A FRAMEWORK OF RISK-BASED DECISION MAKING BY CHARACTERIZING VARIABILITY AND UNCERTAINTY PROBABILISTICALLY: USING ARSENIC IN DRINKING WATER AS AN EXAMPLE

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ABSTRACT

HUEI-AN CHU: A Framework of Risk-Based Decision Making by Characterizing Variability and Uncertainty Probabilistically: Using Arsenic in Dinking Water as an Example (Under the direction of Dr. Douglas J. Crawford-Brown)

Risk-based regulatory decisions generally apply a margin of safety meant to guard against underestimation of risk in the face of inter-subject variability and uncertainty. Since these two components often are unknown or only vaguely characterized, the decisions involved usually employ conservative default assumptions concerning the margin of safety, resulting in regulatory limits that may be more (or less) health protective than necessary if variability and uncertainty could be characterized probabilistically. As a result, it remains impossible in most cases to determine the degree of protectiveness inherent in a standard. The debate about maximum contaminant levels (MCLs) of arsenic is an example. At present, we can only get a vague idea that lowering MCLs results in larger margins of safety, but at the expense of greater compliance costs. If the magnitude of this margin of safety is not taken into account, it is possible that an MCL may be established based on a significantly larger margin of safety than is necessary, reasonable or consistent with that applied to other contaminants. Thus an unnecessarily expensive treatment policy may be selected.

In this study, a new framework of probabilistic risk-based decision making was developed. A meta-analysis was conducted for arsenic in drinking water by combining several epidemiological studies from various regions (such as Taiwan, US, Argentina, Chile and Finland). Then the results of the meta-analysis were incorporated into the framework to

characterize the margin of safety through variability and uncertainty analyses. The final product of this study is a method of probabilistic risk assessment that better deals with variability and uncertainty issues. This risk assessment methodology can help decision-makers make optimal determinations on regulatory limits for a contaminant that adequately protect human health with an ample margin of safety at a more reasonable cost than currently is the case.

DEDICATION

To Jesus Christ for His Grace, the Holy Spirit for His Guidance, and God for His Glory.

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Huei-An Chu (Ann)

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LIST OF ABBREVIATIONS

ADRI	Average Daily Rate of Intake
AR	Absolute Risk
As	Arsenic
AT	Average Time
BW	Body Weight
CSF	Cancer Slope Factor
Cw	Concentration of Exposure
ED	Duration of Exposure
ERR	Excess Relative Risk
GSD	Geometric Standard Deviation
IR	Intake Rate
IRIS	Integrated Risk Information System
MCLs	Maximum Contaminant Levels
MOS	Margin of Safety
NR	Natural Rate
OR	Odds Ratio
PDFs	Probability Density Functions
RR	Relative Risk
SMR	Standardized Mortality Rate
95% CI	95% Confidence Intervals

CHAPTER 1 INTRODUCTION AND STATEMENT OF THE RESEARCH QUESTIONS

1.1. Basic Statement

Risk-based regulatory decisions generally apply a margin of safety (MOS) meant to guard against underestimation in the face of inter-subject variability and uncertainty. Since these two components often are unknown or only vaguely characterized, the decisions involved usually employ conservative default assumptions concerning the margin of safety, resulting in regulatory limits that may be more (or less) health protective than necessary if variability and uncertainty could be characterized probabilistically. As a result, it remains impossible in most cases to determine the degree of protectiveness inherent in a standard. Therefore, if we had good methods of probabilistic risk assessment better dealing with variability and uncertainty issues, we might be able to develop regulatory limits on a contaminant concentration that adequately protect human health with an ample margin of safety at a more reasonable cost than currently is the case.

In this study, I have focused on the following general questions:

- What is the current decision-making framework used in risk-based decision-making, and what is the role of risk assessment within this framework?
- What is the role of margin of safety in risk-based decision-making framework? Is there any way that the margin of safety can be quantified appropriately using probabilistic methods?

- What would decisions be like under the new framework employing fully probabilistic methods?
- How can the assessment and characterization of uncertainty and variability in risk assessment be improved under the new framework?
- When variability and uncertainty are viewed probabilistically, how much does it cost to increase the margin of safety or confidence (in public health protection) when strengthening regulatory limits on concentrations in environmental media?

1.2. Arsenic as a Case Study

I chose inorganic arsenic in drinking water as the example for my framework because "arsenic is a good example of a substance for which better scientific information is needed to improve risk assessment needed for regulatory decisions" (Chappell et al., 1997). Ingestion of drinking water containing inorganic arsenic has become a matter of great public concern, both in the United States and globally. Inorganic arsenic in drinking water can exert toxic effects after acute (short-term) or chronic (long-term) exposures. These health effects include *cancerous effects* (bladder, lung and skin cancer, and probably kidney and liver cancer) and *non-cancerous effects* (cardiovascular, pulmonary, immunological, neurological and endocrine such as diabetes) (NRC, 1999).

The U.S. EPA (USEPA, 2001) reconsidered its arsenic MCL (Maximum Contaminant Level) and proposed potential MCLs of 3, 5, 10 and 20 µg/L (ppb), lowered from the original one of 50 µg/L. EPA finally proposed an enforceable MCL of 10µg/L based on NRC reports (NRC, 1999; NRC, 2001) and application of default uncertainty

factors to provide an adequate margin of safety. This level was also determined to be feasible technologically and economically.

However, arsenic MCLs continue to provoke scientific debate because of the variability and uncertainty issues in risk assessment. These issues include: (Frumkin and Thun, 2001) (1) limitations in the data concerning the risk at low doses of arsenic; (2) uncertainty about the appropriate mathematical models for estimating the risk at low doses based on data obtained from higher doses; (3) identification of any sensitive subpopulation potentially unprotected under new MCLs because of variability of health effects within the population; and (4) lack of a methodology to quantify probabilistically the margin of safety.

These controversies are actually related to each other and are associated with imperfections in the current framework of risk-based decision making. Without appropriate models from animal studies, and because no statistical evidence of arsenic risks has been observed at levels found in U.S. drinking water systems, U.S. EPA and NRC have relied on the epidemiological data from high arsenic areas such as Taiwan (Chen et al., 1988 and 1992 and Wu et al., 1989) to estimate the risk to U.S. populations at lower arsenic levels. These data are criticized for possibly overstating the risk of arsenic ingestion in the U.S. in part because they do not reflect differences in lifestyle, dietary habits, nutriential status and genetics. It might not be appropriate to use the Taiwanese data for the U.S. population without considering previous criticisms.

The use of a linear procedure to extrapolate from a higher, observed data range to a lower range beyond observation might also overestimate the risks. The U.S. EPA assumed linearity for the dose-response assessments for arsenic at low doses, although some research showed that ‘when there is adequate data to characterize the mode of action, the shape of the

dose-response relationship may prove to be sub-linear below the observed range of the high level arsenic in Taiwan' (NRC, 1999).

Moreover, there are several sources of uncertainty and variability involving the risk assessment for arsenic in drinking water. Uncertainty results from lack of knowledge in the underlying science. Variability comes from the differences among subjects in genetics, metabolism, diet, health status and gender. Because of the variability, some individuals or subpopulations may be more sensitive to contaminants and have higher risks than others. Therefore, MCLs are selected to provide a margin of safety for the protection of public health even in the face of inter-subject variability and uncertainty. This margin of safety considers factors such as inter-subject variability, quality of the database, as well as the need to extrapolate across species. However, the margin of safety is usually un-quantified; it remains impossible in most cases to determine the degree of protectiveness inherent in a standard using a particular margin of safety (i.e. the fraction of the population protected and the degree of confidence in this protection). Taking arsenic as an example, right now we can only get a vague idea that lower MCLs result in larger margins of safety, but at the expense of greater compliance costs. If the magnitude of this margin of safety is not taken into account, it is possible that an MCL may be established based on a significantly larger margin of safety than is necessary, reasonable or consistent with that applied to other contaminants. Thus an unnecessarily expensive treatment policy may be selected.

1.3. Study Purposes and Research Products

The first study purpose is to incorporate meta-analysis and to improve the current dose-response assessment. The other main purpose in this study is to understand the margin

of safety for arsenic as it relates to uncertainty and variability, and to understand how an increasing margin of safety relates to the cost of a regulation. In other words, the goal is to better characterize uncertainty and variability in risk assessment, i.e. to improve the methodology of risk assessment, focusing on the variability and uncertainty issues. My research goal is develop a new framework of risk-based decision-making by characterizing probabilistically the variability and uncertainty in risk assessment, using arsenic as an example.

