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Probabilistic Analysis of Human Health Risks Associated with Background Concentrations of Inorganic Arsenic: Use of a Margin of Exposure Approach

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ABSTRACT

Substantial evidence exists from epidemiological and mechanistic studies supporting a sublinear or threshold dose–response relationship for the carcinogenicity of ingested arsenic; nonetheless, current regulatory agency evaluations have quantified arsenic risks using default, generic risk assessment procedures that assume a linear, no-threshold dose–response relationship. The resulting slope factors predict risks from U.S. background arsenic exposures that exceed certain regulatory levels of concern, an outcome that presents challenges for risk communication and risk management decisions. To better reflect the available scientific evidence, this article presents the results of a Margin of Exposure (MOE) analysis to characterize risks associated with typical and high-end background exposures of the U.S. population to arsenic from food, water, and soil. MOE values were calculated by comparing a no-observable-adverse-effect-level (NOAEL) derived from the epidemiological literature with exposure estimates generated using a probabilistic (Monte Carlo) model. The plausibility and conservative nature of the exposure and risk estimates evaluated in this analysis are supported by sensitivity and uncertainty analyses and by comparing predicted urinary arsenic concentrations with empirical data. Using the more scientifically supported MOE approach, the analysis presented in this article indicates that typical and high-end background exposures to inorganic arsenic in U.S. populations do not present elevated risks of carcinogenicity.

Key Words: dose–response relationship, carcinogenicity, margin of exposure, arsenic, background exposures.

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INTRODUCTION AND BACKGROUND

Quantifying the potential carcinogenic risks associated with ingestion of low doses of inorganic arsenic by U.S. populations has been the subject of scientific debate for decades (*e.g.*, USEPA 1988, 1997a, 2001a, 2007; Loehr *et al.* 1989; NRC 1999, 2001). Among the most extensively debated topics are the nature of the dose–response relationship for arsenic carcinogenicity and the most relevant epidemiological data for assessing the carcinogenic potency of arsenic. Choices made regarding these issues have substantial implications for resulting risk estimates and risk-based regulatory and policy decisions.

Most regulatory agency evaluations have applied default generic risk assessment procedures to quantify the carcinogenicity of ingested arsenic. In particular, these analyses have typically included the critical assumption that the arsenic dose–response relationship is linear and has no threshold[1] (*i.e.*, that even low exposures to arsenic are associated with increased cancer risk and that risk increases proportionally with exposure). Such assumptions frequently result in estimated risks that exceed certain regulatory levels of concern at relatively low arsenic exposure levels. However, substantial evidence exists from epidemiological, animal, and mutagenicity studies supporting a sublinear or a threshold dose–response relationship for arsenic at typical U.S. environmental exposure levels. Using this evidence in a scientifically supported approach yields results indicating that ingestion of low levels of arsenic is unlikely to be associated with elevated cancer risk.

The analysis presented in this article assesses the validity of the assumption that the dose–response relationship for carcinogenicity associated with arsenic ingestion is nonlinear at low doses. The conclusions of this assessment are then used to estimate the risk associated with exposure of the U.S. population to typical background levels of arsenic from food, water, and soil. A probabilistic (Monte Carlo) model is used to generate an exposure distribution. Potential risks associated with the estimated exposure levels are evaluated using a margin of exposure (MOE) approach, a method for quantifying potential toxic effects for toxicants when a threshold dose is believed to exist. This risk assessment method provides important perspective on the available scientific database regarding the dose–response relationship for ingested arsenic.

Toxicity Assessment

For compounds considered known or likely carcinogens, the U.S. Environmental Protection Agency (USEPA) and other regulatory agencies typically develop quantitative toxicity factors (*e.g.*, cancer slope factors or CSFs) to estimate the risks associated with specific exposure levels. These factors are usually developed using mathematical models to predict the risks associated with lesser doses by extrapolating risk levels observed at high doses (either in humans or animals), and commonly assume a linear dose–response relationship at low doses.

Some scientists argue that the dose–response relationship for carcinogens is always linear, because of the "additivity to background" factor. The "additivity to background" concept is a mathematical approach to dose extrapolation that is based on

[1]A threshold dose is a dose below which health effects, including carcinogenic health effects, are not induced.

the hypothesis that, like radiation carcinogenesis, chemical carcinogenesis is also caused by direct damage to deoxyribonucleic acid (DNA), and thus has a linear dose–response relationship and lacks a threshold (Crump *et al.* 1976). This concept was developed in the 1940s and 1950s and continued through the 1970s with the development of the Ames assay for mutagenicity and a variety of other genotoxicity assays. However, it was later demonstrated that numerous chemicals that produce cancer, especially in rodents, act by a non-DNA reactive, non-mutagenic mode of action (USEPA 2006a; Cohen 1998a; Cohen *et al.* 2004). These non-DNA reactive modes of action include key events of biological processes that involve other types of toxicity that are nonlinear and have a threshold (Meek *et al.* 2003; Boobis *et al.* 2006).

The clearest example of a threshold effect is the relationship between urinary tract calculi and urinary bladder cancer in rodents (IARC 1999). Calculi can be produced by a variety of chemicals, such as uracil, melamine, fosetyl-A1, carbonic anhydrase inhibitors, sulfonamides, and HIV-protease inhibitors in the rodent bladder. The sustained presence of the calculi in the urinary bladder acts as a physical abrasive, producing cytotoxicity, necrosis, consequent regenerative hyperplasia, and ultimately tumors. Based on the physico-chemical property of solubility, calculi form only when sufficiently high concentrations of the chemical (or metabolite) are present to cause calculi precipitation. If the solubility is not exceeded (*i.e.*, the concentrations are less than the threshold), then calculi do not form and there is no cytotoxicity, hyperplasia, or tumor induction.

Moreover, it must be recognized that even a linear molecular process does not necessarily translate to a linear dose–response relationship for tumorigenicity. The basis for this statement is that subsequent, intervening processes (that are not linear) may influence the dose–response. Moreover, for an agent to add linearly to background occurrence of the response of interest, it is necessary that the agent add to the existing process in a linear manner (Rhomberg 2004). There is no evidence that this linear additivity occurs with inorganic arsenic because of the potential role of cytotoxicity and regenerative hyperplasia in arsenic carcinogenicity (Arnold *et al.* 2007; Lu *et al.* 2007) and the lack of evidence of background cytotoxicity. Thus, additivity to background is unlikely to be relevant to arsenic carcinogenicity (as will be discussed in greater detail in the section *Mechanistic Evidence of a Nonlinear Dose–Response Relationship*).

Cancer slope factor values for inorganic arsenic derived using default linear approach

To date, several government agencies have developed cancer slope factor (CSF) values to quantify cancer risk for ingested arsenic. All of these analyses have assumed a linear dose–response relationship, but have resulted in very different CSF values. Government agency-derived CSFs and key features of their derivation are summarized in Table 1. The derived CSFs for arsenic range from 0.4 $(\text{mg/kg-day})^{-1}$ to 23 $(\text{mg/kg-day})^{-1}$, an almost 60-fold difference (*e.g.*, CALEPA 2004; CPSC 2003; NRC 2001; USEPA 1998, 2001a, 2005b). The differences are due primarily to the type of cancer data used in the evaluation (*e.g.*, data for skin cancer *vs.* internal cancers), and the assumptions used to extrapolate results observed in the study population at high exposures to predict potential health effects at the low exposure levels that are typically encountered in U.S. populations.

Table 1. Summary of cancer slope factors for ingested inorganic arsenic.

Slope Factor $(mg/kg\text{-}day)^{-1}$	Source	Agency	Comments	Reference
1.5	Integrated Risk Information System (IRIS)	USEPA	Currently listed in IRIS; based on skin cancer incidence in SW Taiwan	USEPA (1998)
0.4–3.67	Final Rule for arsenic MCL	USEPA	Range based on Taiwanese water intake and arsenic in food; also based on bladder and lung cancer in SW Taiwan	USEPA (2001a)
23	NRC Arsenic in Drinking Water Report	NAS	Calculated based on excess lung and bladder cancer risk estimates in SW Taiwan	NRC (2001)
3.67	Draft CCA re-registration, CCA risk assessment, and organic arsenic herbicide re-registration	USEPA	Based on upper range established in MCL rule	USEPA (2003)
0.41–23	Petition to ban CCA wood	CPSC	Based on USEPA and NRC assessments	CPSC (2003)
5.7	Proposed IRIS revision	USEPA	Based on bladder and lung cancer in SW Taiwan; uses many of NRC's recommendations	USEPA (2005b)
9.5	Documentation for public health goal in California	CALEPA	Based on bladder and lung cancer but considers data in addition to the SW Taiwan data	CALEPA (2004)

MCL = Maximum Contaminant Level; NRC = National Research Council; CCA = Chromated Copper Arsenate; USEPA = U.S. Environmental Protection Agency; NAS = National Academy of Sciences; CPSC = Consumer Product Safety Commission; CALEPA = California Environmental Protection Agency.

The various evaluations of the arsenic CSF use different assumptions to arrive at different quantitative estimates of arsenic's potency, but all of these analyses contain several qualitative features that make them conservative and likely to overestimate arsenic cancer risk. Most importantly, the assumption of linearity (which assumes any exposure to arsenic results in an increased risk) is not supported by current science and leads to overly conservative risk estimates. Extrapolation is necessary because the data forming the basis for the CSF are from a population in SW Taiwan exposed

to arsenic concentrations in drinking water in the range of hundreds of micrograms per liter (Tseng *et al.* 1968; Tseng 1977; Wu *et al.* 1989). In contrast, overall U.S. arsenic exposure levels are substantially lower with typical arsenic concentrations in U.S. drinking water supplies having a geometric mean value of less than 1 μg/L (*e.g.*, USEPA 2001a).

Scientists and regulatory agencies have recognized that using the data from SW Taiwan and assuming a linear dose–response relationship may overestimate U.S. risks. For example, a USEPA analysis undertaken to support revisions to the arsenic drinking water standard noted,

> Independent scientific panels who have considered the Taiwan study have raised the caution that using the Taiwan study to estimate U.S. risk at lesser levels may result in an overly conservative estimation of U.S. risk. The independent panels have all said that, at concentrations less than the observed range of the high level of contamination in the study from SW Taiwan, the shape of the dose-response relationship is likely to be sublinear. Thus, an assumption that the effects seen per dose increment remain the same from high to low levels of dose may overstate the U.S. risk. (USEPA 2001a, p. 7004)

In addition, in the studies of the populations from SW Taiwan, specific exposure levels experienced by individuals were not precisely measured and thus are uncertain. As explained in more detail in the *Discussion* section, exposures other than arsenic or other factors in the study area also may have caused or contributed to the observed increases in cancer in the study population (see, *e.g.*, Brown and Ross 2002; Lamm *et al.* 2003; Lamm *et al.* 2006). Moreover, as noted later, questions have been raised regarding the degree to which the Taiwanese study population may be more susceptible to the health effects associated with arsenic exposure than U.S. populations, for example, due to differences in dose levels, genetic factors, dietary patterns, and other lifestyle factors affecting arsenic metabolism and detoxification (see, *e.g.*, Steinmaus *et al.* 2005; Meza *et al.* 2005; Hsueh *et al.* 1995).

Basis for selecting nonlinear dose–response approach for inorganic arsenic

Extensive epidemiological and mechanistic studies support the conclusion that the dose–response relationship for arsenic carcinogenicity is nonlinear. Based on these data, several reviews have suggested that linear extrapolation from data reflecting high dose levels may overestimate risks in the United States (USEPA 1997a; NRC 1999; Rossman 2003; Schoen *et al.* 2004; USEPA 2001a). The epidemiological and mechanistic evidence that supports a nonlinear dose–response relationship for inorganic arsenic is described in the following sections.

