2 for dermal exposure to calculate a conservative estimate of human exposure to arsenic compounds in golf course soil. As explained in Section 5.3 of Gradient (2005), the estimate of exposure to arsenic compounds that is calculated in this Section is not solely due to the use of MSMA; because we are using the total measured concentration of arsenic at a specific location, we are not limiting the exposure estimate to arsenic compounds resulting from MSMA use.¹⁰

To obtain arsenic intake from incidental soil ingestion, the relevant values from Table A-1 were substituted into the equation in Section A.1. To obtain arsenic intake from incidental dermal contact with soil, the relevant values from Table A-1 were substituted into the equation in Section A.2. The total

¹⁰ Natural background arsenic and arsenic contributions from other human sources, such as the historic use of inorganic arsenical pesticides and arsenic-containing fertilizers, are combined with any total arsenic contributed to soil by MSMA

arsenic exposure is the sum of the intakes from these two exposure routes. Separate calculations were performed for inorganic arsenic and for organic arsenic compounds because the dermal absorption fraction (*i.e.*, the exposure parameter *DA*) differs for these species, as shown in Table A-1. Also, separate calculations were performed for non-cancer effects and cancer effects, because the averaging time (*i.e.*, the exposure parameter *AT*) for non-cancer effects is equal to the exposure duration, while for cancer, the exposure duration is a 70-year lifetime as described in Section A.1. If one assumes that 100% of the total arsenic in soil is MAA, DMA, or inorganic arsenic, the resulting doses for all of the scenarios described above are shown in Table A-2.

Table A-2
Example Calculated Doses of MAA, DMA, or Inorganic Arsenic
from Incidental Ingestion and Dermal Exposure to Soil

	MAA or DMA Dose (mg/(kg d))	Inorganic Arsenic Dose (mg/(kg d))
Average Daily Dose (Non-Cancer Effects)		
Resident	2.0×10^{-5}	1.9×10^{-5}
Groundskeeper	1.3×10^{-5}	1.2×10^{-5}
Lifetime Average Daily Dose (Cancer Effects)		
Resident	8.7×10^{-6}	8.1×10^{-6}
Groundskeeper	5.7×10^{-6}	5.2×10^{-6}

A.4 Comparison of Estimated Human Exposure to Effects Levels in Laboratory and Epidemiological Studies

The illustrative estimated dose of arsenic compounds due to human exposure to soil in residential and groundskeeper scenarios using soil arsenic concentrations from the Plantation Golf Club (Table A-2) are put in perspective by comparison to the lowest doses at which no observed adverse effects occur (*i.e.*, NOAELs) to humans or laboratory animals (when human data are unavailable) and acceptable risk levels. The comparisons presented in this Section show that conservatively estimated human doses from Table A-2 are orders of magnitude less than human and mammalian NOAELs, indicating that human health risks due to arsenic compounds in soil in these scenarios are negligible. The conservatively estimated cancer risk, in the case of inorganic arsenic, is within the range deemed acceptable by EPA. The comparison of doses to NOAELs and the calculation of risks were performed separately for MAA, DMA, and inorganic arsenic, because each compound has a different toxic potency and results in different effects to organisms.

MAA

There is no evidence that MAA is a carcinogen, so carcinogenicity endpoints were not considered. The lowest NOAEL for non-cancer effects of MAA was chosen for comparison to MAA exposure *via* golf course soil. That NOAEL is from a beagle dog oral chronic exposure study, the outcome of which is 2 mg/(kg d), based on observed diarrhea, vomiting, and excessive salivation (LSRI, 1988).

If the total arsenic measured in the South Florida golf course soil were 100% MAA, the conservative estimate of MAA dose described in Section A.3 (2.0×10^{-5} and 1.3×10^{-5} mg/(kg d), for residents and groundskeepers, respectively) would be approximately 100,000-fold and 150,000-fold less than the mammalian NOAELs for MAA, for residents and groundskeepers, respectively. This indicates that MAA in soil resulting from the long-term use of MSMA would not constitute a human health concern.

DMA

The NOAEL for non-cancer effects of DMA chosen for comparison to the golf course exposures is 0.14 mg/(kg d) for rats, based on a study in which male rats developed kidney lesions (LSRI, 1989). There is evidence that DMA is a threshold rat bladder carcinogen, and a recent two-year study showed that the carcinogenicity NOAEL in rats is 12.5 mg/L in water (Wei *et al.*, 2002). The MAA NOAEL dose in water was converted to a daily body-weight-normalized dose during the course of the experiment by assuming that test animals drank 25 mL of water per day (Derelanko, 2000), and weighed 0.2 kg (Derelanko, 2000). This results in an MAA NOAEL of 1.6 mg/(kg d) ($12.5 \text{ mg/L} \times 0.025 \text{ L/day} \times 1/0.2 \text{ kg}$).