Besides the general questions listed in the beginning, my research questions for the first study purpose include the following:

- In the observational range of available data, can meta-analysis be an appropriate tool to resolve the discrepancies among epidemiological data and get a reasonable generalized dose-response relationship between arsenic intake and cancer risk?
- What are the uncertainty and variability distributions of risk for different MCLs of arsenic? How much confidence do we have that a given MCL will still produce acceptable risk for a reasonable fraction of the population?
- Combining the two questions above, what is the price of this increased confidence? That is, what is the incremental cost associated with an incremental increase in the margin of safety, characterized by an increase in confidence and fraction of protected population?

The final product is a framework of risk-based decision-making to improve the characterization of margin of safety and help to select optimal regulatory regulation limits (i.e. arsenic MCLs) that produce reasonable confidence in public health protection at reasonable cost.

CHAPTER 2 LITERATURE REVIEW

2.1. Current Framework of Risk-Based Decision-Making

2.1.1. Introduction

2.1.1.1. Risk

The definition of risk is "the probability that an individual will suffer injury, disease, or death under a specific set of circumstances" (Moeller, 1997), or the probability and magnitude of suffering harm from any environmental problem. There are two dimensions regarding risk: (1) the *probability* or *likelihood* of the harm; (2) the *severity* of the harm, its magnitude or significance. The risk of concern in environmental policy is mostly from contamination of air, soil and water (Fiorino, 1995).

Generally, there are three major activities in the study of risk: (1) Risk analysis; (2) Risk assessment and (3) Risk management. ***Risk analysis*** is the process of breaking down the concepts or ideas of a problem; for example, defining what is to be meant by the probability of getting cancer and how confidence is to be used in estimating this probability. ***Risk assessment*** is the step of assigning values or numbers to the concepts; for example, calculating the specific probability of getting cancer. And ***risk management*** is the selection of a course of action to reduce risk by integrating the risk assessment results with a variety of other information, such as feasibility and cost.

2.1.1.2. Risk-Based Decision-Making in Environmental Policy

Risk assessment as well as economic analysis (cost-benefit analysis, specifically) serve as the analytical basis for environmental policy-making (Fiorino, 1995). According to Executive Order 128166 (Federal Register, 1993), it is required that all federal agencies compare the risks of each regulatory action and provide cost-benefit analyses of the impacts of the proposed actions when developing new regulations (Moeller, 1997).

Risk assessment can be divided into the following two categories: ***human health risk assessment*** and ***ecological risk assessment***: The object of concern of the former one is people and their well-being, while the object of concern of the latter one is expanded to other animals and plants, as well as the environment itself (Fiorino, 1995).

In a summary, risk assessment is usually used in regulatory decision-making for the following purposes (Russell and Gruber, 1987):

(1) As a scientific basis

Risk assessment helps the EPA to present scientific and rational evidence for the growing burden of proof necessary to defend its regulatory proposals in court. "Risk" also offers a scientific language by which to rationalize the regulatory decisions. With the information from risk assessment, policy makers can select target pollutants for regulation and decide how stringently they want to control the various sources that contribute to a particular problem, and decide what actions provide "safety"; i.e., what degree of residual risk to accept in particular circumstances.

(2) Set priorities for regulation

Risk assessment helps EPA to set priorities for regulation of chemicals of potential concern and evaluate various strategies to manage risks. Quantitative risk-assessment

techniques were developed since the mid-1970s, and were used to set priorities among pesticides, drinking water contaminants, and other toxic chemicals and to justify regulation. After setting the priorities, limited social and government resources can be directed against the most significant risks.

(3) Site-specific risk assessment

Risk assessment helps to make site-specific decisions by considering the nature of the pollutant, the sensitivity of the environmental setting, and the availability of control questions. The most notable example of the application of risk assessment in this context is the Superfund Program.

The current framework of risk-based decision-making is shown in Figure 2-1.

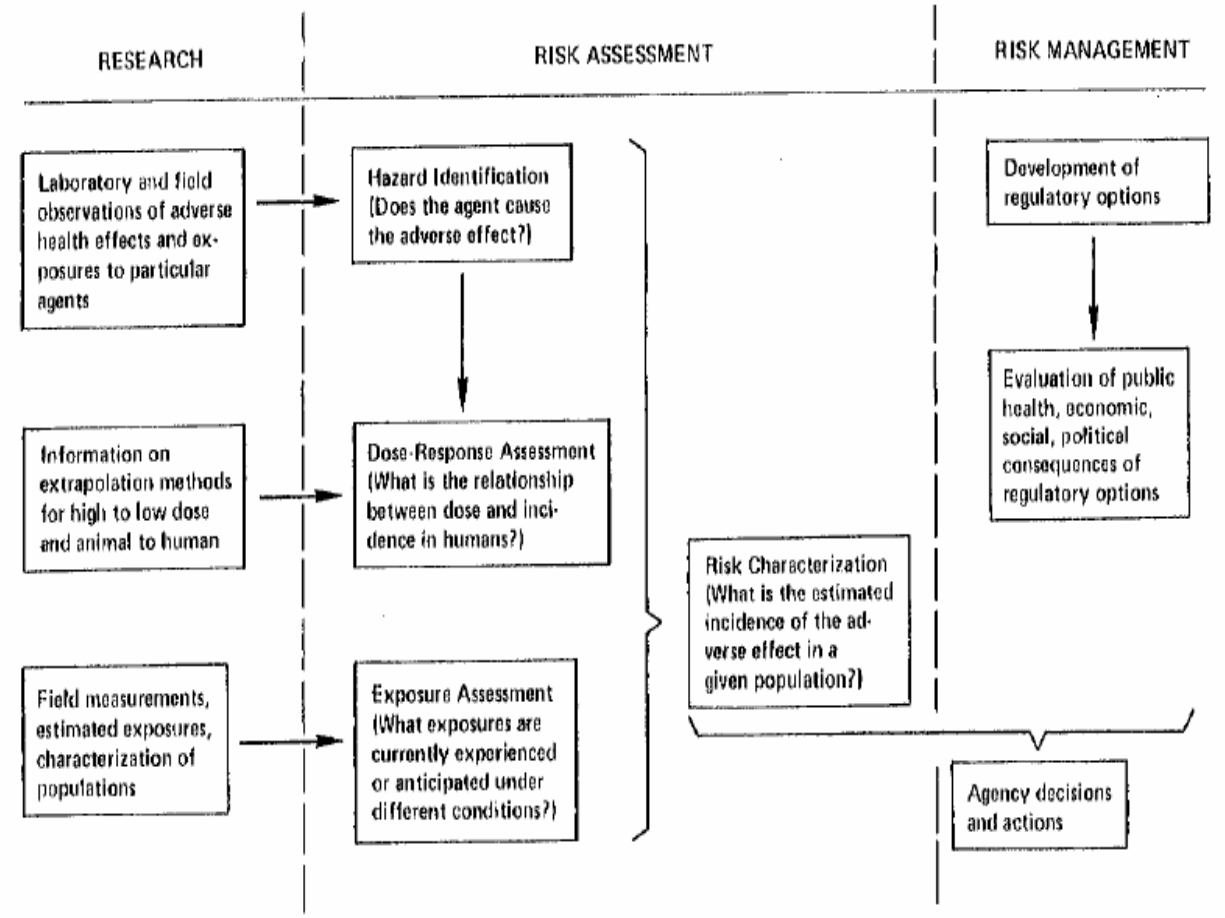

Figure 2-1. Framework of Risk-based Decision-making (NRC, 1983).

2.1.2. Methodology of Risk Assessment

Risk can be expressed qualitatively or quantitatively. An example of the former is EPA's five categories for toxic agent (A - E), assigned depending on an agent's potential for causing cancer in humans. Arsenic has been categorized in list A, which is "known to be human carcinogens" (Frumkin and Thun, 2001). Risk can also be expressed quantitatively; for example, probabilistic risk assessment expresses risk as a probability ranging from zero (certainty that harm will not occur) to one (certainty that harm will occur) (Moeller, 1997). This research focused on quantitative risk assessment.

2.1.2.1. Procedures of Quantitative Risk Assessment and the Scientific Basis

The four procedures of quantitative risk assessment and the scientific basis are explained in the following paragraphs and summarized in Figure 2-2 (NRC, 1983).