Epidemiological evidence of a nonlinear dose–response relationship. Epidemiological studies conducted worldwide have repeatedly demonstrated that cancers associated with inorganic arsenic ingestion are observed only in populations exposed to arsenic concentrations in drinking water that are greater than 150 μg/L. For example, Guo *et al.* (2001) conducted a study in SW Taiwan (using a different cohort than that used in the population studies presented in Tseng *et al.* 1968, Tseng 1977, and Wu *et al.* 1989). The Guo *et al.* (2001) study showed a consistent increase in skin cancer (*i.e.*, basal cell carcinoma) only in males and only in the highest dose group, which

was exposed to arsenic concentrations in drinking water greater than 640 μg/L. Similarly, in a study of a population in Inner Mongolia, increased skin cancer incidence was observed only in individuals exposed to peak arsenic concentrations of 150 μg/L or greater (Tucker *et al.* 2001).

Guo (2004) observed increased risk of lung cancer in a population of males and females in SW Taiwan exposed to arsenic in drinking water, but only when arsenic concentrations were greater than 640 μg/L. In a case-control study of a population from Argentina (including 114 cases and 114 controls), no association was observed between arsenic ingestion and bladder cancer, even in the group exposed to arsenic in drinking water at concentrations of 200 μg/L and greater (Bates *et al.* 2004).

In a recent publication, Lamm *et al.* (2006) reported a revised analysis of the extensive data set available from populations in SW Taiwan (NRC 1999; Wu *et al.* 1989). This data set is the same one that forms the basis for the USEPA's most recently published CSF value for arsenic (USEPA 2001a, 2003). Conducting a linear regression analysis examining the relationship between arsenic exposure and combined bladder and lung cancer mortality based on all of the study villages, Lamm *et al.* (2006) found that arsenic concentration accounted for only 21% of the variance in the standard mortality ratio (SMR; $r^2 = 0.21$, $p = .03$). Through several alternative investigations, the researchers found that a factor related to township location influenced cancer mortality and needed to be accounted for to accurately characterize arsenic's carcinogenic potency.

Specifically, stratifying the data by township showed a relationship between arsenic concentrations in drinking water and combined lung and bladder cancer incidence in only three of the six studied townships (Figure 1). In these three townships (townships 2, 4, and 6), the association between arsenic concentrations in drinking water and cancer risk ($r^2 = 0.748$, $p = .001$) was stronger than when the data set was considered as a whole (*i.e.*, unstratified). The dose–response relationship for these townships had an apparent threshold, with bladder and lung cancer risk significantly increased (*i.e.*, SMR values greater than 100) only at drinking water concentrations greater than 150 μg/L (95% CI: 42–229 μg/L). In townships 0, 3, and 5, however, the association was not significant ($r^2 = 0.053$, $p = .3$); SMRs were high even when arsenic concentrations in drinking water were low. In addition, SMRs did not increase with increasing arsenic exposure, indicating that the elevated lung and bladder cancer mortality in these villages cannot be attributed to arsenic exposure.

A threshold at 150 μg/L of inorganic arsenic in drinking water is consistent with results of studies conducted in the United States, all of which do not show an increased cancer risk in populations exposed to arsenic in drinking water at mean concentrations up to 190 μg/L (Bates *et al.* 1995; Lewis *et al.* 1999; Moore *et al.* 2002; Steinmaus *et al.* 2003; for review, see Schoen *et al.* 2004). For example, the USEPA sponsored and directed a large-scale study in Utah to determine whether elevated arsenic concentrations in drinking water were associated with disease (Lewis *et al.* 1999). This study found no dose-dependent cancer or non-cancer effects at average arsenic concentrations in drinking water up to 190 μg/L (with arsenic concentrations in drinking water supplies ranging from 3.5 to 620 μg/L). Recently, another USEPA study conducted in Fallon, Nevada demonstrated no association between arsenic concentrations up to 100 μg/L in drinking water and multiple cancer types, as well as non-cancer effects (Calderon *et al.* 2006; Rubin *et al.* 2007).

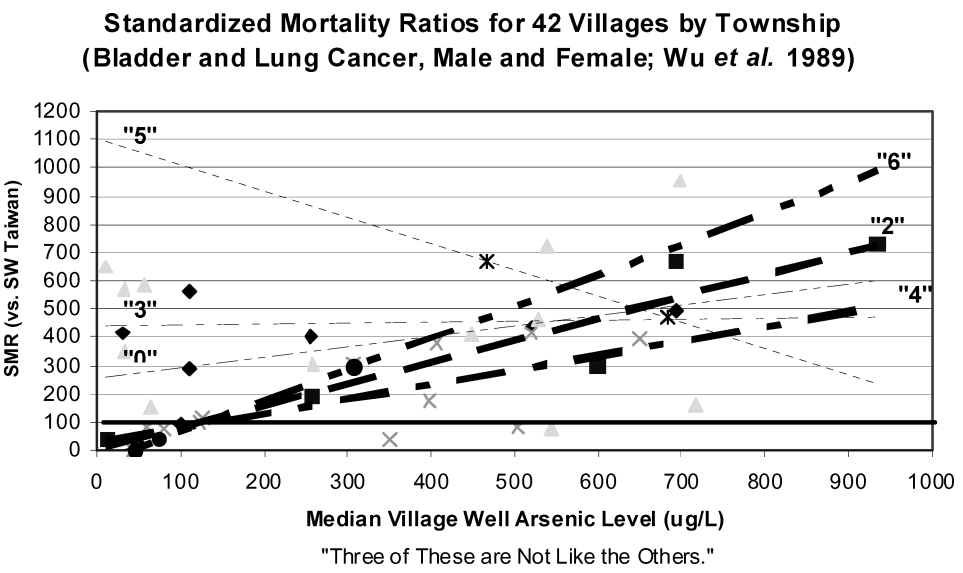

Figure 1. Summary of results of Lamm *et al.* (2006) re-analysis of Taiwanese data. (Adapted from Lamm 2006.) Linear regression analysis of SMR for bladder and lung cancer in males and females *vs.* median village well water arsenic level by township. For townships 2, 4, and 6 (bolded lines), there is a statistically significant relationship between arsenic exposure and increase cancer risk. For townships and 0, 3, and 5 (unbolded lines), the relationship is not significant.

At a September 12–13, 2005 Science Advisory Board (SAB) Arsenic Review Panel meeting, a rigorous meta-analysis was presented demonstrating that "low-level" exposure to arsenic in drinking water (*i.e.*, drinking water concentrations in the range of 100–200 μg/L) is not associated with increased risk of bladder cancer (Mink 2005; Exponent 2005). The meta-analysis had specific criteria for the inclusion of studies. For example, the analysis considered only case-control or cohort studies that included exposure to low levels of arsenic. Based on the selection criteria, a total of eight U.S. and non-U.S. studies was included in the analysis. To ensure that inconsistencies and uncertainties in certain data sets did not affect the results, the researchers conducted the analysis in several different ways. Considering variations in exposure measurements, the influence of smoking, and study location, the overall analysis showed that combined relative risk was not significant. The only relative risks that were statistically elevated were obtained when the analysis was restricted to individuals who had ever smoked ("ever smokers"); however, those results were inconsistent.

Some recent studies conducted in the United States report an association with low levels of arsenic in drinking water and certain adverse health effects. These studies have several methodological problems, however, and cannot be used to establish a relationship between low-level arsenic exposure and disease. Specifically, Knobeloch *et al.* (2006) examined an association between arsenic in drinking water in Wisconsin and self-reported skin cancer. Residents were asked to submit water samples and

fill out a questionnaire regarding skin cancer incidence. Because the skin cancer diagnosis was self-reported and water sampling was not random, results are highly unreliable and subject to bias. Another study conducted in Michigan did not find any evidence of increased cancer risk, but found elevated risk of cerebrovascular disease, diabetes mellitus, and kidney disease (Meliker *et al.* 2007a); however, this study had an ecological design with no information on individual arsenic exposures or any other risk factors.

Several studies conducted in the United States have used toenail arsenic concentrations as an indicator of exposure to evaluate the association between arsenic and cancer. Toenail arsenic measurements are difficult to quantitatively relate to arsenic drinking water concentrations, but are potentially useful for gaining insight into longer term arsenic exposures (*i.e.*, exposure durations that are longer than 3 months). In a case-control study, Karagas *et al.* (2001) examined the relationship between toenail arsenic concentrations and two types of skin cancer (basal cell carcinoma [BCC] and squamous cell carcinoma [SCC]). Overall, no statistically significant association was found for arsenic exposure and skin cancer (Karagas *et al.* 2001; Karagas *et al.* 1998).

Karagas *et al.* (2004) also used toenail arsenic to evaluate the association between arsenic exposure and bladder cancer. This study found no association between arsenic exposure and bladder cancer risk among subjects who were non-smokers. For smokers, there was no dose–response relationship between toenail arsenic and bladder cancer risk.

In summary, multiple epidemiological studies support the conclusion that the dose–response relationship for arsenic-induced cancer is nonlinear and is likely to have a threshold. In particular, elevated cancer risks associated with arsenic exposure have not been observed in U.S. populations exposed to arsenic concentrations in drinking water with mean concentrations up to 190 μg/L (the highest mean concentration in these studies).

Mechanistic evidence of a nonlinear dose–response relationship. The epidemiological evidence of a nonlinear or threshold dose–response relationship for arsenic carcinogenicity is further supported by a mechanistic understanding of how arsenic affects the cellular processes involved in carcinogenesis. As recognized by the recent USEPA Science Advisory Panel (SAP) for arsenic, "Inorganic arsenic (iAs^{III}) and its metabolites are not direct genotoxicants because these compounds do not react with DNA" (USEPA, 2007, p. 5). This conclusion is based on mechanistic studies that demonstrate that arsenic does not interact directly with DNA to produce point mutations (ATSDR 2007; Kligerman *et al.* 2003).

Instead, the available scientific literature demonstrates that arsenic may modify DNA function through one or more indirect mechanisms. These mechanisms include inhibition of DNA repair, induction of dysfunctional cell division, perturbation of DNA methylation patterns, modulation of signal transduction pathways (leading to changes in transcriptional controls and the over-stimulation of growth factors), and generation of oxidative stress (see, *e.g.*, Schwerdtle *et al.* 2003; Germolec *et al.* 1998; Chen *et al.* 2004; Kligerman *et al.* 2005; Rossman 2003; Schoen *et al.* 2004; Snow *et al.* 2005). However, evidence for these indirect genotoxicity mechanisms has been generated using *in vitro* investigations, nearly all of which have used concentrations

of arsenic that are cytotoxic. Such studies raise the question as to which is causative, the genotoxicity or the cytotoxicity.

Cancer ultimately results from the accumulation of multiple genetic alterations in a single cell—either inherited or, more commonly, from somatic mutations arising during DNA replication (Knudson 1971; Greenfield *et al.* 1984; Cohen and Ellwein 1990; Moolgavkar *et al.* 1981; Cohen 1998b). Such DNA alterations can be caused by an agent directly damaging the DNA (with consequent mutation) or by increasing the number of DNA replications in the target cell population (*i.e.*, pluripotential cells of a tissue). Increased replication amplifies the opportunity for "spontaneous" genetic errors. Chemical alterations to DNA occur several hundred to thousands of times per day in each cell secondary to oxidative damage, deamination, exocyclic adducts, and other chemical reactions. Most of these errors are repaired by the exquisite array of enzymes that function to protect the integrity of DNA.

Increased DNA replications are produced either by increased cell births or by decreased cell deaths, both yielding an increased number of cells (Cohen 1998b). The critical parameter is the number of DNA replications, rather than the replication rate. Increased cell births can be caused by direct mitogenesis, involving effects on endocrine or paracrine factors, or by increasing cell deaths with consequent regenerative proliferation. Decreased cell deaths can occur by inhibiting apoptosis or by inhibiting cellular differentiation (a cell death process).