If the total arsenic measured in the South Florida golf course soil were 100% DMA, which is unlikely for the portion of total arsenic that may have originated from the use of MSMA, the conservative estimate of DMA dose described in Section A.3 (2.0×10^{-5} and 1.3×10^{-5} mg/(kg d), for residents and groundskeepers, respectively) would be approximately 7,000-fold and 11,000-fold less than the mammalian non-cancer NOAELs for DMA, for residents and groundskeepers, respectively. The DMA intake *via* soil would be 180,000-fold and 280,000-fold less than the cancer NOAEL, for residents and groundskeepers, respectively. This indicates that any DMA in soil resulting from the long-term use of MSMA would not constitute a human health concern.

Inorganic Arsenic

The EPA Integrated Risk Information System (IRIS) provides toxicity reference data for use in risk assessment.¹¹ EPA recommends a NOAEL for assessing non-cancer toxicity endpoints for inorganic arsenic in IRIS. The inorganic arsenic NOAEL recommended in IRIS is 0.0008 mg/(kg d) in humans, where the toxicity endpoint is hyperpigmentation of the skin.¹² The potential for arsenic to cause cancer at low doses is a matter of scientific debate. In IRIS, EPA recommends that inorganic arsenic be assessed as a no-threshold carcinogen, meaning that there is not a NOAEL established for inorganic arsenic carcinogenicity. In this case, a cancer slope factor (CSF) is recommended in IRIS, which allows the dose shown in Table A-2 to be translated to a cancer risk. The inorganic arsenic CSF recommended in IRIS is 1.5 (mg/(kg d))⁻¹. The lifetime incremental increase in cancer risk due to an inorganic arsenic dose is calculated by multiplying the lifetime average daily dose by the CSF. The result of this calculation is an excess cancer risk of approximately 12 in one million for a resident and 8 in one million for a groundskeeper. The inorganic arsenic concentration range that would constitute an acceptable risk,¹³ in golf course soils according to the conservative, illustrative calculations described in Section A.3 is between 2.85 and 285 mg/kg for a resident, and between 4.4 and 440 mg/kg for a groundskeeper.¹⁴

If the total arsenic measured in the South Florida golf course soil were 100% inorganic arsenic, which is unlikely for the portion of total arsenic that may have originated from the use of MSMA, the conservative estimate of inorganic arsenic dose described in Section A.3 (1.9×10^{-5} and 1.2×10^{-5} mg/(kg d), for residents and groundskeepers, respectively) would be approximately 42-fold and 67-fold less than the human NOAEL, for residents and groundskeepers, respectively. This indicates that any inorganic arsenic in soil resulting from the long-term use of MSMA would not constitute a human health concern. Furthermore, the concentration of arsenic in soil at this South Florida golf course is in the range consistent with U.S. background arsenic concentrations in soil (See Section 1 of Gradient, 2005), and falls at the low end of the range of acceptable excess cancer risk.

¹¹ Internet content, accessed 2/23/04 at: <http://www.epa.gov/iris/subst/0278.htm>

¹² IRIS also lists a non-cancer reference dose (RfD) for inorganic arsenic, which is the dose below which no adverse effects are expected to human populations. This value is 3×10^{-4} mg/(kg d), which is the NOAEL divided by an uncertainty factor of three. However, for consistency, the inorganic arsenic exposures estimated due to exposure to golf course soil is compared to the NOAEL and not the RfD, because no RfD has been established for MAA or DMA, while NOAELs are available in the literature and are used here.

¹³ An excess cancer risk of between one-in-a-million (10^{-6}) and one-in-ten thousand (10^{-4}) is considered acceptable in this illustrative calculation, consistent with US EPA practice in evaluating environmental risks.

¹⁴ These values are calculated using the equations listed in Section 5.3.1 and Section 5.3.2, using the cancer slope factor from IRIS (1.5 (kg d)/mg), and solving for the *EPC* term.

References

Derelanko, MJ. 2000. *Toxicologist's Pocket Handbook*. CRC Press, Boca Raton.

Florida Department of Environmental Protection (FDEP). 2002. "Environmental Risks from Use of Organic Arsenical Herbicides at South Florida Golf Courses." Downloaded from <http://fdep.ifas.ufl.edu/msma.htm> on February 20, 2004. December 27.