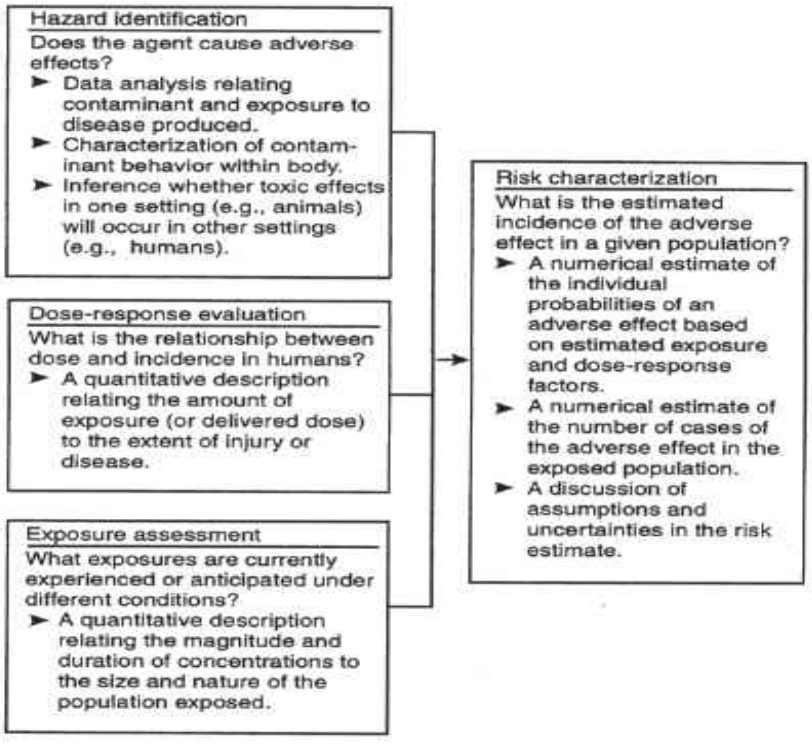

Figure 2-2. Components of risk assessment procedures (Moeller, 1997).

(1) Hazard identification

This procedure produces a qualitative judgment as to whether an agent has any potential to cause adverse health effects following exposure. The question asked in this step, for example, is "does arsenic cause adverse health problems in humans through drinking water?" The evidence can usually be derived from four general classes of information, including epidemiological data, animal-bioassay data, short-term in vitro assays, and comparisons of molecular structure. Their importance in estimating risk to humans is in roughly decreasing order. (Crawford-Brown, 1999) The EPA's integrated risk information system (IRIS) can be a source for information about the potential toxicity of an agent.

(2) Exposure assessment

This procedure identifies populations exposed to the toxicant, describes their composition and size, and examines the routes, magnitudes, frequencies, and durations of such exposures. Example questions in this procedure are: "what is the concentration of arsenic in groundwater?" and "what are the major exposure pathways of arsenic to human populations?"

The first task in this step is to determine the concentration of the chemical to which humans are exposed. This may be done by direct measurement or by a model if exposure data are incomplete or cannot be obtained directly. The second task is to determine which group in the population may be exposed and if there is any subgroup in the population which is more susceptible to the exposure. In the situation of exposure to a mixture of carcinogens, if data are unavailable, synergistic effects are often ignored or accounted for by the use of various safety factors.

(3) Dose-response assessment

This procedure estimates the relationship between dose and response quantitatively. The estimation can be based on epidemiological observations, animal data, or studies of mechanisms of action. A typical question is: "what is the relationship between arsenic intake (dose) and incidence of cancer?" Figure 2-2 presents two possible dose-response curves. If useful human data are absent, a model for animal-to-human dose extrapolation will be used. If available data (epidemiological or animal) are only available at high dose, a model for low-dose extrapolation will be used.

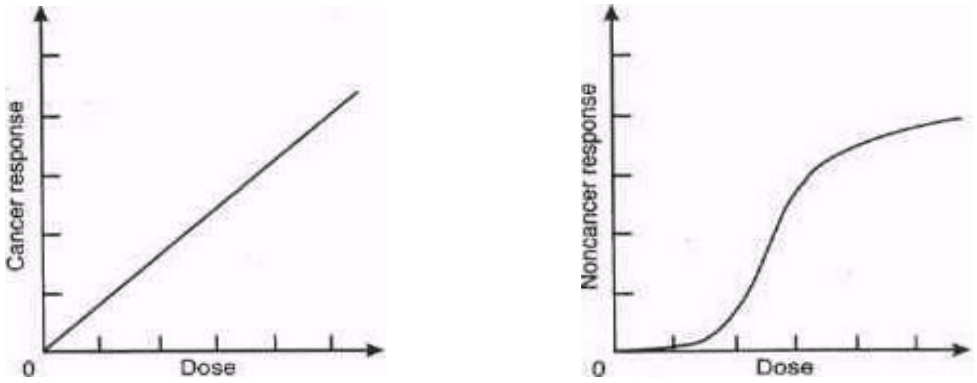

Figure 2-3. **Dose-response relationship: linear non-threshold dose-response curve (left) and nonlinear threshold dose-response curve (right) (Moeller, 1997).**

(4) Risk characterization

This procedure presents the policy-maker with an overall conclusion about the magnitude of risk, the variability of risk in the exposed population, and confidence in estimates of risk. The assumptions underlying the assessment of uncertainty are also provided in this step.

2.1.2.2. Risk Assessment Guidelines

To avoid inconsistent assumptions and value judgments by different programs within the EPA, several Risk Assessment Guidelines have been provided as a consistent approach across programs. The functions of this kind of guideline include informing EPA risk assessors on the best available science and risk assessment techniques, establishing a standard for quality of work and comparison of studies, providing for consistency and orderly decision-making, helping inform the public about how scientific judgments and assumptions have been incorporated into risk assessments, and helping show where additional research and analysis might be necessary. In a word, they can provide EPA staff and decision makers with guidance for developing and using risk assessments, and provide basic information to the public about the Agency's risk assessment methods. However, this kind of guideline is not an official regulation, and represents neither a perfect methodology nor an ideal consensus among scientists (USEPA, 1996; USEPA, 1999; USEPA, 2003).

2.1.3. Flaws in the Current Framework of Risk-Based Decision-Making

2.1.3.1. Precautionary Principle

One of the critiques of the current risk assessment framework is that it is overly conservative due to the precautionary principle. The definition of the precautionary principle is: "when information about potential risks is incomplete, base decisions about the best way to manage or reduce risks on a preference for avoiding unnecessary health risks instead of unnecessary economic expenditures". Based on this "better to be safe than sorry" principle, the most conservative models and assumptions are usually selected for use in risk assessment,

and EPA usually selects an MCL or regulatory limit to provide a large margin of safety (MOS) for the protection of public health to reflect the quality of the database, inter-subject variability and uncertainty; as a result, the compliance cost may be high.

2.1.3.2. Unsound Scientific Basis of Risk Assessment

Another critique is that risk assessment may not provide sound/good science for environmental policy because of uncertainty and variability factors. An NRC report (NCR, 1994) listed the following potential flaws in the scientific bases for risk assessment:

(1) Default assumptions adopted when evidence is not sufficient may have been unduly conservative.

(2) Default options may have become too rigid, with an unnecessarily large barrier to the adoption of new, more scientifically defensible, assumptions.

(3) Aspects of risk established as significant in science (e.g. synergisms/antagonisms) are missing from the risk assessment process.

(4) Uncertainties in risk estimates are inadequately described and knowledge may have been insufficient to justify quantifying risk.

(5) Risk estimates obtained under conservative assumptions for screening may have been applied to final, risk-based, decisions.

(6) Results of risk assessments may have been given too little, or too much, weight of decisions.

In a word, the default assumptions and extrapolation methodology (i.e. linearity assumption in low-dose extrapolation) used in EPA's risk assessments have been criticized

based on the claim that they are unsupported scientifically, raise needless public fears and waste money on costly and unnecessary protective measures.

2.1.3.3. Variability and Uncertainty Issues in Risk Assessment

Another flaw of the conventional framework of risk-based decision making is the inability to characterize the variability and uncertainty well. "Variability means the distribution of some real quantity among things or people even after the application of perfect measurement techniques, whereas uncertainty is a description of the imperfection of our information about a parameter (including a parameter describing real variability)" or lack of knowledge in the underlying science (Hattis et al., 1999). For example, inter-subject variations in factors contributing to risk may include genetics, metabolism, diet, health status, nutrition, gender, and other possible factors, whereas uncertainty may result from model choice.

Considering variability and uncertainty issues in risk assessment, regulatory policy has to apply a "Margin of Safety" as part of regulatory rationality. In other words, margins of safety are generally applied to guard against underestimation in the face of inter-subject variability and uncertainty. Therefore, regulatory decisions usually employ conservative default assumptions to guard against inadequate margin of safety in the face of variability and uncertainty. This may result in regulatory limits that may be more (or less) health protective than necessary. And this also leads to criticism about the margin of safety because it is impossible to estimate the magnitude of that margin.