Cytotoxicity with consequent regenerative cell proliferation is a common mode of action for a variety of chemicals involving several tissues, such as liver, skin, urinary bladder, kidney, and others (Meek *et al.* 2003). Several examples have been recognized by various scientific organizations and regulatory agencies, most notably the induction of liver and kidney tumors by chloroform (Meek *et al.* 2003). A nonlinear, threshold dose response using a margin of exposure approach is, in fact, recommended for chloroform (USEPA 2001b).

Also, dimethylarsinic acid (DMA^{V}) produces bladder tumors in rats at high doses by generating a reactive metabolite, dimethylarsinous acid (DMA^{III}). This metabolite is excreted in the urine at cytotoxic concentrations, producing urothelial necrosis with consequent regenerative hyperplasia and ultimately tumors (Cohen *et al.* 2007). At low oral exposure levels, insufficient DMA^{III} is excreted in the urine to produce cytotoxicity, and consequently no hyperplasia or tumors occur.

A recent study in mice and rats shows that arsenate or arsenite causes a similar cytotoxicity followed by compensatory cell regeneration in bladder epithelial cells, a mode of action associated with a threshold (Arnold *et al.* 2007; Lu *et al.* 2007). This mode of action is supported by *in vitro* inorganic arsenic research demonstrating that, when properly assayed, indirect genotoxicity often appears secondary to arsenic-induced cytotoxicity (USEPA 2007; Komissarova *et al.* 2005).

Inorganic arsenic-induced skin cancer also appears to involve increased cell proliferation, likely associated with cytotoxicity and regeneration (Kirkham 1997). Actinic keratosis—the preneoplastic lesion to epidermal carcinoma in humans—features increased proliferation of the basal and suprabasal keratinocytes and is associated with a chronic inflammatory cellular infiltrate (Kirkham 1997).

A recent collaborative effort between the USEPA and several other research groups has investigated dose-dependent changes in arsenic-induced gene expression and possible implications for carcinogenesis. After reviewing more than 400 papers

of the currently available *in vivo* and *in vitro* literature regarding arsenic-induced gene changes, these scientists found that low level arsenic exposures (between 0.1 and 1 μM) induce a protective or adaptive cellular response. This response is characterized by the induction of genes that commonly respond to proteotoxicity and oxidative stress (*e.g.*, superoxide dismutase, heat shock protein 32). These responses would not be expected to be carcinogenic and may be protective. They appear to occur at doses that are an order of magnitude less than doses that cause tumorigenic changes, and provide further support for a nonlinear or threshold dose–response relationship (Clewell *et al.* 2007).

At greater concentrations (1–10 μM), gene markers for cellular toxicity are also observed, but genes related to apoptosis, DNA-repair, and proliferation become upregulated, indicating recognition of DNA damage and a possible compensatory response. Importantly, at the higher end of this range of concentrations (>5 μM), the key DNA repair gene—DNA ligase—becomes suppressed. The authors suggest that these gene changes likely reflect early pre-cursor events in the cytotoxicity-related carcinogenic mode of action (Clewell *et al.* 2007). The identification of a precise tumorigenic threshold from changes in transcription of genes related to carcinogenesis is complicated, particularly when using data from animal and *in vitro* studies. In addition, consideration must be given to the magnitude of the transcriptional changes, and their relationship to changes in protein synthesis, as well as to changes in the transcription of other genes related to carcinogenesis. Because of the complex nature of the carcinogenic process and the involvement of multiple events, the actual tumorigenic threshold would be greater than the transcriptional threshold dose.

Moreover, inorganic arsenic may have hormetic effects, that is, low doses of inorganic arsenic may have a beneficial health effect (Calabrese and Baldwin 2003; Calabrese 2005). This potential hormetic effect was also recognized by the SAB Arsenic Review Panel (USEPA 2007). Support for hormetic effects of inorganic arsenic comes from both *in vitro* and *in vivo* studies. *In vitro* studies demonstrate that exposures to low levels of inorganic arsenic elicit different cellular responses than exposures to greater doses (Clewell *et al.* 2007), and that low-level exposures can be protective against other toxic insults (Snow *et al.* 2005; Calabrese and Baldwin 2003; Calabrese 2005). Snow *et al.* (2005) demonstrated that low-level exposure to inorganic arsenic (0.5 μM) reduced the amount of reactive oxygen species constitutively generated in keratinocytes and fibroblasts. In addition, these authors showed that inorganic arsenic reduced the amount of reactive oxygen species in these cell types when they were challenged with the oxidizing agent menadione.

In animal studies, hormetic effects have been observed in several species including mice, rats, hamsters, minipigs, goats, and chickens. For example, Snow *et al.* (2003) demonstrated that mice exposed to 0.2–2 μg/L arsenate in drinking water were protected against skin tumors induced by dimethylbenzanthrazene (DMBA)/phorbol 12-tetradecanoate 13-acetate (TPA). Uthus and Davis (2005) demonstrated that rats fed 0.5 μg/g of inorganic arsenic had lesser levels of aberrant crypt foci in colon cells compared to rats fed either 0 or 50 μg/g of inorganic arsenic. Uthus (2003) has noted that the beneficial effects of low-level inorganic arsenic exposure may be related to the methyl recycling of DNA, with both inorganic arsenic deprivation and excessive supplementation disrupting DNA methylation patterns. It is unknown,

however, if it is the modulation of DNA methylation or other mechanisms that are responsible for beneficial effects noted in these animal studies (Uthus 1992). Also, a recent study showed that exposure to arsenic yielded a "U-shaped" dose–response relationship in mean arterial pressure in *in vivo* and *in vitro* models. Arsenic caused a decrease in mean arterial pressure at low doses and an increase at high doses (Bae *et al.* 2008). Although a hormetic effect of inorganic arsenic requires further investigation, these observations strongly support a nonlinear dose–response relationship for inorganic arsenic.

As described earlier, information reviewed by the recent SAB arsenic review panel provided strong evidence of nonlinearity for the dose–response of inorganic arsenic carcinogenicity (USEPA 2007). The Panel ultimately decided, however, to recommend linear extrapolation at low doses, noting that due to uncertainties in arsenic pharmacokinetics and pharmacodynamics, there was "insufficient justification for the choice of a specific nonlinear form of the dose-response relationship" (p. 44). The Panel noted that this decision is in accordance with the USEPA *Guidelines for Carcinogen Risk Assessment* (Cancer Guidelines) (USEPA 2005a). However, according to USEPA guidance, nonlinear models should be considered in risk assessment when the mode of action supports a nonlinear dose–response relationship, even if there is some uncertainty with respect to the specific mechanisms involved in a particular mode of action.

A framework for evaluating mode of action and its human relevance was developed initially by several U.S. and international agencies involved in chemical evaluations (*e.g.*, the International Life Sciences Institute—Risk Science Institute, the USEPA, Health Canada, and the International Programme on Chemical Safety; Meek *et al.* 2003; Boobis *et al.* 2006; Seed *et al.* 2005), and is now an integral part of the USEPA's evaluation of carcinogens. The framework specifies that modes of action for non-DNA reactive carcinogens can have commonly recognized toxicological effects (such as cytotoxicity) and be associated with nonlinear, threshold dose–response relationships. The USEPA's current Cancer Guidelines state that "A nonlinear extrapolation method can be used for cases with sufficient data to ascertain the mode of action and to conclude that it is not linear at low doses but with not enough data to support a toxicodynamic model" (USEPA 2005a, p. 3-23).

In several recent risk assessments, the USEPA has determined that certain chemicals exhibit a nonlinear dose–response relationship and has characterized human cancer risk using an MOE approach. For example, the USEPA has used a nonlinear approach for chloroform since 2001 (USEPA 2001b) and for captan since 2004 (USEPA 2004a). Also, in its recent review of the USEPA's evaluation of dioxin toxicity, the National Academy of Sciences (NAS) recommended that, based on mode of action information, the USEPA should estimate risks for dioxin using both a linear and nonlinear approach (NRC 2006). In January 2006, the USEPA's Office of Pesticide Programs (OPP) concluded that dimethylarsinic acid (DMA, a metabolite of inorganic arsenic) causes bladder cancer in rats through a nonlinear mode of action (*i.e.*, cytotoxicity followed by regeneration). As a result, the USEPA recommended that risks associated with DMA exposure be characterized using a nonlinear approach (USEPA 2006a). Thus, for substances where there is sufficient evidence of nonlinearity, it is appropriate and consistent with USEPA guidance and practice to use nonlinear models, including an MOE approach to characterize cancer risks.

The Margin of Exposure (MOE) approach for inorganic arsenic

In light of the substantial evidence supporting a nonlinear dose–response relationship for the carcinogenicity of ingested inorganic arsenic, it is scientifically appropriate to use an MOE analysis to estimate cancer risks associated with inorganic arsenic. To calculate an MOE, an estimated exposure level is compared with a dose level reflecting a specific level of risk for a particular health endpoint. In the current analysis, a NOAEL was selected based on an analysis of available epidemiological data and was compared to an exposure estimate derived for a specific exposure scenario, that is, exposures of the U.S. population to typical background levels of arsenic from food, water, and soil. In this analysis, calculated MOE values that are greater than 1 indicate that the estimated exposure level is less than the NOAEL, an exposure level associated with no elevated risk of cancer.

The recent study by Lamm *et al.* (2006) provides a reliable quantitative estimate of an arsenic no-effect level and a basis to derive an NOAEL that can be used to evaluate the potential carcinogenic risk associated with exposure to inorganic arsenic. As discussed in detail earlier, the Lamm *et al.* (2006) analysis uses data from a study conducted in SW Taiwan to demonstrate a threshold for arsenic-induced bladder and lung cancer at an arsenic concentration in drinking water of 150 μg/L—a value supported by numerous other epidemiological studies (*e.g.*, Bates *et al.* 1995; Lewis *et al.* 1999; Moore *et al.* 2002; Steinmaus *et al.* 2003; Schoen *et al.* 2004). Some scientists have offered alternative estimates of a potential NOAEL for arsenic carcinogenicity. A summary of alternative NOAELs and the data on which they are based is presented in the *Discussion* section.

For this MOE calculation, the selected NOAEL value (expressed as a drinking water concentration) was converted into a daily dose using intake assumptions recommended by USEPA workgroup (USEPA 2005c). Specifically, it was assumed that an average 55 kg Taiwanese male ingests 3.5 L/day of drinking water directly and an additional 1 L/day of water through use in cooking, and also ingests 30–50 μg/day of inorganic arsenic through other dietary sources. Using these exposure assumptions, a NOAEL for ingested inorganic arsenic of 0.013 mg/kg-day was calculated for use in the MOE evaluation presented in this article.[2]

EXPOSURE ASSESSMENT

The exposure assessment component of this analysis quantitatively estimated U.S. exposures to inorganic arsenic from typical background sources, focusing on ingestion of inorganic arsenic *via* the diet, drinking water, and soil. Potential exposures *via* inhalation or dermal exposure routes were not included in the exposure calculations because these pathways are negligible contributors to overall arsenic exposures, as demonstrated in Valberg *et al.* (1997), Cohen *et al.* (1998), and Meacher *et al.* (2002).

This assessment focuses on the potential for inorganic arsenic exposures to increase carcinogenic risks; therefore, the relevant exposure estimate is the lifetime

[2]This value is calculated using the following equation: ([arsenic concentration in water × water intake] + dietary intake)/ (body weight × conversion factor), or (150 μg/L × 4.5 L/day) + 40 μg/day)/(55 kg × 1,000 μg/mg).

average intake of arsenic (see, *e.g.*, USEPA 1989). Thus, the exposure calculations were designed to derive the average background arsenic intake of typical U.S. individuals throughout an entire lifetime. Exposures were assumed to occur during every year of an individual's lifetime, and appropriate parameters for different life stages (*i.e.*, children *vs.* adults) were incorporated into the analysis.