Gradient Corporation (Gradient). 2005. "The Environmental Fate of Monosodium Methanearsonate (MSMA): A Review of Important Processes" Prepared for the MAA Research Task Force. February 28.

Life Science Research Israel Ltd. (LSRI). 1988. "Methanearsonic Acid: Fifty-two Week Chronic Oral Toxicity Study in Beagle Dogs. Volumes I and II." Report to Pamol Ltd., Tel Aviv, Israel. January 25.

Life Science Research Israel, Ltd. (LSRI). 1989. "Cacodylic Acid: Combined Chronic Feeding and Oncogenicity Study in the Rat. Volumes I - X. Report to Luxembourg Industries (Pamol), Ltd., Tel Aviv, Israel. LSRI Project No. PAL/010/CAC. October 30.

Miami Dade County Department of Environmental Resources Management (DERM) in cooperation with Florida Department of Agriculture and Consumer Services. 2002. "Environmental Quality Monitoring at Five Municipal Golf Courses in Miami-Dade County." Downloaded from http://www.co.miamidade.fl.us/derm/land/library/golf_course.pdf. December.

Roberts, SM; Weimar, WR; Vinson, JRT; Munson, JW; Bergeron, RJ. 2002. Measurement of arsenic bioavailability in soil using a primate model. *Toxicol. Sci.* 67(2):303-310.

US EPA. 1997. "Exposure Factors Handbook. Volume I: General Factors." Office of Research and Development, Washington, D.C. EPA/600/P-95/002Fc. August.

US EPA. 2000. Section. 3.3.4 of the DSMA/MSMA HED Chapter of the Reregistration Eligibility Decision Document (RED). US EPA, OPP, Washington, DC. September 28.

US EPA. 2001. "Risk Assessment Guidance for Superfund Volume I: Human Health Evaluation Manual (Part E, Supplemental Guidance for Dermal Risk Assessment) Interim." Office of Emergency and Remedial Response, Washington, DC. EPA/540/R/99/005. September.

Wei, M; Wanibuchi, H; Morimura, K; Iwai, S; Yoshida, K; Endo, G; Nakae, D; and Fukushima, S. 2002. Carcinogenicity of dimethylarsinic acid in male F344 rats and genetic alterations in induced urinary bladder tumors. *Carcinogenesis* 23(8):1387-1397.



APC Holdings
KMG-Bernuth, Inc.
Luxembourg-Pamol, Inc.

DSMA MASTER LABEL (SUPPORTED BY MSMA TASK FORCE)

The Master Label is based on data submitted for re-registration of DSMA.

The Master Label includes:

- Use patterns
- Type and timing of application; Application limitations
- Maximum application rate
- Maximum number of application per crop
- Pre-grazing interval

The Master Label does not include:

- Ingredient statements
- Precautionary statements
- Environmental hazards
- Worker Protection Standard information
- Restricted Entry Interval (REI)
- Comprehensive directions for use
- Storage and disposal statements

Differences from present labels:

- Citrus (bearing) is no longer a supported use
- Use in Florida as spot treatment only will be allowed in Non-bearing Orchards
- The restriction under Lawn and Ornamental Turf, “Do not apply with hose-end applicators.” was removed.
- The restriction, “Use on Golf Course greens is prohibited.” was added.
- Spot treatment with boom sprayer was added to Lawn and Ornamental Turf.
- Maximum number of application for Lawn and Ornamental Turf was added.
- Maximum number of application and spraying interval for Non-crop areas were added

DSMAMasterLabel-9/15/05

MAA RESEARCH TASK FORCE

■ P.O. Box 33856, Washington D.C. 20033-0856, PHONE: (800) 890-3301, FAX: (202) 557-3836, E-mail: meldan@luxpam.com ■



APC Holdings
 KMG-Bernuth, Inc.
 Luxembourg-Pamol, Inc.

PROPOSED DSMA MASTER LABEL

COTTON

TYPE OF APPLICATION	Maximum Application Rate (Lbs. Disodium methanearsonate hexahydrate (DSMA.6H ₂ O) /A)	Maximum Number of Application per Crop	Use Precautions and Restrictions
By Ground or Air: Pre-plant or post-plant up to cracking	3.6 (2.268 lbs. DSMA/acre)	1	Apply no later than initial soil cracking before cotton emerge. Do not feed treated forage to livestock or graze treated areas.
By Ground or Air: Post-emergent over-the-top	3.6 (2.268 lbs. DSMA/acre)	1	Apply only when cotton has 1 – 2 true leaves to first square. Do not feed treated forage to livestock or graze treated areas.
Directed Application: Broadcast	3.6 (2.268 lbs. DSMA/acre)	2	Apply when cotton is 3 inches high to first bloom. Do not apply after first bloom. Second application should be timed 1 to 3 weeks after the first if needed. Do not feed treated forage to livestock or graze treated areas.
Directed Application: Band application	For band application in 40" rows per inch of band width: 0.09 lbs. DSMA.6H ₂ O (0.0567 lbs. DSMA/acre)	2	Apply when cotton is 3 inches high to first bloom. Do not apply after first bloom. Second application should be timed 1 to 3 weeks after the first if needed. Do not feed treated forage to livestock or graze treated areas.