2.1.4. Conclusion

Considering these flaws in the current framework, arsenic in drinking water may be a good case study to improve the risk assessment methodology and the whole risk-based regulatory decision-making (Chappell et al., 1997). The controversies in the arsenic case are due to imperfections in the current framework of risk-based decision making. If the problems in arsenic case can be examined in detail and solved, these should contribute to a better risk assessment methodology needed for regulatory decisions. More specifically, if we had good methods of probabilistic risk assessment better dealing with variability and uncertainty issues, we could develop regulatory limits on a contaminant concentration that adequately protect human health with an ample margin of safety at a more reasonable cost than currently is the case. Details regarding the issue of arsenic in drinking water will be addressed in the following sections.

2.2. Studies on Arsenic and its Health Effects

2.2.1. Source, Fate and Transport of Arsenic

Arsenic and its compounds are mobile in the environment. Water is the primary medium for arsenic transport in the environment (Pontius et al., 1994). The pentavalent species (As^{5+}, arsenate) is the predominant compound; trivalent arsenic (As^{3+}, arsenite) is only found under anaerobic conditions (NRC, 1999). The cycling of arsenic in the environment is presented in Figure 2-4 (USEPA, 2000).

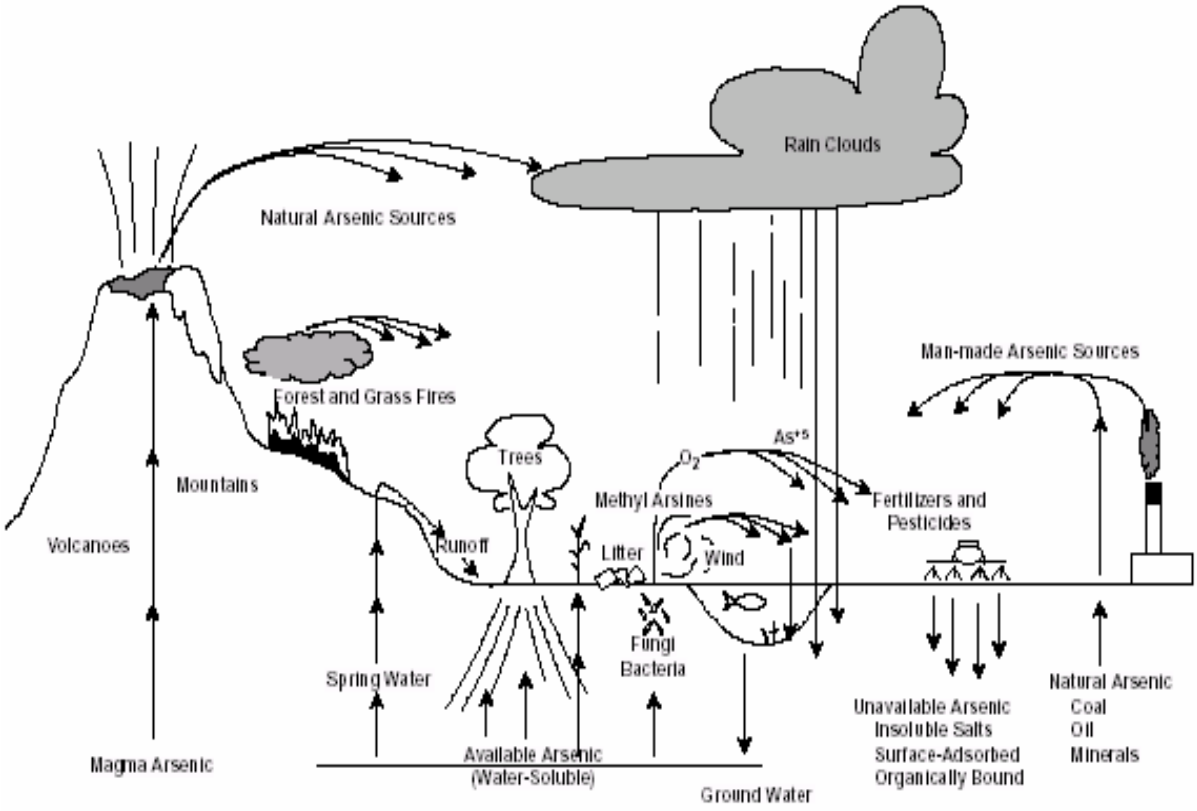

Figure 2-4. Environmental Cycling of Arsenic (USEPA, 2000).

Although arsenic is released to the environment from both natural and anthropogenic sources, most arsenic is naturally occurring in the environment in both inorganic and organic forms. The major natural source of arsenic is from the erosion, dissolution or weathering of arsenic-containing minerals, rocks or soils; the dissolved arsenic enters groundwater or surface water. Other natural sources include volcanic eruption and forest fires. Anthropogenic sources are from industrial processes, such as mining, smelting, wood preserving, pesticide spraying and coal burning (USEPA, 2000).

2.2.2. Exposure Routes

Humans are exposed to various forms of arsenic with different toxicities. The metallic form of arsenic (0 valence) has not been shown to be associated with any adverse effects; a volatile compound such as arsine (AsH_3) is toxic, but is not contained in water or food; organic forms of arsenic (primary arsenobetaine and arsenocholine), which can be found in fish and shellfish, have little or no toxicity; inorganic arsenic, i.e. arsenite (As^{3+}) and arsenate (As^{5+}), are the most prevalent toxic forms found in drinking water, and have been reported to be more toxic than the organic ones. Moreover, the trivalent form (+3) is more toxic than the pentavalent one (+5) (USEPA, 2001).

Inhalation of air, food intake and ingestion of water are the major routes for humans to be exposed to arsenic. Among these routes, drinking water and food are the most significant ones; only a relatively small amount of arsenic is inhaled. Other routes, such as absorption of arsenic through the skin or ingestion of arsenic-containing soils or dust are possible but thought to be insignificant (Pontius et al., 1994; Abernathy et al., 1996; Abernathy et al., 2003).

Occupational exposure is the major cause of arsenic inhalation, such as workers who manufacture arsenical pesticides or work in mines and copper smelters (Frumkin and Thun, 2001). Besides occupational inhalation, air mostly represents a minor source of exposure for the general population (Buchet and Lison, 2000).

As for non-occupational exposure, drinking water and food are the major sources (Borum and Abernathy, 1994). Dietary intake is a significant source of arsenic. Food such as seafood, fruits and vegetables contain organic arsenic. About half of the dietary intakes come from seafood, such as fish and shellfish, followed by meat and poultry, grain and grain products, and vegetables. Infants and toddlers also get arsenic through their diet from milk and milk products. However, most adverse health effects of arsenic are from drinking water rather than food, because most food arsenicals are organic. Organic arsenic in food is less toxic than inorganic forms and most can be excreted rapidly (Pontius et al., 1994; Abernathy et al., 2003). But the dietary contribution to daily intake of arsenic may become dominant if arsenic intake through drinking water is at low concentrations (Hering, 1996).

Ingestion of arsenic through drinking water is the major concern of arsenic exposure. Arsenic concentration is generally higher in groundwater than in surface water, especially high in places where geochemical conditions favor arsenic dissolution (Pontius et al., 1994). Table 2-1 lists the global arsenic contamination in ground water (Nordstrom, 2002). And the following regions have been found to be geological strata naturally rich in arsenic: Taiwan, West Bengal, Mexico, Chile, Argentina, Mongolia, Finland, Hungary and the western and southwestern states and Alaska of the US (Chappell et al., 1997; Thornton and Farago, 1997). In these regions, the natural arsenic concentration may reach levels up to several hundreds of μg/L or even a few mg/L (Buchet and Lison, 2000). About 98% of the U.S. population uses

drinking water with concentrations less than 10 µg/L. But some portion of the remaining 2% of the population is exposed to arsenic concentrations that may reach 50-100 µg/L (Chappell et al., 1997).