Background exposures to arsenic vary among members of the U.S. population due to differences in arsenic concentrations in source media to which individuals may be exposed (*e.g.*, in soil or water), or due to different behavioral patterns that may affect arsenic intake (*e.g.*, differences in food consumption). Therefore, a probabilistic Monte Carlo approach was used to estimate a range of potential exposure levels in the U.S. population. A Monte Carlo analysis accommodates a distribution of values for a given input parameter (*e.g.*, a range of water intake rates or arsenic concentrations) and allows different combinations of input parameter values to be modeled based on the specified distributions. In this case, the Monte Carlo analysis was conducted using Crystal Ball® software and incorporated 10,000 iterations of the exposure estimate calculations.

To estimate exposures of children and adults *via* ingestion of arsenic in food, water, and soil, the following basic exposure algorithm was developed.

$$\begin{aligned} ALDD_{As} = &(((I_{f\text{-adult}} \times CF_1) + (C_w \times I_{w\text{-adult}}) + (RBA_s \times C_s \times I_{s\text{-adult}} \times CF_2)) \\ &\times (ED_{adult}/(BW_{adult} \times LT))) + (((I_{f\text{-child}} \times CF_1) + (C_w \times I_{w\text{-child}}) \\ &+ (RBA_s \times C_s \times I_{s\text{-child}} \times CF_2)) \times (ED_{child}/(BW_{child} \times LT))) \end{aligned}$$

where: $ALDD_{As}$ is Average lifetime daily dose of arsenic (mg/kg-day), I_f is Intake of arsenic from food (μg/day), CF_1 is Conversion factor (1 mg/1,000 μg/mg), C_w is Concentration of arsenic in water (mg/L), I_w is Intake of drinking water (L/day), RBA_s is Relative bioavailability adjustment factor for arsenic in soil (unitless), C_s is Concentration of arsenic in soil (mg/kg), I_s is Incidental soil ingestion rate (mg/day), CF_2 is Conversion factor (1 kg/1,000,000 mg), ED is Exposure duration (years), BW is Body weight (kg), LT is Lifetime (years).

This algorithm reflects standard components and approaches for estimating exposures as presented in risk assessment guidance (*e.g.*, USEPA 1989). Values for each of the input parameters that best reflect currently available scientific data were selected based on a review of information available in the scientific literature and other sources. The input assumptions for arsenic intake *via* the diet, water, and soil are summarized in Table 2 and are described in more detail in the following sections.

Input Assumptions for Dietary Exposure

Dietary arsenic has been shown to be an important contributor to human arsenic exposures. Previous studies have estimated dietary intake rates; however, most studies only include information regarding total arsenic or organic arsenic (the more prevalent form of arsenic in food) rather than inorganic arsenic, which is the more toxicologically relevant form (*e.g.*, Tao and Bolger 1999; Dougherty *et al.* 2000). Two studies of dietary arsenic intake in U.S. children and adults provide the most comprehensive and well-supported estimates of dietary intake of inorganic arsenic that are currently available (Yost *et al.* 2004; Schoof *et al.* 1999a). Therefore, the distributions reported in these studies were used in this Monte Carlo analysis.

Table 2. Summary of Monte Carlo parameter assumptions and inputs.

Parameter	Assumptions: Distribution type	Assumptions: Values	Source	Basis for selection
Diet				
Dietary intake—Child (1 to 6 years)	Lognormal	GM = 0.18 μg/kg-day GSD = 1.70 95th percentile = 0.41	Yost *et al.* (2004)	(a) Most comprehensive available data regarding dietary intake of inorganic As in U.S. populations (b) Provides speciated arsenic data and distribution of intake estimates (c) Reflects primary food sources and typical food intake patterns
Dietary intake—Adult	Lognormal	GM = 0.032 μg/kg-day GSD = 2.36 95th percentile = 0.13	Schoof *et al.* (1999a)	Same considerations as above
Drinking water				
As concentrations in drinking water—Groundwater	Lognormal	GM= 0.78 μg/L GSD = 4.85 95th percentile = 10.5	USEPA (2001a)	Most recent and comprehensive national data regarding arsenic concentrations in drinking water supplies
As concentrations in drinking water—Surface water	Lognormal	GM= 0.19 μg/L GSD = 5.70 95th percentile = 3.26	USEPA (2001a)	Same considerations as above
Drinking water intake—Child	Lognormal	GM = 0.41 L/day GSD = 2.06 95th percentile = 1.25	USEPA (2004b) (Table 4.1.D1)	Most recent and comprehensive national data regarding water intake; based on intake data from CSFII survey (from 1994–1996) and reflecting total direct and indirect water ingestion from a variety of sources
Drinking water intake— Adult	Lognormal	GM = 1.19 L/day GSD = 1.91 95th percentile = 3.19	USEPA (2004b) (Table 4.1.D1)	Same considerations as above

Soil				
Soil intake—Child	Lognormal	GM = 45 mg/day GSD = 1.85 95th percentile = 124	Stanek and Calabrese (1995a, 2000)	(a) Based on well-conducted mass balance study (Amherst, MA) (b) Reflects effort to predict longer-term average intakes (c) Appears to be conservative based on values observed in other analyses, *e.g.*, Anaconda, MT study (Stanek and Calabrese 2000) and Washington study (Davis and Mirick 2006)
Soil intake—Adult	Lognormal	One-half of that for children	Calabrese *et al.* (1990); Davis and Mirick (2006); Stanek *et al.* (1997); USEPA (1997b)	(a) Consistent with USEPA standard deterministic recommendations for soil ingestion rates and available study data (b) Implicitly takes into account efforts to estimate long-term intake based on short-term data
As concentrations in "background" soil	Lognormal	GM = 5.2 mg/kg GSD = 2.23 95th percentile = 19.5	Dragun and Chekiri (2005)	Recent comprehensive summary of national data for the United States
Bioavailability	Triangular	vertices at 0.01, 0.16, 0.5 (unitless)	Roberts *et al.* (2002, 2007)	(a) Based on primate studies conducted using consistent, sound methodology and soils with a variety of arsenic sources (16 sites) (b) Range reflects results found in scientific literature (c) Middle vertex reflects median value observed in Roberts *et al.* studies (d) Accounts for uncertainties regarding applicability of range of soil types for "background" arsenic in soil

(Continued on next page)

Table 2. Summary of Monte Carlo parameter assumptions and inputs. *(Continued)*

Parameter	Assumptions: Distribution type	Assumptions: Values	Source	Basis for selection
Other				
Body weight—Child (3–4 year old)	Normal	mean = 15.7 kg SD = 1.7 95th percentile = 18.5	Finley *et al.* (1994)	(a) Based on NHANES II data (from 1976–1980) (b) Values generally consistent with USEPA's Exposure Factors Handbook (c) For young children, used average values for mid-point of age range of interest
Body weight—Adult (>18 years old)	Normal	mean = 71 kg SD = 15.9 95th percentile = 97.2	Finley *et al.* (1994)	Same considerations as above
Exposure duration	Point	70 years	USEPA (1997b)	Used a point estimate because estimating typical lifetime background intake
Lifetime	Point	70 years	USEPA (1997b)	Same considerations as above

GM = geometric mean; GSD = geometric standard abbreviation; NHANES = National Health and Nutrition Examination Survey.

To derive the distributions presented in these two dietary studies, Yost and Schoof and their colleagues measured inorganic arsenic concentrations in 40 food types that they had determined to be the source of approximately 90% of the inorganic arsenic intake in the U.S. population (Yost *et al.* 1998; Schoof *et al.* 1999b). The concentrations of arsenic in these foods were then combined with information from the U.S. Department of Agriculture's Continuing Surveys of Food Intakes by Individuals (CSFII) regarding U.S. national food consumption patterns to derive a distribution of arsenic intake rates. Reflecting diary information collected for two nonconsecutive days from a representative sample of U.S. residents, the CSFII database includes information regarding regional and intraindividual variability in daily food intake. Separate evaluations were performed for children and adults, yielding the two distributions applied in these Monte Carlo calculations (shown in Table 2).[3,4]

Very little information is available regarding the absorption of ingested inorganic arsenic from food in the gastrointestinal tract. As a conservative assumption, this Monte Carlo analysis assumed that 100% of ingested dietary arsenic would be absorbed from the gastrointestinal tract; although several publications report less than complete absorption of dietary arsenic (*e.g.*, Laparra *et al.* 2005; Juhasz *et al.* 2006).

Input Assumptions for Drinking Water Exposure

Arsenic concentrations in drinking water

A number of sources exist for data regarding arsenic concentrations in water supplies. In particular, several national surveys of drinking water quality have been conducted over the past three decades (*e.g.*, Chappell *et al.* 1994; Frey and Edwards 1997; Focazio *et al.* 2000; USEPA 2000). These surveys vary in size and scope, but generally were designed to provide representative data from water supplies throughout the United States.

The most recent of these surveys was conducted by the USEPA to support decision-making regarding the MCL for arsenic (USEPA 2000, 2001a). This survey is based on compliance sample data supplied by 25 states, reflecting more than 18,000 community water supply systems. For most states, the compliance monitoring data represent almost all of the groundwater and surface water community water supply

[3]Note that these articles did not provide raw data or specific information regarding the shapes of the distributions they generated for dietary intake. Based on the available information, it was found that use of a normal distribution required truncation of the lower portion of the distribution to avoid incorporation of negative dietary intake estimates in the Monte Carlo analysis. Because a lognormal distribution also provided a reasonable fit to the available information and avoided the issue of truncation, such a distribution was used in the Monte Carlo analysis. To assess the implications of the alternative distribution assumptions, the exposure calculations were performed using both a lognormal and a truncated normal distribution for the dietary intake estimates. Use of the truncated normal distribution did not yield substantially different results from those presented in this article.

[4]Note that a recent publication indicates that regional variations may exist in arsenic concentrations in U.S. rice, an important dietary source of background arsenic intake (Williams *et al.* 2007). Review of the recent data indicates, however, that consideration of these data would not significantly alter the exposure and risk assessment conclusions derived in the current MOE analysis.

systems in the state, although some areas in New England, the mid-Atlantic states, and the southeastern portion of the United States had limited numbers of compliance monitoring data sets. In addition, the USEPA considered data from smaller, non-community water supply systems that were included in the states' compliance data sets. These data were considered to be less reliable because they included large numbers of values that were less than identified detection limits. Thus, the USEPA analyzed these non-community data separately.

This latest USEPA survey reflects the most current and comprehensive nationwide analysis of drinking water supplies from both groundwater and surface water sources. Therefore, these data were used to derive inputs for the Monte Carlo exposure model. Specifically, based on the USEPA documentation, the lognormal distributions shown in Table 2 were used to represent arsenic concentrations in U.S. drinking water supplies derived from surface water and groundwater sources. In light of the limitations and uncertainties in the non-community water supply data, the distributions used in this analysis were based on the community water supply data. Comparison of the USEPA data with the results observed in two less comprehensive water supply surveys (Frey and Edwards 1997; Focazio *et al.* 2000) indicated that the USEPA results were consistent with those observed in the other surveys, further supporting the use of the USEPA data as a representative data source for the Monte Carlo analysis.

The available survey data generally indicate greater concentrations of arsenic in groundwater than in surface water (*e.g.*, USEPA 2000). In addition, regional differences were observed. For example, Frey and Edwards (1997) found that arsenic concentrations in surface water from the east coast, southeastern regions, and the midwestern portion of the United States are less than those in the rest of the nation. They also observed that high arsenic concentrations in groundwater were prevalent in the western parts of the United States. These regional differences in arsenic concentrations may not be fully distinguished in the available overall distributions of arsenic concentrations in drinking water. Therefore, this issue was explored further in the sensitivity analyses conducted for this assessment.