MAA RESEARCH TASK FORCE



APC Holdings
KMG-Bernuth, Inc.
Luxembourg-Pamol, Inc.

LAWN AND ORNAMENTAL TURF

TYPE OF APPLICATION	Maximum Application Rate (Lbs. Disodium methanearsonate hexahydrate (DSMA.6H ₂ O) /A)	Maximum Number of Application per Crop	Use Precautions and Restrictions
By ground	5.227 (3.293 lbs. DSMA/acre)	4	Do not use on St. Augustine, Centipede, Carpetgrass or Dichondra.
Spot treatment (with Boom sprayer)	5.227 (3.293 lbs. DSMA/acre)		Apply at 14 day intervals. Use on Golf Course greens is prohibited.

NON-BEARING ORCHARDS (Almonds, Apples, Apricots, Cherries, Citrus, Peaches, Pears, Plums, Prunes, Walnut) AND VINEYARDS

TYPE OF APPLICATION	Maximum Application Rate (Lbs. Disodium methanearsonate hexahydrate (DSMA.6H ₂ O) /A)	Maximum Number of Application per Crop	Use Precautions and Restrictions
Directed application	7.7 (4.85 lbs. DSMA/acre)	3	Apply as spot treatment only in Florida. Do not apply around trees or vines from which fruit will be harvested within 1 year of treatment.

MAA RESEARCH TASK FORCE



APC Holdings
KMG-Bernuth, Inc.
Luxembourg-Pamol, Inc.

NON-CROP AREAS

TYPE OF APPLICATION	Maximum Application Rate (Lbs. Disodium methaneearsonate hexahydrate (DSMA.6H ₂ O) /40 gallons of water)	Maximum Number of Application per Crop	Use Precautions and Restrictions
Ground application	4.0 (2.52 lbs. DSMA/40 gal of water)	4	Apply at 10 to 14 days interval. Do not contaminate water used for domestic purposes, by animals (including wildlife and aquatic life) or for irrigation purposes.

MAA RESEARCH TASK FORCE



APC Holdings
KMG-Bernuth, Inc.
Luxembourg-Pamol, Inc.

MASTER LABEL FOR RE-REGISTRATION OF MSMA (SUPPORTED BY MSMA TASK FORCE)

The Master Label is based on data submitted for re-registration of MSMA.

The Master Label includes:

- Use patterns
- Type and timing of application; Application limitations
- Maximum application rate
- Maximum number of application per crop
- Pre-grazing interval

The Master Label does not include:

- Ingredient statements
- Precautionary statements
- Environmental hazards
- Worker Protection Standard information
- Restricted Entry Interval (REI)
- Comprehensive directions for use
- Storage and disposal statements

Differences from present labels:

- Citrus (bearing) is no longer a supported use
- The restriction under Lawn and Ornamental Turf, “Do not apply with hose-end applicators.” was removed.
- Spot treatment with boom sprayers was added under Lawn and Ornamental Turf
- Pre-harvest interval (PHI) was added to Orchards, nonbearing.
- Maximum number of application and spraying interval for Non-crop areas were added.

MSMAMasterLabel-9/15/05

MAA RESEARCH TASK FORCE

■ P.O. Box 33856, Washington D.C. 20033-0856, PHONE: (800) 890-3301, FAX: (202) 557-3836, E-mail: meldan@luxpam.com ■



APC Holdings
KMG-Bernuth, Inc.
Luxembourg-Pamol, Inc.

COTTON

Type of Application	Maximum Application Rate (lbs. a.i./A)	Maximum Number of Application per Crop	Use Precautions and Restrictions
By Ground or Air: Pre-plant or Post-plant (up to cracking)	2.0	1	Do not apply no later than initial cracking of soil.
By Ground or Air: Post-emergent (as over-the-top broadcast spray) OR Post-emergent (as over-the-top broadcast spray)	1.875 0.9375	1 2	Apply when Cotton is 3 to 6 inches high or up to early first square stage as salvage operation only. Do not make more than two applications total of either DSMA or MSMA or a combination per crop.
By Ground: Post-emergent (directed spray application)	2.0	2	Do not apply after first bloom. In Florida, confine application to band treatment. Do not graze treated areas or feed treated foliage to livestock.