Table 2-1. Global Arsenic Contamination in Ground Water (Nordstrom, 2002)

Country/Region	Potential Exposed Population	Concentration (µg/liter)	Environmental Conditions
Bangladesh	30,000,000	<1 to 2,500	Natural; alluvial/deltaic sediments with high phosphate, organics
West Bengal, India	6,000,000	<10 to 3,200	Similar to Bangladesh
Vietnam	>1,000,000	1 to 3,050	Natural; alluvial sediments
Thailand	15,000	1 to >5,000	Anthropogenic; mining and dredged alluvium
Taiwan	100,000 to 200,000	10 to 1,820	Natural; coastal zones, black shales
Inner Mongolia	100,000 to 600,000	<1 to 2,400	Natural; alluvial and lake sediments; high alkalinity
Xinjiang, Shanxi	>500	40 to 750	Natural; alluvial sediments
Argentina	2,000,000	>1 to 9,900	Natural; loess and volcanic rocks, thermal springs; high alkalinity
Chile	400,000	100 to 1,000	Natural and anthropogenic volcanogenic sediments; closed basin; lakes, thermal springs, mining
Bolivia	50,000	-	Natural; similar to Chile and parts of Argentina
Brazil	-	0.4 to 350	Gold mining
Mexico	400,000	8 to 620	Natural and anthropogenic; volcanic sediments, mining
Germany	-	<10 to 150	Natural: mineralized sandstone
Hungary, Romania	400,000	<2 to 176	Natural; alluvial sediments; organics
Spain	>50,000	<1 to 100	Natural; alluvial sediments
Greece	150,000	-	Natural and anthropogenic; thermal springs and mining
United Kingdom	-	<1 to 80	Mining; southwest England
Ghana	<100,000	<1 to 175	Anthropogenic and natural; gold mining
USA and Canada	-	<1 to >100,000	Natural and anthropogenic; mining, pesticides, As_2O_3 stockpiles, thermal springs, alluvial, closed basin lakes, various rocks

2.2.3. Health Effects

As mentioned previously, inorganic arsenic is considered to be significantly more toxic than the organic form. Thus exposure to organic arsenic is usually not considered in assessing health risks (Hering, 1996). Inorganic arsenic (hereafter called arsenic) in drinking water can exert toxic effects after acute (short-term) or chronic (long-term) exposures (NRC, 1999). The health effects caused by arsenic are positively correlated with the dose and duration of exposure (NRC, 2001), and are classified in Table 2-2.

Table 2-2. Health Effects of Arsenic

Health Effects	Symptoms	References
Acute toxicity	Gastrointestinal irritation accompanied by difficulty in swallowing, thirst, abnormally low blood pressure, and convulsions. Death because of cardiovascular collapse.	(Pontius et al., 1994)
Chronic non-cancerous effects	Dermal changes, such as skin pigments, hyperkeratosis, and ulcerations. Vascular effects, such as blackfoot disease Cardiovascular, pulmonary, immunological, neurological and endocrine (e.g., diabetes) effects.	(Pontius et al., 1994) (NRC, 1999)
Chronic cancerous effects	Skin cancer Internal cancers, such as bladder, lung, and liver cancer. The evidences for other cancers, such as kidney, nasal passages, prostate, and other internal sites cancer are not strong.	(NRC, 1999)

2.2.3.1. Cancerous Effects

Ingestion of inorganic arsenic may have chronic cancerous effects. The 1999 NRC report confirmed that arsenic in drinking water causes bladder, lung and skin cancer, and might cause kidney and liver cancer. Skin cancer has been established as a health effect.

However, skin cancer is not as great a concern as other internal cancers because internal cancers are life threatening but most skin cancers are not (NRC, 2001).

The evidence for lung and urinary bladder cancers has been strengthened by recent studies in Taiwan, Argentina, and Chile. But most of these epidemiological studies for cancer were from areas with relatively high arsenic concentration (at least several hundred micrograms per liter, which is much higher than the average concentration in the U.S.). Cancer risk at lower concentrations of ingested arsenic, however, has been seldom addressed in such studies. Other cancers, such as kidney and liver cancer, have also been found to have an association with ingestion of inorganic arsenic. Nevertheless, their association is not strong enough to allow reliable identification of increased risk in existing studies. Therefore, further confirmatory studies are needed to establish arsenic as a cause of cancers other than skin, lung and bladder cancers (NRC, 1999).

2.2.3.2. Non-cancerous Effects

Ingestion of inorganic arsenic may also have chronic non-cancerous effects on multiple-organ systems. These effects are dependent on the magnitude of the dose and the time course of exposure. The toxicokinetic and toxicodynamic interaction between the dose and exposure time has still not been well characterized. From the available data, some general findings have emerged, such as hypertension and diabetes, although the NRC found the relationship still unquantifiable. Effects noted by the NRC include (NRC, 1999):

(1) Nonmalignant dermal effects, such as diffuse or spotted hyperpigmentation and palmar-plantar hyperkeratoses.

(2) Obvious nonspecific gastrointestinal complaints, such as diarrhea or cramping.

(3) Hematological effects, such as anemia and leukopenia.

(4) Neurological effects, such as a sensory predominant axonal peripheral neuropathy.

(5) Cardiovascular effects, such as irreversible noncirrhotic portal hypertension and cardiovascular mortality.

(6) Peripheral vascular disease, such as Blackfoot disease.

(7) Cerebrovascular disease, but the evidence for this effect is not clear.

(8) Diabetes (diabetes mellitus).

(9) Immune function effects, but these effects have not been adequately studied in field research.

(10) Respiratory effects, but the specific pathology of this effect has not been investigated.

(11) Reproductive and development effects. Arsenic may be teratogen and can cause stillbirth, increase of infant mortality, preterm births, or spontaneous abortions.

2.3.3.3. Blackfoot Disease in Taiwan

Blackfoot disease is a peripheral vascular disease and has been endemic in a small area on the southwest coast of Taiwan since 1954. Disease symptoms start with spotted discoloration of the skin of extremities, especially the foot. The spots change from white to brown, then to black. Affected skin gradually thickens, cracks, and ulcerates (Tseng et al., 1968). A considerable percentage of patients suffered from great pain and even tried to commit suicide because the pain was intolerable. Some of them finally had to cut their affected extremities. This has caused much inconvenience and difficulty in daily lives and social problems. It has been found that the prevalence of Blackfoot disease was related to the ingestion of water from deep wells with high arsenic concentration.

People who have lived in villages along the southwest coast have used artesian well water with high concentration of arsenic since the 1900s. Artesian well water was no longer used during the mid-1970s because the tap-water system had been gradually installed since 1956. The government also persuaded residents not to drink arsenic-containing well water or groundwater. As time went by, the Blackfoot disease cases decreased gradually and were almost eliminated. However, 40 years later in 1996, about 20 people got a similar disease in the northeast area of Taiwan. The groundwater in this area also contains high concentrations of arsenic (Chiou et al., 2001). The fact that Blackfoot disease was prevalent in the areas with high arsenic concentration in groundwater has been noted, and substantial studies have been done in Taiwan.

2.2.4. Epidemiological Studies of Arsenic Exposure and Cancer Risk

Inorganic arsenic is not typically found to cause tumors in standard laboratory animal tests, while the observational studies of human exposures to arsenic through ingestion have been strongly associated with increases in skin and internal cancers (Clewell et al., 1999). Still, the association between arsenic exposure and cancerous effects is controversial and not well established in the epidemiological field. Varied or even opposite results have been found in different epidemiological studies of different regions. Some studies (e.g. studies in Taiwan) showed significantly elevated incidence or mortality of cancers for the population exposed to arsenic, while some others (e.g. studies in the US) failed to show an association between arsenic in drinking and the adverse health effects.

2.2.4.1. Epidemiological Studies in Taiwan

Since 1968, researchers in Taiwan kept finding that populations in these Blackfoot-endemic areas also had high rates of some cancers, such as skin, bladder, kidney, liver, and lung cancer (Tseng et al., 1968; Tseng, 1977; Chen et al., 1985; Chen et al., 1988; Wu et al., 1989; Chen and Wang, 1990; Chen et al., 1995; Chen et al., 1996; Chiou et al., 1997; Hsu et al., 1997; Hsueh et al., 1997; Tsai et al., 1998; Tsai et al., 1999). Most of these epidemiological studies showed that there was a significantly elevated incidence of cancers for the study population (which is confined in the Blackfoot disease endemic area) compared with lesser-exposed populations in both communities with similar socio-economic structure as well as with the general population in Taiwan. Some studies also showed dose-response relationships with increasing arsenic concentrations (NRC, 1999). Chappell *et al.* (1997) remarked on the possible shortcomings of these studies, noting that "these studies from Taiwan demonstrate a dose-response relationship for cancer at various sites and arsenic concentrations in water, but the data are not sufficiently precise for accurate quantitative assessment of the magnitude of cancer risk at different arsenic concentrations needed to set an MCL in the United States because the studies report exposures for groups of people rather than for individuals" (Chappell et al., 1997).