Relative contributions of surface water and groundwater sources to overall background arsenic exposures were estimated in the Monte Carlo analysis by apportioning the exposures from each source based on the proportion of the U.S. population served by each source type. Information to support this apportionment was derived from the USEPA data indicating that approximately 67% of the U.S. population obtains drinking water from surface water sources, whereas 33% rely on groundwater sources of drinking water (USEPA 2006b).[5]

Drinking water intake

Drinking water intake rates of the U.S. population have been studied in a number of surveys (*e.g.*, USEPA 1997b). In 2004, the USEPA published updated data on per capita water ingestion rates in the United States to support decision-making regarding the MCL for arsenic in drinking water (USEPA 2004b). Intake rates were

[5]USEPA data indicate that 11,403 community water systems rely on surface water sources and serve 178.1 million people, whereas 42,661 systems rely on groundwater sources and serve 85.9 million people (USEPA 2006b).

estimated based on dietary and demographic data collected during the U.S. Department of Agriculture's (USDA) CSFII survey conducted in 1994 through 1996 and in 1998. As noted earlier, the CSFII surveys collect data on intake of food and beverages for two nonconsecutive days and are designed to be representative of the entire U.S. population. In the survey, participants were asked to specify the amount of water consumed from various sources, including community water, bottled water, and other sources. In addition, the survey yielded information regarding "indirect" water consumption rates by combining food consumption data with recipe and nutritional information. The survey did not specifically solicit information from population subgroups that may have unusual patterns of water intake due to lifestyle characteristics, climate, or other factors; however, the potential impact of these unusual water intake rates was explored in the uncertainty and sensitivity assessments that were undertaken for this analysis.

The data from the USEPA's most recent comprehensive survey (USEPA 2004b) were selected as the basis for the distributions used in the Monte Carlo analysis because they provide representative information for U.S. residents and reflect a wide range of direct and indirect sources of water intake. The values used in the Monte Carlo analysis (shown in Table 2) are based on USEPA's data for total direct and indirect water intake. Water ingestion rates were modeled as lognormal distributions because this distribution best fit the data presented by the USEPA and this approach is consistent with other analyses of drinking water intake rates (*e.g.*, Roseberry and Burmaster 1992).

Input Assumptions for Soil Exposure

Arsenic concentrations in soil

The distribution of background arsenic concentrations in U.S. soils that was used in the Monte Carlo analysis was derived from a comprehensive compilation of background element concentrations in soils (Dragun and Chekiri 2005). The authors reviewed 300 papers and books addressing background concentrations in soil and included only those studies reporting background concentrations that were not influenced by anthropogenic sources. This compilation was selected for use in the Monte Carlo analysis because it reflects the most recent and comprehensive evaluation of background soil data.

Reflecting limitations in available analytical methods for soil measurements, this compilation provides background concentrations of total arsenic and does not present data regarding speciated forms of arsenic present in soil. Arsenic occurs in soil primarily in its inorganic form (Meacher *et al.* 2002); therefore, in the Monte Carlo analysis, the soil concentrations of total arsenic were used, and were assumed to represent inorganic arsenic concentrations, as a conservative approach. For the conterminous United States, Dragun and Chekiri (2005) reported that arsenic concentrations range from <0.01 to 97 μg/g. The values represent the results of a survey of 1257 samples collected by the U.S. Geological Survey at locations throughout the coterminous United States. These samples were collected from the upper 20 cm of soil at locations selected to focus on soils that were undisturbed or minimally disturbed. These data formed the basis of the lognormal distribution used in the Monte Carlo analysis (shown in Table 2).

Incidental soil ingestion rate

A number of studies have been undertaken to estimate children's incidental ingestion of soil (*e.g.*, Stanek and Calabrese 1995a,b, 2000; Stanek *et al.* 1999, 2001a,b; Davis and Mirick 2006). These studies have estimated incidental ingestion rates (in units of mg of soil intake per day) using a mass balance approach comparing concentrations of various trace elements in residential soil and dust with concentrations of the same trace elements in food and fecal samples for the studied children. A range of potential values for this parameter exists because of inter-individual variability among different children and intra-individual variability in ingestion rates on different days and under various exposure conditions. Analyses of the available study data have examined the relative reliability of the trace elements used in the studies, the inter- and intra-individual variability in daily soil ingestion rates observed in the studied children, and the implications of using data from short-term studies to estimate long-term patterns of soil ingestion.

The goal of this analysis is to estimate long-term daily exposure to background sources of arsenic. Therefore, a distribution designed to predict long-term average incidental soil ingestion rates was selected for use in these calculations and is shown in Table 2 (Stanek and Calabrese 1995a, 2000). This distribution is based on a study of 64 children between the ages of 1 and 4 years old residing in the town of Amherst, Massachusetts. This distribution was selected because it reflects one of the most comprehensive and detailed studies of children's incidental soil ingestion that has been conducted to date, and because it incorporates an effort to predict longer-term average intake rates. In addition, this distribution appears to be conservative (*i.e.*, health-protective) based on values observed in other studies (*e.g.*, Stanek and Calabrese 2000; Davis and Mirick 2006), that is, the results from this study generally yield greater soil ingestion rates than indicated by these other recent studies. Moreover, because children between the ages of 1 and 4 years old tend to have greater incidental soil ingestion rates than other age groups (see, *e.g.*, USEPA 1994, 1997b), use of this distribution to estimate soil ingestion rates for the broader age range examined in this analysis (*i.e.*, 0- to 6-year-old children) will tend to overestimate likely actual soil ingestion rates for young children in this analysis.

Data regarding incidental soil ingestion rates in adults are far more limited, particularly information regarding the likely distributions of soil ingestion rates or long-term average rates (*e.g.*, Calabrese *et al.* 1990; Stanek *et al.* 1997; Davis and Mirick 2006). In the absence of such information, the incidental soil ingestion rate for adults was assumed to be one-half of that for children. This assumption is consistent with the USEPA standard risk assessment guidance, which recommends a mean soil ingestion rate for adults that is one-half of the recommended value for children less than 6 years old (USEPA 1997b) and is also consistent with approaches used in other analyses (*e.g.*, Buck *et al.* 2001, Georgopoulos *et al.* 2007) and with other reviews of available data that have generally estimated incidental soil ingestion rates for adults as one-half or less of rates estimated for young children (*e.g.*, as summarized in Paustenbach *et al.* 1992). Basing the adult distribution on the selected distribution for young children also inherently incorporates efforts to adjust data collected in short-term studies to derive long-term average intake rates.

Relative bioavailability adjustment factor for soil

A critical factor in evaluating the potential intake of arsenic from soil is arsenic's bioavailability, that is, the amount of ingested arsenic that is actually absorbed into the body. It is generally recognized that arsenic that is adsorbed to ingested soil or other solid media is absorbed by the body less than ingested arsenic that is dissolved in water (*e.g.*, USEPA 1989; NEPI 2000). A number of studies have been undertaken to measure the relative bioavailability of ingested inorganic arsenic from soil and other solid media in a variety of experimental systems, including studies using primates, rats, pigs, and *in vitro* systems designed to mimic conditions in the gastrointestinal tract (*e.g.*, Freeman *et al.* 1993, 1995; Groen *et al.* 1994; Valberg *et al.* 1997; Rodriguez *et al.* 1998, 1999; Ruby *et al.* 1999; NEPI 2000; Ellickson *et al.* 2001; Roberts *et al.* 2002, 2007; Palumbo-Roe *et al.* 2005; Carrizales *et al.* 2006; Rieuwerts *et al.* 2006; Juhasz *et al.* 2007). Arsenic sources in these studies included mining, milling, and smelting facilities; pesticides and herbicides; and bog ore and ironstone. In all of these studies, arsenic bound to soil and other solid media has been found to be less bioavailable than soluble arsenic compounds, with nearly all of the reported RBA estimates for arsenic in soil and other solid media in these studies being less than 50%.

The toxicity factors commonly used to quantify arsenic carcinogenicity are derived from studies of populations exposed to arsenic in drinking water,[6] a medium from which arsenic bioavailability is considered to be 100%. When estimating exposure and risk associated with arsenic in soil, an RBA factor that reflects the absorption of arsenic from soil relative to that from water needs to be incorporated. Such an approach has been recommended by several regulatory agencies (*e.g.*, USEPA 1989; WVDEP 1998; MIDEQ 2000; FDEP 2004, 2005; University of Florida 2005) and has been applied in certain decision-making settings, for example, determining risk-based cleanup requirements at specific sites (*e.g.*, Gradient 2000; ODEQ 1994; Larson [MIDEQ] 1995).

In selecting an appropriate distribution for this parameter, it was determined that a distribution reflecting results from a range of types of arsenic sources would best reflect the likely diversity in arsenic bioavailability from potential sources for background exposures. In addition, in identifying specific quantitative values for the distribution, primary emphasis was placed on two recent studies that used primates as the test animal; used a consistent, sound test methodology; and conducted studies for soil types reflecting a wide spectrum of arsenic sources (Roberts *et al.* 2002, 2007).

Specifically, using *Cebus* and *Cynomolgus* monkeys, these researchers derived RBA values for soil samples from 16 sites spanning a wide variety of arsenic sources (including soils from smelter and mining sites; herbicide, pesticide, and chemical plant facilities; residential yards; wood treatment sites; orchards; cattle dip vat sites; and electrical substations; Roberts *et al.* 2002, 2007). The tested sites were also diverse geographically, including sites from New York, Florida, Colorado, Montana, and Hawaii. RBA values for these soils ranged from 5% to approximately 30%, with a median of 16%.

Because of the uncertainties regarding the actual contributions of specific arsenic source types to "background" soil exposures, a triangular distribution was selected to

[6]As discussed in the *Toxicity Assessment* section.

reflect the potential diversity in bioavailability of various source materials, as shown in Table 2. The middle vertex of the triangular distribution was set based on the median value observed in the Roberts studies. The lower and upper vertices were selected based on RBA observations reported in the scientific literature. In particular, although the upper vertex (50%) is greater than the maximum RBA value observed in the Roberts studies, it was selected as a conservative (*i.e.*, health-protective) value to reflect a high-end estimate of RBA presented in the published literature and the potential uncertainties associated with bioavailability from a variety of source materials of background arsenic in soil.

Other Input Parameters

The intent of the exposure analysis was to estimate average lifetime exposures to ubiquitous background sources of arsenic; therefore, certain input parameters related to the duration of exposure were set as deterministic point estimates. Thus, it was assumed that individuals experienced the estimated exposures throughout their lifetimes and no reductions in exposure duration were assumed to occur for such life changes as moving to a different residence. As a result, the overall lifetime was set at a point estimate of 70 years, the standard USEPA default assumption for lifetime duration used in calculating cancer toxicity criteria (USEPA 1997b). The overall lifetime was allocated between an exposure duration of 6 years for the portion of the total lifetime spent as a young child, and 64 years for the remaining portion spent as an older child and adult, again based on standard USEPA risk assessment assumptions (USEPA 1997b).

The distributions of body weights used in the Monte Carlo analysis were derived based on the second National Health and Nutrition Examination Survey (NHANES II), conducted by the U.S. Public Health Service. In this survey, conducted between 1976 and 1980, information was collected regarding the height and weight of several thousand men and women residing in the United States. The data are statistically weighted to represent the entire U.S. population based on age, sex, and race. The normal distributions applied in this Monte Carlo analysis (shown in Table 2) reflect the Brainard and Burmaster (1992) reanalyses of these data, which are still the most reliable and comprehensive data currently available for estimating body weight distribution, as summarized by Finley *et al.* (1994). For the child age range of 0 to 6 years old examined in the Monte Carlo analysis, a weight distribution for 3-year-old children (the midpoint of the range) was used. The average body weights from these distributions are consistent with the standard USEPA-recommended deterministic estimates for adults and young children (USEPA 1997b).