MAA RESEARCH TASK FORCE



APC Holdings
KMG-Bernuth, Inc.
Luxembourg-Pamol, Inc.

LAWN AND ORNAMENTAL TURF

Type of Application	Maximum Application Rate (lbs. a.i./A)	Maximum Number of Application per Crop	Use Precautions and Restrictions
By Ground: On Athletic field, Golf course, Parks	2.6136	4	Apply at 10 to 14 day intervals. On new lawns, do not treat until after three mowings.
By Ground: On well established actively growing Turf	2.178		Do not apply to St. Augustine grass except for commercial sod production.
By Ground: On established Bermudagrass and Zoysiagrass	3.9204		Do not apply to Carpetgrass, Centipedegrass or to Dichondra. Do not reseed until two weeks after the last application.
Spot Treatment (with boom sprayer)	2.178		Use on Golf Course Greens is prohibited.

MAA RESEARCH TASK FORCE



APC Holdings
KMG-Bernuth, Inc.
Luxembourg-Pamol, Inc.

NON-BEARING ORCHARDS (Almonds, Apples, Apricots, Cherries, Citrus Peaches, Pears, Plums, Prunes and Walnut) AND VINEYARDS

Type of Application	Maximum Application Rate (lbs. a.i./A)	Maximum Number of Application per Crop	Use Precautions and Restrictions
By Ground: Directed application	4	3	Apply at 10 to 14 day intervals. Do not apply around trees or vines from which fruit will be harvested within 1 year of treatment. In Florida, apply as spot treatment only.

NON-CROP AREAS

Type of Application	Maximum Application Rate (lbs. a.i./A)	Maximum Number of Application per Crop	Use Precautions and Restrictions
By Ground: On Drainage ditch banks, Right-of-ways, Storage yards and similar non-crop areas	4.5	4	Apply at 10 to 14 day intervals. Do not contaminate waters used for domestic purposes, or by animals, including wildlife and aquatic life, or water used for irrigation.

MAA RESEARCH TASK FORCE



APC Holdings
 KMG-Bernuth, Inc.
 Luxembourg-Pamol, Inc.

Questions and Requests for Information for the MAA Research Task Force

March 14, 2005

B. Use and Usage

Question 6: Below are the application rates EPA intends to use for the MSMA and DSMA risk assessments. Please confirm these are accurate or provide corrections.

Response 6:

The table below includes EPA's original details and the MAATF's comments in the dark rows:

Use Site		MSMA	DSMA
Cotton	Labeled rate		
	EPA:	2 aerial applications, each at 3.0 lb a.i./acre, 14 days apart	2 aerial applications, each at 3.6 lb a.i./acre, 14 days apart
	MAATF:	2 annual applications (max) of 2 lbs a.i./acre each, 1-3 weeks apart	2 annual applications (max) of 3.6 lbs DSMA·6H ₂ O /acre = 2.27 lbs DSMA/acre) 1-3 weeks apart
	Field trial rate		
	EPA:	2 aerial applications, each at 2.0 lb a.i./acre, 14 days apart	2 aerial applications, each at 3.0 lb a.i./acre, 14 days apart
	MAATF:	Correct	2 applications, each at 2.2 lb a.i./acre, 1-3 weeks apart (PTRL 768)

Use Site		MSMA	DSMA
Citrus, bearing	Labeled rate		
	EPA:	3 ground applications, each at 4.7 lb a.i./acre, 14 days apart	3 ground applications, each at 6.3 lb a.i./acre, 14 days apart
	MAATF	Bearing citrus is being deleted from MSMA and DSMA labels	
	Field trial rate	3 ground applications, each at 4.0 lb a.i./acre, 14 days apart	3 ground applications, each at 4.9 lb a.i./acre, 14 days apart
	MAATF	Correct	Correct
Turf / Liquid formulation	EPA:	?? ground applications , each at 4.1 lb. a.i./acre (0.094 lb a.i./gallon), ?? days apart	?? ground applications , each at 6.1 lb. a.i./acre (0.056 lb a.i./gallon), ?? days apart
	MAATF:	4 applications (max), each at 2-4 lbs a.i./acre	5.3 lbs DSMA-6H ₂ O/acre = 3.3 lbs DSMA/acre
Turf / Wettable powder	EPA:	?? ground applications , each at 2.2 lb. a.i./acre (0.01 lb a.i./gallon), ?? days apart	?? ground applications , each at 7.56 lb. a.i./acre (0.076 lb a.i./gallon), ?? days apart
	MAATF:	Not applicable – All Powders are applied as liquid formulations	Not applicable – All Powders are applied as liquid formulations
Turf Granular	EPA:	?? ground applications , each at 2.65 lb. a.i./acre, ?? days apart	?? ground applications , each at 3.9 lb. a.i./acre, ?? days apart
	MAATF:	Not applicable – Granular products are applied as liquid formulations	Not applicable – Granular products are applied as liquid formulations
Orchard, Non- bearing	Labeled rate	3 applications, each at 15.5 lb a.i./acre, ?? days apart	3 applications, each at 15.5 lb a.i./acre, ?? days apart
	Master label	3 applications (max), each at 4 lbs./acre	3 applications (max), each at 7.7 lbs DSMA-6H ₂ O/acre = 4.8 lbs. DSMA/acre