The two prevalence studies of skin cancer conducted by Tseng and his colleagues (Tseng et al., 1968; Tseng, 1977) were recognized as the best available data for EPA to conduct quantitative risk assessment (USEPA, 1984; USEPA, 1988). However, the shortcomings of these studies are that the exposure categories are too broad and too few: There were only three defined exposure categories (0-290 µg/L, 300-590 µg/L, 600 µg/L and above, and undetermined) and the upper limit of the lowest exposure category was quite high

(290µg/L). Another shortcoming is that these studies were ecological in design and the data were analyzed by using all residents in a given village instead of an individual as a unit (Guo and Valberg, 1997). Chen and his colleagues did another important epidemiological study (Chen et al., 1985; Chen et al., 1988). They studied the same regions as Tseng et al. did, but used mortality data. They found an increased occurrence of cancer in internal organs, including bladder, liver, lung and other sites. Their studies had similar shortcomings with the ones of Tseng el al. with respect to exposure grouping and ecological study design. U.S. EPA (USEPA, 1988) used the Tseng study data to conduct a dose-response assessment for skin cancer, while Smith el al. (Smith et al., 1992) used the Chen study data to conduct a dose-response assessment for internal cancers (bladder, liver, lung, kidney) (Brown et al., 1997).

While most of the previous Taiwanese studies were conducted in an area with relatively high arsenic concentration (200 ppb or more), recent studies have discovered that low-dose exposure to arsenic may also increase the risk of certain types of cancer, diabetes and vascular disease. This study conducted by Chiou et al (2001) examined cases of urinary tract cancer in villagers exposed to arsenic levels as low as 10 to 50 ppb. His research concluded that there was a significantly increased incidence of urinary cancers for the study cohort compared with the general population in Taiwan, even at low arsenic concentration. This study had a better study design that estimated arsenic exposure at an individual level (i.e., based on the arsenic concentration in his or her own well water), making the study result more reliable (Chiou et al., 2001). Also, this study and the one done in Chile (Ferreccio et al., 2000) were said to “have adequate data to contribute to quantitative assessment of risk” in NRC’s arsenic report in 2001 (NRC, 2001).

2.2.4.2. Epidemiological Studies of Arsenic in the U.S.

Despite there being substantial studies outside the U.S., it is still unclear whether arsenic in drinking water occurring at environmental levels leads to adverse health effects in the U.S.

Early US studies (Goldsmith et al., 1972; Morton et al., 1976; Harrington et al., 1978; Southwick et al., 1983; Valentine et al., 1985) in communities with high arsenic levels in water supplies have failed to show an association between arsenic in drinking water and adverse health effects. However, Bates el al. (1992) pointed out that "these studies have had cross-sectional designs, and the exposed populations have been small, probably relatively mobile and with access to alternative water sources" (Bates et al., 1992). These factors generated statistical power too low to detect effects (Pontius et al., 1994). Other epidemiological studies (Valberg et al., 1998) showed the same results of health effects in high-arsenic regions; i.e. no association between skin-cancer prevalence and arsenic in drinking water was found. This result could be due to an absence of risk in the U.S. populations or statistical limitations due to small sample sizes (Chappell et al., 1997).

More recently, the Utah Study (Lewis et al., 1999) did not find any excess bladder or lung cancer risk with exposure to arsenic at concentrations from 14 to 166 µg/L. They estimated excess risk by comparing cancer rates among the study population, in Millard County, Utah to background rates in all of Utah, and the result showed that there are important differences between the study and comparison populations besides their consumption of arsenic. One explanation for such a difference is that Millard County is mostly rural, while Utah as a whole contains some large urban populations. Another explanation is that the subjects of the Utah study were all members of the Church of Jesus

Christ of Latter Day Saints, who for religious reasons have relatively low rates of tobacco and alcohol use. Therefore, this study was criticized in that "the comparison of the study population to all of Utah is not appropriate for estimating excess risks" (USEPA, 2001). The Agency (USEPA, 2000) reanalyzed the Utah data by an alternative method of comparing cancer rates only among people within the study population who had high and low exposures. The results showed that there was still no detectable increased risk of lung or bladder cancers due to arsenic, even among subjects exposed to more than 100 µg/L on average". And the EPA finally concluded: "The Utah study is not powerful enough to estimate excess risks with enough precision to be useful for the Agency's arsenic risk analysis" (USEPA, 2001).

Karagas and his colleagues (2001) conducted a case-control study to investigate the relationship between skin cancer risk and arsenic exposure in New Hampshire. They used toenail arsenic concentrations as a biological marker of arsenic exposure through drinking water. While the risks did not appear elevated at the toenail arsenic concentrations detected in most study subjects, the authors could not exclude the possibility of a dose-related increase at the highest levels of exposure experienced in the New Hampshire population (Karagas et al., 2000; Karagas et al., 2001). Schoen et al. (2004) summarized epidemiological studies in the U.S. in the following Table 3 (Schoen et al., 2004).

2.2.4.3. Epidemiological Studies of Arsenic in Other Areas

Results of arsenic studies in other areas have been mixed. An association was found between bladder cancer mortality and arsenic in drinking water in Argentina (Hopenhayn-Rich et al., 1996). They also found that arsenic ingestion increases the risk of lung and kidney cancers, but the association between arsenic and mortality from liver and skin cancers

was not clear in another study (Hopenhayn-Rich et al., 1998). Another case-control study in Argentina done by Bates et al. (2004) found increased bladder cancer risks associated with high levels of arsenic in drinking water, but little information exists about risks at lower concentrations. This study suggests lower bladder cancer risks for arsenic than predicted from other studies, but the authors add that the latency for arsenic-induced bladder cancers may be longer than previously thought (Bates et al., 2004).

Kurttio *et al.* (1999) studied the association of arsenic exposure from drilled well water with the risk of bladder and kidney cancers in Finland. In spite of very low exposure levels, some evidence of an association between arsenic and bladder cancer risk was found. But none of the exposure indicators was statistically significant in the association with the risk of kidney cancer (Kurttio et al., 1999).

Increased mortality in bladder and lung cancers were found in a region of northern Chile (Smith et al., 1998). Ferreccio et al. (2000) conducted a case-control study in cities in northern Chile where arsenic concentration was 860 µg/L in drinking water in the period 1958–1970 and reduced to 40 µg/L since then. They investigated the relation between lung cancer and arsenic in drinking water over time. Strong evidence has been shown that ingestion of inorganic arsenic is associated with lung cancer (Ferreccio et al., 2000). Due to many strengths of this study, the data from this study were evaluated to be useful in further quantitative risk assessment (NRC, 2001).

A complete list and summary of current major epidemiological studies from different regions, in which cancers are the end points to be investigated, are presented in NRC reports (NRC, 1999; NRC, 2001). Please see Tables 2-3 for details (Schoen et al., 2004).

Table 2-3. Summary of US-based epidemiological studies of cancer risks from exposure to arsenic (Schoen et al., 2004).

Reference	US study location	Study type	Study population	As drinking water levels (µg/l)	Risk ratios (and 95% CI)	Key findings related to cancer health effects
Lamm et al., 2004	Nationwide (133 counties)	Ecologic	75 million person-years of observations	Range: 3 to 60 µg/l	SMR: 0.73 (0.41–1.27) for bladder cancer at highest exposure level	After reviewing groundwater arsenic levels in 133 counties in the US dependent on groundwater as a drinking source, the authors found no relationship between arsenic exposure and bladder cancer.
Moore et al., 2002	Nevada	Ecologic	327, 947 children between 0 and 19 years of age	Mean levels: 0–91.5	SMR: 1.37 (0.96–1.91); for all cancers, except leukemia at highest exposure level	No evidence of excess childhood cancers for any of the exposure levels. Also no association between arsenic and leukemia was established (SIR = 0.86) for highest exposure group.
Steinmaus et al., 2003	Nevada and California	Case-control	181 bladder cancer cases	Range: 0 to 1000 µg/l	OR: 0.50 (0.12, 2.05) Bladder cancer for lifetime cumulative exposure in non-smokers (40 year exposure lag)	Overall, there was no association between bladder cancer and arsenic intake, even in the highest exposure category of >80 µg/day.
Tollestrup et al., in press	Ruston, Washington in vicinity of American Smelting and Refining company (ASARCO) copper smelter	Retrospective cohort	3132 children residing near the smelter between 1907 and 1932	Unknown: exposure was through soil and air, but increased exposure was known because of increased As levels in urine	Hazard ratio: 1.51 (0.93–2.44) for all neoplasms in males in highest exposure category	Despite extremely elevated childhood As exposures, no elevated incidence of cancer mortality was observed in deceased members of cohort. Even lower associations were seen in relation to bladder and skin cancer.
Karagas et al., 2001	New Hampshire	Population-based case-control	871 skin cancer cases (BCC and SCC)	0.01–2.57 µg/g toenail arsenic	OR: BCC 1.44 (0.74–2.81) for highest exposure group; SCC 2.07 (0.92–4.66) for highest exposure group	No statistically significant association was found for toenail arsenic content and either BCC or SCC carcinoma in any of the exposure categories.