EXPOSURE AND RISK CALCULATIONS

Using the approaches and assumptions described earlier, the Monte Carlo model was run to estimate lifetime-averaged exposures to ingested inorganic arsenic from background sources. The estimates of the total ALDDs for ingestion of arsenic from background sources ranged from 2.91×10^{-5} mg/kg-day for the 5th percentile estimate to 2.25×10^{-4} mg/kg-day for the 95th percentile estimate (summarized in Table 3 and Figure 2). Dietary sources were the primary contributors to overall

Table 3. Summary of background arsenic intake results.

	Average lifetime daily dose (mg/kg-day)			
Exposure source	Mean	5th percentile	50th percentile	95th percentile
Diet	6.08×10^{-5}	1.99×10^{-5}	4.80×10^{-5}	1.44×10^{-4}
Water	3.39×10^{-5}	1.16×10^{-6}	$1.11\text{E} \times 10^{-5}$	1.22×10^{-4}
Soil	1.07×10^{-6}	8.07×10^{-8}	5.86×10^{-7}	3.56×10^{-6}
Total	9.57×10^{-5}	2.91×10^{-5}	7.07×10^{-5}	2.25×10^{-4}

background exposures to arsenic, with drinking water sources providing the next highest contributions. Incidental soil ingestion was a negligible contributor to the overall exposure estimates. For example, based on the mean ALDD estimates, diet contributed 64%, drinking water contributed approximately half as much (35%), and incidental soil ingestion contributed approximately 1% of the total background intake. At the higher percentiles of the exposure distribution, drinking water is a more significant contributor to overall exposures than at the lower percentiles (illustrated in Figure 2). This observation suggests that drinking water can be a significant contributor to overall arsenic exposures for individuals living in areas with high arsenic concentrations in drinking water or with high consumption rates of arsenic-containing water.

Other analyses of arsenic intake also identified dietary sources followed by drinking water sources as the primary contributors to exposure (*e.g.*, Valberg *et al.* 1997; Meacher *et al.* 2002; Tsuji *et al.* 2007; Georgopoulos *et al.* 2007), consistent with the results of the current analysis. Moreover, the amount of arsenic intake estimated from background exposure sources is consistent with values calculated by other researchers (*e.g.*, Meacher *et al.* 2002; Meliker *et al.* 2007b; Georgopoulos *et al.* 2007; Tsuji *et al.* 2007; illustrated in Table 4).

The exposure estimates generated by the Monte Carlo analysis were used to evaluate the potential health risks associated with exposures to inorganic arsenic from

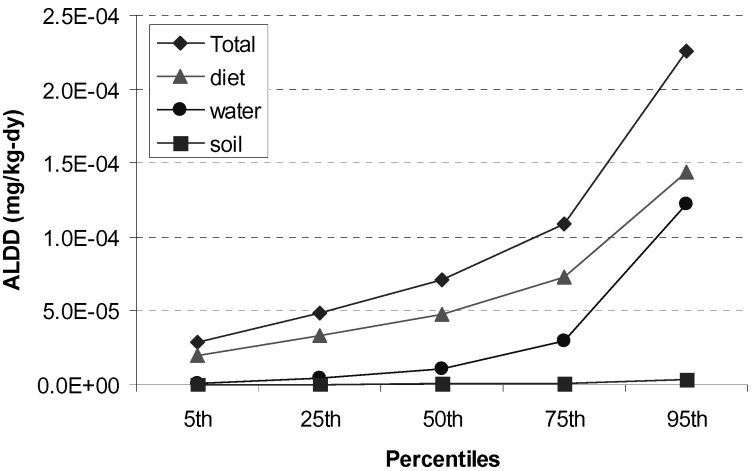

Figure 2. Summary of results of probabilistic exposure analysis.

Table 4. Summary of background arsenic exposure estimates.

	Estimated exposure		
Exposure source	Mean	5th percentile	95th percentile
U.S. background exposures *via* diet, water, and soil (current analysis)	7 μg/day[a]	2 μg/day[a]	16 μg/day[a]
U.S. background exposures (Meacher *et al.* 2002)	6.3 μg/day (males) 5.2 μg/day (females)	1.4 μg/day (males) 1.0 μg/day (females)	15.9 μg/day (males) 13.2 μg/day (females)
SE Michigan exposures *via* diet and water (Meliker *et al.* 2007b)[b]	3 to 9 μg/day	—	15 to 30 μg/day
U.S. background exposures*via* diet and water (Tsuji *et al.* 2007)	5.6 μg/day	—	10.5 μg/day
U.S. background exposures *via* diet, water, air, and soil in Franklin County, OH (Georgopoulos *et al.* 2007)[c]	5.85 μg/day (males) 4.70 μg/day (females)	—	—

[a]Calculated from exposure estimates assuming a 70-kg body weight.
[b]This analysis incorporated consideration of lifetime spatial and temporal differences in exposures.
[c]This analysis used an integrated, biologically based model (MENTOR) to assess exposures and also included results for Hunterton County, NJ and Pima County, AZ. Although specific exposure estimates weren't provided for the 5th and 95th percentiles, these authors indicated that their exposure results were generally in agreement with those of Meacher et al. (2002).

background sources. To provide a basis for comparison, potential health risks were estimated using approaches reflecting both the generic linear dose–response assumption and the MOE approach reflecting a nonlinear or threshold dose–response relationship, which is more strongly supported by available scientific data.

To derive standard cancer risk estimates reflecting the generic default assumption of a linear dose–response relationship, the following standard formula was used:

$$\text{LICR} = \text{ALDD} \times \text{CSF}$$

where: LICR is Lifetime Incremental Cancer Risk (unitless), ALDD is Average Lifetime Daily Dose (mg/kg-day), and CSF is Cancer Slope Factor ($[\text{mg/kg-day}]^{-1}$).

In this analysis, LICR values were generated using two possible values for the CSF—the standard default value of 1.5 $[\text{mg/kg-d}]^{-1}$, which is listed in the USEPA's IRIS database (USEPA 1998), and an alternative value of 3.67 $[\text{mg/kg-d}]^{-1}$, which was recently developed by the USEPA's OPP and used in several recent risk assessments for inorganic arsenic (USEPA 2001a, 2003).

Table 5. Summary of risk calculation results.

	Mean	5th percentile	50th percentile	95th percentile
Exposure estimate (ALDD)	9.57×10^{-5}	2.91×10^{-5}	7.07×10^{-5}	2.25×10^{-4}
MOE estimate[a]	140	450	180	58
LICR estimate—Based on IRIS CSF[b]	1.4×10^{-4}	4.4×10^{-5}	1.1×10^{-4}	3.4×10^{-4}
LICR estimate—Based on alternative value[c]	3.5×10^{-4}	1.1×10^{-4}	2.6×10^{-4}	8.3×10^{-4}

ALDD—Average Lifetime Daily Dose (mg/kg-day).
IRIS—Integrated Risk Information System developed by the U.S. Environmental Protection Agency.
MOE—Margin of Exposure (unitless).
LICR—Lifetime Incremental Cancer Risk (unitless).
[a]MOE calculation based on Point of Departure value of 0.013 mg/kg-day.
[b]Calculation based on CSF value presented in USEPA's IRIS database: 1.5 $(\text{mg/kg-day})^{-1}$.
[c]Calculation based on alternative CSF value used in recent USEPA risk assessments: 3.67 $(\text{mg/kg-day})^{-1}$.

The lifetime incremental cancer risk estimates generated by this analysis are generally within the 10^{-4} range (as shown in Table 5). For example, the 50th percentile estimate of the LICR obtained using the CSF listed in IRIS is 1.1×10^{-4}, indicating that a lifetime of exposure to arsenic at this level would be associated with an approximately one-in-ten-thousand excess lifetime risk of developing cancer (*i.e.*, that one additional case of cancer would be expected in a population of 10,000 people experiencing this exposure).

To estimate the MOE values associated with the exposure estimates, the following formula was used:

$$\text{MOE} = \text{NOAEL}/\text{ALDD}$$

where: MOE is Margin of Exposure (unitless), NOAEL is No-Observable-Adverse-Effect-Level (mg/kg-day), and ALDD is Average Lifetime Daily Dose (mg/kg-day).

The results of the risk calculations are shown in Table 5.

DISCUSSION

Implications of Risk Calculation Results

The exposure and risk assessment results presented in Table 5 demonstrate that the choice to use an MOE approach rather than the generic default linear dose–response assumption when evaluating the potential cancer risks associated with ingestion of inorganic arsenic has significant implications for conclusions regarding the potential health risks associated with low-level arsenic exposures. As noted earlier, the cancer risk estimates calculated using the generic linear dose–response model are generally within the 10^{-4} range. In risk-based decision-making, risk levels that are less than 1×10^{-6} (or one-in-one-million) have generally been viewed as *de minimis* and too low to warrant protective action. Risk levels that are greater than

1×10^{-4} (or one-in-ten-thousand) generally have been viewed as requiring additional evaluation, although not all risk levels near or exceeding this level have been determined to require additional mitigation, including some evaluations for arsenic (*e.g.*, USEPA 1992, 2001c; USEPA Region 8 and MT DEQ 1996; USEPA Region 10 1993). Thus, these results suggest that inorganic arsenic exposures arising due to ubiquitous background sources such as arsenic in food, water, and soil may present risks of developing cancer that could exceed permissible limits in some contexts.

By contrast, use of the more scientifically sound MOE approach yields results indicating that typical background exposures to inorganic arsenic would not lead to elevated cancer risks, even for individuals experiencing exposures at the high end of the range of potential exposure levels. Specifically, an MOE value greater than 1 indicates that the estimated exposure is less than the identified NOAEL (*i.e.*, 0.013 mg/kg-day) and that increased cancer risk would not be expected. The magnitude of the MOE values derived in this analysis are substantial, even for the MOE corresponding to the high-end exposure estimates, as indicated by the results shown in Table 5. For example, the MOE for the mean exposure level is 140, the MOE for the 5th percentile exposure level is 450, and the MOE for the 95th percentile exposure level is 58. As discussed earlier, the NOAEL dose level was identified for ingested inorganic arsenic based on available epidemiological studies and reflects a conservative estimate of a threshold exposure level at which no increased cancer risk has been observed. Thus, the results of the MOE analysis demonstrate that exposures to typical levels of inorganic arsenic from background sources are not elevated above levels associated with increased cancer risk, and that additional exposures could be accommodated without exceeding the NOAEL.

Implications of Alternate Assumptions and Sensitivity Analysis

The results of the MOE analysis demonstrate that exposures of the U.S. population to typical background levels of arsenic do not yield elevated cancer risks. These results were obtained despite the use of conservative (*i.e.*, health-protective) assumptions in the exposure assessment. Thus, use of alternative values would be unlikely to change the overall conclusions of the analysis and would strengthen the basic findings. For example, despite data suggesting less than complete arsenic absorption from some media, arsenic was assumed to be relatively well-absorbed from all assessed media. For food and water (the predominant contributors to background arsenic exposure estimates), absorption of ingested arsenic was assumed to be 100%, despite the existence of studies suggesting that absorption may be less than complete under certain circumstances (*e.g.*, Pomroy *et al.* 1980; Vahter 1983; Cohen *et al.* 1998; Meacher *et al.* 2002). For example, the absorption of arsenic from cooked rice was reported to be 63% in an *in vitro* study evaluating bioaccessibility (Laparra *et al.* 2005), and 33% in an *in vivo* study assessing bioavailability (Juhasz *et al.* 2006). For absorption of arsenic from soil, the high end of the assumed distribution of RBA values used in the Monte Carlo analysis was set at 50% despite the observation of a maximum RBA value of approximately 30% in the primate studies that were determined to provide the most scientifically sound source of data for these evaluations. This conservative choice was made to reflect information available in the

scientific literature and to minimize the potential for underestimating the actual arsenic exposures arising from background sources.