Question 7: Please describe the application methods for cotton, citrus, turf, and orchard.

Response 7:

Cotton

MSMA is applied to cotton pre-plant or post-plant up to cracking. It is applied to weeds post emergence, over the top or directed. Over the top applications are done by ground boom sprayer or aerially. Band or directed treatment is done with hooded sprayers or with special shields that protect the crop from the spray.

Citrus

MSMA is no longer used on bearing citrus.

Turf

MSMA is applied to turf as spot or broadcast treatment. Spot treatment by back pack and hand pressurized spray cans. Broadcast is done by hose and reel hand guns or boom sprayers.

Orchard

In orchards, MSMA is used as spot treatment with back packs and hand pressurized spray cans.

Question 8: What label and application rate changes have the MAATF submitted since 1999?

Response 8:

The MAATF does not have records of all the label changes that were done since 1999. The current applications and rates are detailed in the Master label that is attached (see Appendix Q-8) and is being submitted to EPA's Registration Branch.

Question 9: Does the MAATF intend to submit label or application rate changes that it would like EPA to consider during reregistration (e.g., master labels)?

Response 9:

The current applications and rates to be considered during reregistration are detailed in the Master label that is attached and is being submitted to EPA's Registration Branch.

Question 10: Please provide annual usage estimates for MSMA, DSMA, CAMA, and cacodylic acid (DMA) and the sources for usage information.

Response 10:

The total estimated usage of MAA, based on total sales of MSMA, DSMA, CAMA and cacodylic acid in the USA during 2004, is 4,839,103 lbs.

Question 11: What is a typical rotation cycle for cotton? How many years does the field rest before it is replanted with cotton? In general, for how many consecutive years is MSMA/DSMA/CAMA/DMA applied to cotton fields?

Response 11:

Most of the MSMA used in cotton is in areas where weather conditions favor both cotton and weed growth: Alabama, Georgia, Louisiana, Arkansas, Mississippi, Tennessee and South Carolina. Less MSMA is used in areas where the weed problem is less severe due to drier weather: Arizona, New Mexico, Texas, Oklahoma, Missouri and California.

Many growers in the Mississippi Delta areas of Mississippi, Louisiana and Arkansas grow cotton crops annually with no rotation with other crops. In other cotton growing areas, the cotton crop is rotated, usually every other year, with corn or soybeans.

We estimate that no more than 20% of cotton acreage in the US is treated with MSMA.



Response to Questions and Requests for Information from the MAA Research Task Force

March 14, 2005

C. Follow up

Question 12: *In regard to the January 12, 2005 meeting, please provide the MOE calculations used to generate the slides (and from what the exposure inputs were derived) including both the food and the water calculations.*

Response 12:

At our meeting on January 12, 2005 at EPA, we presented a hypothetical margin of exposure (MOE) calculation for dimethylarsinic acid (DMA) in drinking water in the US. Using a precursor indicator of cancer as the endpoint of concern, the MOE analysis yielded an estimate of 400,000. This memo responds to your request to provide the technical basis for these calculations.

The MOE was calculated using the following equation:

$$MOE_{(cancer\ precursor)} = \frac{NOEL}{Dose} = \frac{NOEL}{C \times IR_{water} \div BW}$$

Where:

NOEL = No Observed Effect Level (in mg/kg/day) for the cancer precursors, bladder necrosis and hyperplasia in two year bioassay

C = Concentration of DMA in drinking water

IR_{water} = Average water ingestion rate

BW = Average adult body weight

The specific assumptions and their basis are described below.