Lewis et al., 1999	Millard County, Utah	Retrospective cohort	4058 adults	Range: 3.5–620; Median: 14–166	SMR: 0.82, (0.70–0.95) for all cancers in males	No dose-response relationship between arsenic intake and all malignant cancers (including bladder and lung cancer).
Bates et al., 1995	88 towns in Utah	Case-control	117 bladder cancer cases and 266 population-matched controls	Range: 0.5–160; Mean: 5.0	Never smoked: 0.53 (0.1–1.9); Smokers: 3.32 (1.1–10.3)*	No statistically significant association was found between bladder cancer and arsenic exposure in any age group. Some evidence of increased bladder cancer incidence in smokers, but response was not consistent with respect to latency period.
Tollestrup et al., 1995	Wenatchee area of Washington State	Retrospective cohort	1231 people working and residing in orchard area contaminated with lead-arsenate from 1890 to 1940	56–140 µg/l urinary arsenic levels	OR: 1.2 (0.59–2.44) for all cancers in male orchardists; OR: 1.31 (0.48–3.6) for all cancers in female orchardists	Odds ratios were based on mortality rates in orchardists compared to residents of the community. No statistically significant increases in any cancers were observed among orchardists.
Engel and Smith, 1994	30 US counties with population-weighted mean averages	Ecologic	Residents of 30 US counties between 1968 and 1984	Range of means: 5.4–91.5	SMR: 1.0, (1.0–1.1)* for all malignant neoplasms in males	No association was observed between arsenic intake and any cancers in both males and females. Associations with vascular disease were noted with variable significance.
Frost et al., 1987	Ruston, Washington in the vicinity of American Smelting and Refining company (ASARCO) copper smelter	Ecologic and case control	Women residing within 40 miles of the smelter both with and without lung cancer	Exposure based on proximity to smelter. No levels were quantified.	OR: 0.94 (upper CI = 1.05) for cohort study; OR: 1.6 for case control study in highest exposure category	An elevated risk of lung cancer was not detected when evaluating observed vs. expected lung cancer incidence. However, an association was observed in the case-control analysis, but it was not statistically significant.

2.3. Cancer Risk Assessment of Arsenic in the U.S.

2.3.1. Existing Risk Assessment for Arsenic

Cancer risk has been the driving effect in regulatory decisions because non-cancer effects are likely to be significant only at concentrations well above the considered MCLs (USEPA, 2001). Therefore, the discussion about arsenic risk assessment in this chapter is focused on cancer.

Most arsenic cancer risk assessments have been based on epidemiological studies. In the United States, the risk assessments of arsenic from drinking water were at first done for skin cancer. And it was agreed that ingested arsenic causes enhanced skin cancer risk. Then, several risk assessments were done for internal organ cancers (lung, liver, kidney, bladder) from drinking arsenic-rich water, and it was also shown to cause increased risk in these end points. However, because of uncertainty and variability issues in risk assessment, there have been several debates about the validity of these risk assessments.

2.3.1.1. Skin Cancer

The U.S. EPA (1984, 1988) conducted a risk assessment for skin cancer by using data from southwestern Taiwan where Blackfoot disease is endemic (Tseng et al., 1968; Tseng, 1977). The EPA used the "cancer slope factor" (CSF) or the "cancer potency factor" as an estimation of carcinogenic potency and assumed a linear dose-response relationship (USEPA, 1988; Brown, 1998). The upper-bound excess cancer risk from lifetime exposure to water containing 1 μg As per liter (unit risk) was calculated to equal to 5×10^{-5} by using a generalized multistage model. Consuming drinking water at the MCL of 50 μg/L (which was the MCL of arsenic at that time) entailed a lifetime risk of 2.5×10^{-3}. However, the unit risk

calculated by the EPA could overestimate the actual risk for skin cancer. That is because the EPA extrapolated data from Taiwan with high-level arsenic exposures linearly to generate risk estimates for low-level exposures in the U.S. For this extrapolation, the EPA hypothesized that a linear dose-response relationship applies in the low-dose exposure region and that carcinogens do not have a threshold. The appropriateness of these assumptions and the validity of the risk assessment evoked significant debate (Chappell et al., 1997; Guo and Valberg, 1997; Clewell et al., 1999). Guo et al. (1997) did a quantitative review of epidemiological studies observing arsenic exposure below 290 μg/L, which is the lowest exposure category in the Taiwan study used by the EPA. Their review suggested, "The EPA model is unlikely to be able to predict the risk of skin cancer accurately when the arsenic exposure level is between 170 and 270 μg/L" (Guo and Valberg, 1997). Subsequently, using data from four epidemiological studies in the U.S. (Harrington et al., 1978; Southwick et al., 1983; Vig et al., 1984) and the EPA cancer slope factor (CSF) for ingested arsenic, Valberg et al. (1998) calculated the incidence of skin cancer in the U.S. population. Then, they conducted a likelihood ratio analysis to test the null hypothesis that there were no extra skin cancer cases caused by arsenic (i.e. no risk) *versus* the alternative hypothesis of a predicted risk, which was not apparent due to random variability. Their result showed that a null hypothesis was approximately 2.2 times more likely than the alternative hypothesis, favoring the hypothesis of no additional skin cancer risk from arsenic. Although several sources of uncertainty in the U.S. data, such as exposure duration and misclassification, affected their predictions of skin cancer prevalence, the authors suggested "the CSF derived by EPA from the Taiwanese population may be an overestimate of the skin cancer risk in the U.S. (Valberg et al., 1998)." Many other questions had been raised about EPA's risk assessment, including

applicability of the risk assessment to the U.S. population, the role of arsenic as an essential nutrient, the relevance of skin lesions as the basis for the risk assessment, and the role of arsenic intake via food (Morales et al., 2000).

Brown et al. (1989) also conducted a risk assessment for skin cancer from ingesting inorganic arsenic based on the study of Tseng et al (1968). The derived lifetime risks of developing skin cancer are 3.0×10^{-3} (2.1×10^{-3}) for U.S. males (females) if exposed to 1 μg/kg/day for a 76-year lifespan using the linear model, and are 1.3×10^{-3} (6.0×10^{-4}) for U.S. males (females) using the quadratic model. The authors pointed out that this study might overestimate the skin cancer risk from ingested arsenic since other sources were not considered. On the contrary, this study might underestimate the risk since people dying from gangrene and skin cancer were not counted in the prevalence study of Tseng et al. (1968). Different diet habits between the Taiwanese and U.S. populations are another source of uncertainty (Brown et al., 1989).

2.3.1.2. Internal Cancers

Smith et al. (1992) conducted a risk assessment for cancer risks of liver, lung, kidney and bladder associated with inorganic arsenic in drinking water. They established the dose-response relationship for the U.S. population by linear extrapolation using Taiwan data from the epidemiological studies of Chen et al. (1988) and Wu et al. (1989). The results of their study showed that at an MCL of 50 μg/L, the lifetime risk of dying from these internal cancers from drinking 1 L/day of water could reach to 13 per 1000 persons (1.3×10^{-2}); when considering the average arsenic levels and water consumption patterns in the U.S. population, the population-averaged risk estimate was around 10^{-3} (Smith et al., 1992). This study had

drawn attention to the potential for internal cancer risks in the U.S., but its uncertainty has also been noted (Pontius et al., 1994). Carlson-Lynch et al. (1994) commented that some flaws in the study of Smith et al. may lead to an approximately 10 fold higher CSF (18 per mg/kg-day) than the current CSF in IRIS (1.75 per mg/kg-day). One flaw was that the linear regression contained the assumption that the arsenic intake of the control population was zero. This unrealistic assumption might artificially increase the slope factor. Other flaws included the uncertainties in the use of Taiwanese data, the possible correlation of humic acids, and different diets and protein intake between Taiwanese and U.S. populations (Carlson-Lynch et al., 1994).

Chen et al. (1992) calculated cancer potency indices of the lung, liver, bladder and kidney based on the mortality data (Chen et al., 1985; Chen et al., 1986; Chen et al., 1988) of residents in the Blackfoot-endemic areas in southwestern Taiwan by using the Armitage-Doll multistage model. The excess lifetime risk of developing liver, lung, bladder and kidney cancers due to an intake of 1 μg/kg/day of arsenic was estimated as 4.3×10^{-4}, 1.2×10^{-3}, 1.2×10^{-3}, and 4.2×10^{-4}, respectively, for males; as well as 3.6×10^{-4}, 1.3×10^{-3}, 1.7×10^{-3}, and 4.8×10^{-4}, respectively, for females in study area (Chen et al., 1992).