The assumptions used for incidental soil ingestion rates also incorporated conservative elements. First, the assumptions used to estimate young children's soil ingestion rates were based on data collected from children between the ages of 1 and 4 years old, the age range during which the maximum incidental intake of soil is thought to occur. Actual average soil ingestion rates in the broader age range for young children examined in this Monte Carlo analysis (*i.e.*, children between 0 and 6 years old) would be less. Because the adult soil ingestion rate estimates were directly based on the children's soil ingestion rates, the conservative aspects of the children's estimates also apply to the adult estimates. Moreover, the assumption that adult soil ingestion rates are one-half of those observed in young children between the ages of 1 and 4 years old also is likely to overestimate typical soil ingestion by adults. Despite these conservative assumptions, exposures to background levels of arsenic *via* incidental soil ingestion are a negligible component of overall background exposures, contributing only approximately 1% of the total background exposures.

To evaluate the possibility that certain subsets of the U.S. population may experience exposures to background levels of arsenic that are greater than those estimated in the Monte Carlo analysis, a sensitivity analysis was conducted. As a first step, the variance in the exposure estimates that was contributed by each of the input parameters was explored by calculating rank correlation coefficients between each input parameter and the exposure estimates and using the coefficients to calculate the variance contributions from each parameter. The results of this evaluation paralleled the findings regarding the most important contributors to overall exposures. Specifically, adult dietary intake was found to contribute 62% of the overall variance, while dietary arsenic intake during childhood contributed 7% of the variance. Other important contributors to variance in the exposure estimates were associated with arsenic concentrations in groundwater (17% of the variance), arsenic concentrations in surface water (7% of the variance), and adult water intake (6% of the variance). All of the other parameters contributed less than 0.3% of the variance in the exposure estimates.

Based on these results, additional sensitivity analyses were undertaken to explore the impacts of alternative assumptions regarding dietary intake, water intake, and concentrations in groundwater and surface water—the key input parameters identified in the variance analysis. These analyses explored impacts on the ALDD and MOE estimates of increasing or decreasing the mean estimates of these parameters (by 50% in each case). An additional "worst-case" analysis was also conducted, in which the ALDD was calculated using maximum or reasonable maximum (*i.e.*, 95th percentile estimates) values for each input parameter.

The results of these evaluations are summarized in Table 6. As can be seen, changing the mean input parameters by 50% changed the resulting ALDD estimates by a much smaller amount. For example, for the adult dietary intake estimate (the parameter identified as having the most substantial contribution to variance in the exposure estimates), changing the input values by 50% changed the ALDD by only 23%. In each case, the MOE estimate generated for the modified ALDD estimates was greater than 100. These sensitivity analysis results provide further support for the conclusion that typical background exposures to inorganic arsenic are less than

Table 6. Summary of sensitivity analysis results.

Analysis	Exposure estimate (ALDD)	MOE estimate	% Change in ALDD
Original point estimate	9.30×10^{-5}	140	NA
Dietary intake—Adult			
+50%	1.14×10^{-4}	110	+23%
−50%	7.18×10^{-5}	180	−23%
Dietary intake—Child			
+50%	1.02×10^{-4}	130	+10%
−50%	8.41×10^{-5}	160	−10%
Water intake—Adult			
+50%	1.07×10^{-4}	120	+15%
−50%	7.91×10^{-5}	160	−15%
Water intake—Child			
+50%	9.51×10^{-5}	140	+2%
−50%	9.08×10^{-5}	140	−2%
Groundwater concentration			
+50%	1.03×10^{-4}	130	+10%
−50%	8.33×10^{-5}	140	−10%
Surface water concentration			
+50%	9.92×10^{-5}	130	+7%
−50%	8.67×10^{-5}	150	−7%
Worst-case analysis[a]	1.73×10^{-3}	8	NA

ALDD—Average Lifetime Daily Dose (mg/kg–day).
MOE—Margin of Exposure (unitless).
[a]The "worst-case" results were calculated using 95th percentile value estimates for all input parameters with the exception of the following parameters: the relative bioavailability adjustment (RBA) factor assumed for arsenic ingested in soil, and arsenic concentrations in surface water, groundwater, and soil. The assumed RBA value was set at 50% (the maximum value included in the distribution used in this analysis) and the media concentrations were set at the maximum values reported in underlying documentation (i.e., soil data from Dragun and Chekiri 2005 and water data from Chappell et al. 1994).

levels of concern for elevated cancer risk and that, even with greater arsenic exposures, risk levels of concern would not be exceeded.

A worst-case calculation provides further support for the conclusion that risk levels are unlikely to be elevated as a result of U.S. population exposures to background arsenic. In this calculation, individuals were assumed to be exposed simultaneously to maximum or near-maximum arsenic exposure levels in their diet, drinking water, and soil and—at the same time—to exhibit behavior patterns enhancing their exposure throughout their entire lifetimes.[7] Even under the implausible exposure conditions assumed in this worst-case analysis, the resulting MOE is 8, indicating that background arsenic exposure levels are unlikely to result in elevated cancer risks even under extreme and unlikely exposure conditions.

[7]No actual U.S. populations experiencing such combined high-end exposures are known to exist. For example, an evaluation of regional differences in background arsenic exposures

Important sources of uncertainty in the exposure analyses were also considered in interpreting the exposure assessment results. Although relatively extensive data are available for some of the input parameters used in this analysis (*e.g.*, water intake rates), limited data are available for others (*e.g.*, the bioavailability of ingested inorganic arsenic derived from background soil sources and from the diet). As discussed earlier, these uncertainties were addressed in the Monte Carlo analysis by using conservative high-end or maximum assumptions for these parameters. As a result, any future refinements in scientific knowledge regarding these parameters would serve to decrease the exposure and risk estimates derived based on this Monte Carlo analysis.

Another pervasive source of uncertainty in the results is the use of input parameter estimates based on short-term exposure data to estimate long-term exposure patterns. This source of uncertainty affects estimates of dietary intake, water intake, and incidental soil ingestion rates. Specifically, in this analysis, the exposure scenarios of concern were exposures spanning an entire lifetime. By contrast, available data regarding dietary, water, and soil intake reflect studies in which data were collected over a few days. Specifically, the USDA CSFII surveys that form the basis for the food and water intake rates used in this analysis collect food and beverage consumption data from a representative sample of the U.S. population for only a two-day period, while the soil ingestion studies typically span only a few days.

Because estimates based on short-term behavior patterns are inherently more variable than long-term average estimates, this issue may affect upper and lower percentile estimates of these intake rates, that is, exposures may be overestimated for percentiles greater than the median (Stanek *et al.* 1998; Stanek and Calabrese 2000; Givens *et al.* 2007). However, overall estimates of the mean values of the input parameters should be relatively unbiased. As described earlier, analyses are available that account for this factor and adjust the short-term incidental soil ingestion rate data for young children to estimate long-term average rates (Stanek and Calabrese 2000). These adjusted rates were used for young children in the Monte Carlo analysis and were also reflected in the adult exposure calculations (because the adult ingestion rates were estimated directly based on the child data). No such adjustments are available for water or dietary intake estimates; however, the use of the short-term data to estimate these exposure pathways should tend to overestimate high-end exposures, resulting in conservative estimates of actual exposures and risks.

Another source of uncertainty in the exposure analyses stems from the question of whether the populations from whom the available exposure data were derived are representative of typically exposed populations, or whether subpopulations exist with significantly different exposure patterns. For example, the water intake rates

found that typical exposures to inorganic arsenic *via* dietary sources were relatively similar across the United States, with the highest intakes estimated for residents of the northeastern United States (Meacher *et al.* 2002). These differences were attributed to differences in the types of food consumed rather than regional differences in arsenic concentrations in food. By contrast, inorganic arsenic exposures *via* drinking water were more variable, with the highest exposures estimated for residents of the western United States and the second highest exposures found in residents of the midwestern United States.

were estimated based on the CSFII data; however, intake rates for specific population subgroups may vary due to factors such as lifestyle characteristics, climate, or medical conditions. This source of uncertainty was examined in the Monte Carlo analysis by evaluating a hypothetical "worst-case" exposure scenario, in which high-end exposure conditions from all exposure sources (*i.e.*, diet, drinking water, and soil) were assumed to occur simultaneously. The MOE value resulting from these combined assumptions indicated that there is no elevated cancer risk, even for individuals exposed to background sources of arsenic under unlikely combined extreme conditions.

Uncertainties in the toxicity assessment portion of the analyses were also considered, including those associated with deriving the NOAEL from a drinking water concentration. Calculating the NOAEL required assumptions regarding the water intake and the amount of dietary arsenic ingested by the study subjects from SW Taiwan. As described earlier, to derive the NOAEL used in this Monte Carlo analysis, assumptions were used that are consistent with those used by the USEPA when developing the arsenic MCL (NRC 2001; USEPA 2005c).

The uncertainties in the assumed intake factors from SW Taiwan were discussed in a USEPA work group report (USEPA 2005c). Based on the limited available literature, the work group concluded that an individual from SW Taiwan is likely to drink between 1 and 4.6 L/day of water (Abernathy *et al.* 1989; Chowdhury *et al.* 2001, as cited in USEPA 2005c; Watanabe *et al.* 2004; Yang and Blackwell 1961). The amount of water consumed during cooking is even less studied; however, a few studies from Bangladesh and West Bengal indicate that 1 L of water per day is a reasonable estimate (Bae *et al.* 2002; Chowdhury *et al.* 2001, as cited in USEPA 2005c; Watanabe *et al.* 2004). Finally, the USEPA work group concluded that dietary arsenic intake was likely to range from 30 to 50 μg/day; however, this estimate is based on a single study of the Taiwanese diet (Schoof *et al.* 1998). By contrast, dietary analyses from Bangladesh and West Bengal reported much higher dietary arsenic rates (ranging from 120 to 285 μg/day; Watanabe *et al.* 2004; Chowdhury *et al.* 2001, as cited in USEPA 2005c). Although the USEPA work group remarked that arsenic dietary intakes in these countries could not be directly compared to Taiwanese intakes because of variable dietary habits and arsenic concentrations in food, this range of values was used in an approximate way to explore the impacts of the assumed intake factors on the NOAEL estimate**.**

To assess the potential impact of the SW Taiwan dietary and water intake assumptions on the derived NOAEL and the resulting MOE, a sensitivity analysis was conducted exploring a range of intake values. Although the NOAEL estimate is sensitive to these assumptions, the MOE estimates calculated based on the 95th percentile estimates of background inorganic arsenic exposure in the United States do not exceed a level of concern even when the most conservative estimates of SW Taiwan water and dietary arsenic intake are used (as shown in Table 7).

The uncertainty in exposure estimates is increased by the lack of information on individual exposure estimates in certain SW Taiwanese villages that had multiple wells with variable concentrations of arsenic. In some cases, the arsenic concentration in various wells in a given village could span orders of magnitude. In the absence of information regarding arsenic exposure on the individual level, most analyses (including USEPA 2001a) have quantified exposure by assuming that individuals

Table 7. MOE estimates based on range of plausible water and dietary arsenic intakes in Taiwan compared to 95th percentile background exposure estimates in the United States.

		Arsenic in diet (μg/day)				
Water intake		**30**	**40**	**50**	**100**	**200**
(drinking + cooking	**1**	15	15	16	20	28
water) (L/day)	**2**	27	28	28	32	40
	3	39	40	40	44	53
	4.5	57	58	59	63	71
	5	63	64	65	69	77
	6	75	76	77	81	89

living in villages with multiple wells were exposed to the median village well concentration.

Brown and co-workers have evaluated the implications of using median well concentrations to represent exposure in multi-well villages (Brown and Chen 1995; Brown and Ross 2002; Brown 2007), showing how the use of median arsenic concentrations can distort the dose–response relationship between arsenic exposure and disease. In the most recent analysis, Brown (2007) re-analyzed the Taiwan dataset and quantified risk using only those villages where there was only one well or where the arsenic concentrations in different village wells did not vary by more than 25 μg/L of arsenic. The Brown (2007) analysis resulted in a flat or even a downward trend in risk as arsenic concentrations in drinking water increased to 100 μg/L. Moreover, similar to the analysis of Lamm *et al.* (2006), which used township stratification, this analysis demonstrated a high background incidence of lung and bladder cancer that was unrelated to arsenic exposure. Although Brown (2007) analyzed the SW Taiwanese data differently from Lamm *et al.* (2006), the findings of both researchers are consistent qualitatively as well as quantitatively.