For identification of a no observed effect level (NOEL) appropriate for carcinogenicity, we used a chronic two-year DMA bioassay, in which bladder tumors were observed in female rats at 8.0 mg/kg/day, but not at 3.2 mg/kg/day (Life Science Research, 1991; USEPA, 2001b). There was evidence of pre-neoplastic changes (*i.e.*, bladder cell necrosis and hyperplasia) at 3.2 mg/kg/day, but not at 0.79 mg/kg/day.

Because bladder cell necrosis and hyperplasia are critical events in the mode of action for rat bladder tumors, the value of 0.79 mg/kg/day was chosen for the NOEL for female rats. This is a conservative approach, because the NOEL for bladder tumors is 4 times higher. For completeness, we also present the MOE calculation using the NOEL for bladder cell necrosis and hyperplasia for male rats.

For the exposure assessment in the assessment presented at EPA, we chose a hypothetical concentration of DMA in drinking water. We did not present an MOE calculation based on food at the January 12, 2005 meeting, because EPA has recently waived the tolerance for DMA in meat, milk, poultry and eggs for the reason that no residues were found in these matrices (Federal Register, Feb. 11, 2004). In addition, no DMA residues have been found in food matrices from cotton (MRID 44087401). However, some estimates of the amount of DMA in the diet were presented in an earlier EPA document (US EPA, 2001b) thus, we present an additional analysis below based on those data.

Because there are no data regarding concentrations of DMA in drinking water, we conservatively estimated an upper bound value. Available information indicates that concentrations of DMA in groundwater are negligible and often below method detection limits (Chatterjee *et al.*, 1995; Chen *et al.*, 1994, as cited in NRC, 1999). Thus, we assumed arsenic was present in drinking water at the maximum contaminant level (MCL) (USEPA, 2001a) and that 1% of the arsenic was in the form of DMA (*i.e.* 0.1 µg/L DMA). Additionally, we used an average water intake of 1.4 L/day for a 70 kg adult as recommend by the USEPA (USEPA, 1997). The values that were used in the calculation and the appropriate citations are presented in Table 12-1.

Table 12-1: MOE Assumptions for Cancer Analysis

	Value	Basis
DMA in Drinking Water	0.1 µg/L	Negligible amounts of DMA in water (as cited in NRC, 1999)
Water Intake	1.4 L	Average adult water intake (USEPA, 1997)
Body Weight	70 kg	Approximate Average adult body weight (USEPA, 1997)
Health Endpoint From Animal Studies	0.79 mg/kg/d	NOEL for bladder cell necrosis and hyperplasia in female rats in two-year bioassay (USEPA, 2001)
Health Endpoint From Animal Studies	0.73 mg/kg/d	NOEL for bladder cell necrosis and hyperplasia in male rats in two-year bioassay (USEPA, 2001)

Using these assumptions the average adult daily dose for DMA from drinking water is 2×10^{-6} mg/kg/day, and the resulting MOEs are approximately 365,000 for males and 400,000 for females.

An alternate calculation uses an average lifetime dietary daily dose estimate of DMA for the US population, of 2×10^{-7} mg/kg/d. EPA published this estimate in the HED Chapter of the Deregistration Eligibility Decision Document for DMA (US EPA, 2001b).

Using NOEL values from Table 12-1 and DMA dietary intake, the MOE values are calculated according to the equation below. Resulting MOEs are well over 3,000,000 for males and females.

$$MOE_{(cancer\ precursor)} = \frac{NOEL}{Dose}$$

for males:

$$MOE_{(cancer\ precursor)} = \frac{NOEL}{Dose} = \frac{0.73}{2.0 \times 10^{-7}} = 3,650,000$$

for females:

$$MOE_{(cancer\ precursor)} = \frac{NOEL}{Dose} = \frac{0.79}{2.0 \times 10^{-7}} = 3,950,000$$

Combing the hypothetical calculation of DMA and drinking water with daily dietary dose estimates yields an MOE of approximately 330,00 for males and 360,000 for females. These calculations are presented below:

for males:

$$MOE_{(cancer\ precursor)} = \frac{NOEL}{Dose} = \frac{0.73}{2.0 \times 10^{-6} + 2.0 \times 10^{-7}} = 331,818$$

for females:

$$MOE_{(cancer\ precursor)} = \frac{NOEL}{Dose} = \frac{0.79}{2.0 \times 10^{-6} + 2.0 \times 10^{-7}} = 359,090$$

In view of the recently published “Science Issue Paper: Mode of Action for Cacodylic Acid (Dimethylarsinic Acid, DMA(V)) and Recommendations for Dose Response Extrapolation” (US EPA, 2005), we added an alternative calculation of the MOE based on a point of departure (POD) from a benchmark dose analysis. According to EPA’s Science issue paper, the BMDL₁₀¹ for cell proliferation is 0.29² mg/kg/day. Using this BMDL₁₀ as a POD, the MOE is 145,000 based on the hypothetical upper bound DMA drinking water intake and 1,450,000 based on the DMA dietary intake from the HED chapter. Combining estimates of DMA in food and water, the resulting MOE is 131,800³. All of these MOE values are large enough to indicate that DMA exposure from food and water would be associated with negligible risk.

We also calculated an MOE for noncancer endpoints using data from the same two-year chronic bioassay in rats and the estimated human exposures described above. The assumptions used for this calculation are described in Table 12-2. Using the theoretical exposure concentration of 0.1 µg/L for DMA in drinking water and the chronic dietary daily dose derived by EPA, we calculated an MOE of approximately 47,000 for noncancer endpoints.

Table 12-2: MOE Assumptions for Noncancer Analysis

	Value	Basis
DMA in Diet	1 x 10 ⁻⁶ mg/kg/day	Chronic dietary dose to assess noncancer risk (USEPA, 2001b)
DMA in Drinking Water	0.1 µg/L	Negligible amounts of DMA in water (as cited in NRC, 1999)
Water Intake	1.4 L	Average adult water intake (USEPA, 1997)
Body Weight	70 kg	Approximate Average adult body weight (USEPA, 1997)
Health Endpoint From Animal Studies	0.14 mg/kg	NOEL for increased follicular epithelial cell height in male rats in two-year bioassay (USEPA, 2001)

¹ The lower 95th confidence interval on the benchmark dose associated with a 10 % response. We chose the BMDL₁₀ as a more appropriate POD than the BMDL₁ because the BMDL₁₀ is associated with less uncertainty while still being conservative.

² EPA calculated a BMDL₁₀ of 0.29 mg/kg/day using DMA doses that reflected rat body weight and food consumption at the end of the study period. It is more appropriate, however, to calculate the BMDL₁₀ assuming average body weight and food consumption over the whole study period. Using revised doses that reflect average rat body weight and food consumption, the corrected BMDL₁₀ is 0.43 mg/kg/day.

³ Using the correct value of 0.43 mg/kg/day for the BMDL₁₀, these values are: 215,000 for drinking water exposure, 2,150,000 for food exposure and 195,000 for the combined exposure.

Table 12-3 summarizes the results of MOE analyses for various endpoints and exposures:

Table 12-3: Summary of MOEs Based on Various Endpoints and Exposures

Endpoint	MOE		
	Hypothetical intake in water	Dietary intake	Dietary intake and hypothetical water combined
NOEL for bladder cell necrosis and hyperplasia (males)	365,000	3,650,000	330,000
NOEL for bladder cell necrosis and hyperplasia (females)	400,000	3,950,000	360,000
BMDL ₁₀ based on cell proliferation data (females only)	145,000	1,450,000	131,800
NOEL for noncancer endpoint (males only)	70,000	140,000	47,000

In summary, based on consideration of chronic exposure to DMA from water and food, the calculated values for the MOE range from approximately 130,000 to 400,000 for cancer precursor endpoints, and from approximately 47,000 to 140,000 for noncancer endpoints. The magnitudes of these MOE values indicate that DMA is unlikely to be of toxicological concern at any plausible human exposures.

References

National Research Council, Subcommittee on Arsenic in Drinking Water. 1999. *Arsenic in Drinking Water*. National Academy Press (Washington, DC) 310p.

USEPA. 1997. Exposure Factors Handbook - Volume 1. General Factors; EPA/600/P-95/002Fa. National Center for Environmental Assessment, Office of Research and Development, August.

USEPA. 2001a. "National Primary Drinking Water Regulations; Arsenic and Clarifications to Compliance and New Source Contaminants Monitoring (Final rule.)" Fed. Reg. 66:6975-7066. January 22.

USEPA. Locke D. 2001b. Internal memorandum to K. Monk re: Cacodylic acid and sodium salt. [Review of] The HED chapter of the Reregistration Eligibility Decision document (RED). 61p, February 20.

US EPA. 2005. "Science Issue Paper: Mode of Action for Cacodylic Acid (Dimethylarsinic Acid, DMA(V)) and Recommendations for Dose Response Extrapolation." Office of Pesticide Programs, Health Effects Div. July 26. Accessed on August 18, 2005 at http://www.epa.gov/oppsrd1/reregistration/cacodylic_acid/.