Analyses were also undertaken to explore the uncertainties inherent in the NOAEL estimate (expressed as a drinking water concentration) based on the Lamm *et al.* (2006) analysis. Specifically, alternative MOE estimates were derived using the lower bound on the 95% confidence interval for the NOAEL derived from the Lamm study. Using this alternative NOAEL value of 42 μg/L (rather than the best estimate value of 150 μg/L derived from this study), the MOE for the mean exposure level calculated in the Monte Carlo analysis would be 44, the MOE for the 95th percentile exposure level would be 19, and the MOE for the 5th percentile exposure level would be 140.

Additional uncertainties associated with the underlying data used to derive the NOAEL were also considered. Because the recommended NOAEL is based on human data, uncertainty due to interspecies differences is not an issue (such as occurs when deriving human toxicity criteria based on data from animal studies). In addition, because the NOAEL is based on data from chronic exposures, there is no uncertainty with respect to an adequate exposure duration. Uncertainty associated with intra-individual variability in response is also minimized because studies of arsenic-exposed populations in Taiwan and India provide evidence that nutritional

deficiencies in these populations have enhanced their responsiveness to arsenic-induced heath effects (*e.g.*, Steinmaus *et al.* 2005; Meza *et al.* 2005; Hsueh *et al.* 1995; Guha Mazumder *et al.* 1998; Hsueh *et al.* 1997; Mitra *et al.* 2004). Failure to consider these studies in developing toxicity assessment approaches for inorganic arsenic exposure may lead to overestimates of risks for U.S. populations where arsenic exposures (*e.g.*, from water and food) are significantly less, nutritional status is better, and socioeconomic status is higher. It should also be noted that members of the SW Taiwan population have been exposed to arsenic in drinking water over their entire lifetimes. Thus, their exposures extend over *in utero*, childhood, and adult life stages. As a result, even if certain life stages are particularly sensitive to arsenic toxicity, the exposure patterns of the population from SW Taiwan—and the resulting effects data—capture any potential period of sensitivity. Thus, consideration of these potential sources of uncertainty in the NOAEL indicates that the derived value represents a health-protective value for use in assessing potential risks for U.S. populations.

Given these uncertainties, attempts to quantify arsenic's carcinogenic potential have produced variable results and generated significant controversy regarding the selection of the most appropriate dataset, exposure assumptions, and mathematical models. The analysis presented in this article has relied on the quantitative information presented in Lamm *et al.* (2006) to establish a NOAEL for use in the MOE calculations. As detailed earlier, Lamm *et al.* (2006) uses a refined SW Taiwanese dataset and a linear regression analysis to quantify the carcinogenic potency of ingested arsenic and to identify a NOAEL of 150 μg/L. Importantly, the NOAEL identified by Lamm *et al.* (2006) is supported by the scientific literature on arsenic carcinogenicity in humans (Guo 2004; Tucker *et al.* 2001; Bates *et al.* 1995; Lewis *et al.* 1999; Moore *et al.* 2002; Steinmaus *et al.* 2003; for a review, see Schoen *et al.* 2004).

Previous attempts to quantify the carcinogenic potency of arsenic have used the SW Taiwanese dataset as a whole. An extensive analysis, conducted in the context of the 2001 NRC review of arsenic, used different mathematical models and alternative assumptions to predict the ED_{01}[7] (*i.e.*, the effective dose associated with a 1% excess risk) and LED_{01} (the 95% lower confidence limit on the ED_{01}) for bladder, lung, and liver cancer (Morales *et al.* 2000; NRC, 2001). The analysis demonstrated that the estimated ED_{01} was extremely sensitive to the mathematical model used as well as to the choice to use an internal or external comparison group. For example, varying these parameters, ED_{01} estimates ranged from 17 to 365 μg/L and LED_{01} estimates ranged from 9 to 211 μg/L for bladder cancer in females. When the USEPA conducted a risk assessment in support of the arsenic MCL, the agency used a generalized linear model without a comparison population as presented in Morales *et al.* (2000). This approach resulted in an ED_{01} of 189 μg/L for combined bladder and lung cancer in males and an ED_{01} of 127 μg/L for combined lung and bladder cancer in females. In a more recent USEPA draft report to update the arsenic CSF for inclusion in the IRIS database, the USEPA selected a different model with an external comparison population. This model predicted ED_{01} values that were lower.

[7]For epidemiological data, the ED_{01} or LED_{01} is typically used as a point of departure; it can be used as the "NOAEL" in an MOE analysis or the starting point for linear extrapolation.

Both USEPA analyses used linear extrapolation to estimate low-dose arsenic risks based on the ED_{01} (USEPA, 2005b).

Although the SW Taiwanese data have formed the basis of most quantitative risk estimates, alternative datasets have been suggested as a starting point for developing a NOAEL. For example, based on the results of preliminary animal experiments, Clewell *et al.* (2007) recently proposed a NOAEL of 50 μg/L. This NOAEL was derived using a model that showed no significant changes in cancer-related gene expression in the bladder cells of mice administered 50 μg/L of arsenic in drinking water. (It should be noted that considering this dose as a NOAEL is a conservative assumption, because there are no studies that demonstrate bladder tumors in mice at this dose). Using typical assumptions for mouse body weight and water ingestion rates, a drinking water concentration of 50 μg/L is equivalent to a dose of approximately 1.3×10^{-2} mg/kg-day. In the absence of a validated physiologically based pharmacokinetic model in mice and humans for arsenic, standard risk assessment procedures would adjust this dose across species by using the $(\text{body weight})^{3/4}$ scaling factor[8] (USEPA 2002; Beck and Clewell 2001). This adjustment results in an equivalent human NOAEL of 1.86×10^{-3} mg/kg-day, and would yield an MOE of 26 based on 50th percentile background exposures.

In another study of gene transcription, Andrew *et al.* (2007) observed widespread changes in gene expression in the lungs of mice exposed to arsenic in their drinking water at concentrations of 0.1, 1, and 50 μg/L. The complexity of the changes are of interest, but difficult to interpret quantitatively with respect to carcinogenicity. For example, the same gene showed both increased and decreased expression depending on dose. The authors suggested that some of the changes at low levels may be indicative of a protective or adaptive response, but that more research was necessary (Andrew *et al.* 2007). In another series of experiments (Soucy *et al.* 2003; Kamat *et al.* 2005), researchers observed angiogenic[9] changes in mice administered arsenic in drinking water at concentrations ranging from 5 μg/L to 50 μg/L. At these concentrations, there was evidence that arsenic increased vascularization surrounding a matrigel implant (injected subcutaneously) and caused implanted melanomas to grow larger and metastasize more efficiently. Although these studies are useful for understanding the potential angiogenic properties of arsenic, they are not suitable for establishing a NOAEL for arsenic carcinogenesis, because the design involves an existing tumor or matrigel implant. Finally, some scientists have concluded that, based on the concept of "additivity to background," arsenic would be a no-threshold carcinogen, even in the absence of direct DNA interaction (Farland 2005). The shortcomings of this interpretation are discussed in the *Toxicity Assessment* section.

Thus, although scientists may support alternative views of arsenic carcinogenicity, overall a nonlinear dose–response relationship or threshold for arsenic is supported by the most current understanding of arsenic carcinogenicity from both a

[8]In the absence of specific pharmacokinetic information, the USEPA recommends deriving a human equivalent dose using a default scaling factor. This step stems from the general consideration that distribution, clearance, and metabolism of toxins are more rapid in smaller animals than in humans.

[9]Angiogenesis is the growth of new blood vessels, particularly those that supply blood to cancerous tissues.

mechanistic and epidemiological perspective. In particular, the data indicate that arsenic is not DNA-reactive and the available human evidence strongly suggests a threshold at approximately 150 μg/L.

As an additional approach to assess the validity of the results obtained in this exposure analysis, urinary arsenic concentrations estimated based on the modeled exposure estimates were compared to arsenic concentrations measured in the urine of individuals exposed to background concentrations of inorganic arsenic. For example, the 50th percentile daily dose of arsenic estimated by this analysis is 7.07×10^{-5} mg/kg-day. This estimated daily intake corresponds to an expected urinary arsenic concentration of 2.5×10^{-3} mg/L to 6.2×10^{-3} mg/L using the following assumptions: an average human adult weighs 70 kg and excretes 0.8 to 2 L/day of urine (MedlinePlus 2007), and 100% of the ingested dose is excreted in the urine. In fact, between 50 and 80% of an arsenic dose ingested in water is excreted in urine, whereas the excreted amount resulting from intake of arsenic in food and soil is even less, due to decreased bioavailability (ATSDR 2007). As a result, actual urinary arsenic concentrations corresponding to the 50th percentile inorganic arsenic intake estimated in this MOE analysis would likely be less.

Comparison data were obtained from the control population of a large-scale study conducted near a former copper smelter in Tacoma, Washington (Kalman *et al.* 1990). In this study, urinary arsenic levels were measured in 696 individuals in the control population. These individuals were asked to refrain from eating seafood, which is the predominant source of organic forms of dietary arsenic. Thus, the contribution of organic arsenic exposures to the total urinary arsenic levels observed in this population can be assumed to be negligible. In the Kalman *et al.* (1990) study, the median urinary arsenic concentration was 7.5×10^{-3} mg/L, a value that is consistent with the range of estimated urinary concentrations calculated based on the 50th percentile exposure estimate derived in this background exposure analysis (2.5×10^{-3} to 6.2×10^{-3}mg/L). These results indicate that the typical exposures to background inorganic arsenic estimated in this analysis are plausible in light of available empirical data. A similar finding was reported in a recent comparison of modeled and measured urinary arsenic levels associated with background exposures conducted by Georgopoulos *et al.* (2007).

CONCLUSIONS

Using currently available data regarding potential background sources and intake patterns for ingested inorganic arsenic, the analyses presented in this article yield a distribution of background inorganic arsenic exposures for U.S. populations. Dietary intake was identified as the primary contributor to total background arsenic intake, whereas arsenic intake *via* drinking water was determined to be the second largest contributor. Other potential exposure sources, including arsenic intake *via* incidental ingestion of soil, were found to be negligible contributors to overall exposures to background sources of inorganic arsenic. The exposure estimates derived from these analyses are consistent with conclusions reached in other exposure studies of key sources of background exposures to inorganic arsenic (*e.g.*, the studies summarized in Table 4).

The sensitivity analysis findings and examination of the key uncertainties influencing the exposure assessment results indicate that the exposure estimates generated in this analysis represent conservative estimates of typical background exposures for U.S. populations. These evaluations indicate that the exposure analyses have not underestimated significant arsenic exposure sources that would lead to different conclusions regarding arsenic risks. The plausibility of the exposure estimates generated in this analysis is also supported by comparing estimated urinary arsenic concentrations (based on the background exposure estimates generated in this Monte Carlo study) to empirical measurements of urinary arsenic concentrations for a U.S. population without elevated arsenic exposures. The estimated exposures were found to be consistent with the empirical observations.

The information presented in this article demonstrates that nonlinear dose–response approaches (specifically, an MOE approach) are strongly supported by the scientific literature regarding the carcinogenicity of ingested inorganic arsenic. Moreover, the risk calculations presented in this article show that the choices made in quantifying potential carcinogenic risks associated with inorganic arsenic ingestion are critical, because alternative choices yield very different outcomes regarding potential risks. Specifically, although the default linear risk assessment approach suggests that background exposures could present elevated risk levels, the MOE approach leads to the conclusion that exposures to ingested inorganic arsenic from typical U.S. background sources do not present any elevated risk of carcinogenicity.

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