Brown and Chen (1995) used the Taiwanese data (Chen et al., 1985) for dose-response assessment. Identifying some problems in the raw data, the authors deleted some outliers and adjusted some exposure values. They found “for all endpoints and both genders, an upturn in response begins in the region where arsenic concentration is above 100 μg/L”, but the resultant dose-response patterns showed no evidence of excess risk below arsenic concentrations of 100 μg/L. Moreover, the dose-response relationships between internal

cancers (bladder, liver, and lung) prevalence and arsenic exposure was nonlinear (Brown and Chen, 1995).

At the request of the EPA to independently review the scientific database and evaluate the scientific validity of its 1988 risk assessment, the National Academy of Science's National Research Council (NRC) presented a more detailed summary of the evidence linking arsenic exposure to internal cancer in its report "Arsenic in Drinking Water" in 1999. NCR also made several recommendations for the risk assessment of arsenic from drinking water in this report (NRC, 1999):

(1) To improve the scientific validity of arsenic risk assessment, additional epidemiological evaluations are needed to characterize the does-response relationship, especially at low doses.

(2) Since the mechanism (or mode of action) by which inorganic arsenic causes cancer is not well established, biologically based models (chronic studies in a suitable animal model) at low-dose might increase this understanding.

(3) Due to the variation in human sensitivity to the toxic effects of inorganic arsenic exposure, factors that influence sensitivity to or expression of arsenic-associated cancer effects need to be better characterized. The possible factors are genetics, gender, metabolism, diet, health status, and nutritional status.

(4) More data are needed that tie biomarkers of absorbed arsenic dose to arsenic exposure concentration, especially in different parts of the U.S.

In the absence of a well-designed and well-conducted epidemiological study that includes individual exposure assessments, NRC (1999) concluded, "Ecological studies from the arsenic endemic area of Taiwan provide the best available empirical human data". After characterizing risks at an MCL of 50 μg/L "based on observed epidemiological findings,

experimental data on the mode of action of arsenic, and available information on the variations in human susceptibility", the NRC (1999) concluded that risk at an MCL of 50 µg/L was still too high to achieve EPA's goal for public-health protection.

The EPA also released details of a regulatory risk assessment for arsenic in drinking water, and the basis for a decision on a proposed rule for arsenic and its MCL through the Federal Register in June 2000 and January 2001 (USEPA, 2001). These reports utilized slightly revised unit risk factors developed by the NRC (NRC, 1999) to estimate risks from arsenic exposure through drinking water. Specifically, the unit risk factor was approximately 2.6×10^{-5} per µg/L in the EPA assessment and 2×10^{-5} per µg/L in the NRC assessment.

Morales et al. (2000) produced a risk assessment for cancers of the bladder, liver, and lung from exposure to arsenic in water, based on a set of epidemiological data from an arseniasis-endemic region of Taiwan (Chen et al., 1985; Chen et al., 1988; Wu et al., 1989; Chen et al., 1992). The excess lifetime risk was estimated by considering several variations of models and alternative methods for incorporating background rates into the analysis. Their results agreed with the conclusion of the NRC (1999) that "The standard of 50 µg/L at that time is associated with a substantial increased risk of cancer and is not sufficiently protective of public health". The authors also argued that they did a better risk assessment than that of the EPA for the following reasons (Morales et al., 2000):

(1) Their study focused on mortality from bladder, lung, and liver cancers identified through national death records.

(2) In the EPA analysis, they grouped data (Tseng et al., 1968) into three broad exposure intervals [low (< 300 µg/L), medium (300-600 µg/L), and high (> 600 µg/L)]. But data used by Morales et al. (2000) provided exposure at the individual village level.

In another report of "Arsenic in Drinking Water: 2001 Update", the NRC (2001) concluded: "Arsenic-induced internal (lung and bladder) cancers should be the principal focus of arsenic risk assessment for regulatory decision-making". They used the additive Poisson model as the statistical fit for human data from southwestern Taiwan. Their estimates of mean theoretical lifetime excess risk of lung cancer and bladder cancer for U.S. populations at different MCLs of concern in drinking water are shown in Table 2-4 (NRC, 2001).

Table 2-4. Theoretical Lifetime Excess Risk (Incidence per 10,000 People) of Lung Cancer and Bladder Cancer for U.S. Populations at Different MCLs in Drinking Water.

Arsenic Concentration (μg/L)	Bladder Cancer		Lung Cancer	
	Females	Males	Females	Males
3	4	7	5	4
5	6	11	9	7
10	12	23	18	14
20	24	45	36	27

Table Source: (NRC, 2001)

2.3.2. Variability Issues in Arsenic Risk Assessment

There exist variability and uncertainty issues in risk assessment for science-based environmental policy. Variability comes from differences in outcome due to inter-subject variation in factors contributing to risk; uncertainty comes from lack of knowledge in the underlying science. The purpose of studying variability and uncertainty is to make sure a reasonable fraction of the population is protected with an ample margin of safety and confidence.

Human sensitivity or susceptibility to adverse health effects of arsenic exposure is likely to vary because of genetics, metabolism, diet, health status, nutrition, sex, and other possible factors. These factors can have important impacts on arsenic risk. For example, poor nutrition and arsenic intake from food might affect the epidemiological results in Taiwan or the results of extrapolation to the United States (NRC, 1999).

Existing risk assessments, however, do not fully quantify the risks to sensitive and susceptible subpopulations, but only reflect the average risk in a population. The possible sensitive subpopulations include people with poor nutritional status, infants or children, pregnant and lactating women. Generally speaking, they are more susceptible because of variations in metabolism and sensitivity among individuals or groups. For example, they may have reduced ability to methylate arsenic, and therefore retain more arsenic in their bodies, placing them at greater risk for toxic effects (NRC, 1999). Infants and children might be especially susceptible because their tissue dose of arsenic might be, on average, higher than that of adults exposed to similar waterborne concentration due to their higher fluid and food intake on a body-weight basis (NRC, 2001). Also, studies in northern Argentina showed that children might have lower arsenic-methylation efficiency than adults (Concha et al., 1998; Concha et al., 1998). As for pregnant and lactating women, there are no reliable data that indicate increased susceptibility to arsenic. But they might be especially important to consider as a separable subpopulation due to possible adverse reproductive and developmental effects of arsenic (USEPA, 2000). People with poor nutritional status might have decreased ability to methylate arsenic, resulting in increased arsenic concentrations in tissues and the development of toxic effects (NRC, 1999). Because these individuals or

subpopulations may have higher risks than the general population, a wider margin of safety might be needed when selecting risk management options for arsenic.

2.3.3. Uncertainty Issues in Arsenic Risk Assessment

The following three are the factors that are most often addressed in the literature on uncertainty as it relates to arsenic risks: (1) model choice in the dose-response relationships; (2) data limitations; and (3) other sources of exposure, such as dietary intake. Brown et al. (1997) also pointed out four sources of uncertainty in calculating the magnitude of risk at low concentrations of arsenic: model choice, data aggregation, intra-village variability of arsenic in well water, and arsenic intake from food (Brown et al., 1997). Only the issues of model choice and data limitations are addressed here since they relate to the topic of the proposed research.

2.3.3.1. Model Choice in the Dose-Response Relationship

In the case of arsenic risk, several primary sources of uncertainty make the choice of dose-response model controversial: lack of good animal models from experimentation; inaccurate dose-response models due to inadequate epidemiological data; and incomplete knowledge of the uptake, bio-transformation, and distribution of arsenic in the body (Chappell et al., 1997).

The shape of the dose-response relationship between health risks and arsenic exposure from drinking water may be based on experimental animal data or epidemiological data (Wright et al., 1997). Present experiments in animals are thought to be not appropriate for use in the quantitative human health risk assessment for arsenic, while many extensive

human epidemiological studies of arsenic exposure and cancer risk are available. However, very limited epidemiological data in the U.S. are available to assess the dose-response relationship (Guo and Valberg, 1997). Therefore, researchers and policy-makers in the U.S. mostly used the studies of cancer in Taiwanese villagers exposed to arsenic from wells from the 1920s to 1960s as the primary body of data to develop their risk estimates (NRC, 1999). Taiwan is currently the place with the most complete data because Blackfoot disease has been endemic in southwestern regions. However, those arsenic data from Taiwan were obtained at relatively high concentrations of 200 µg/L or more. To estimate risks at levels below 50 µg/L, experts have used the default linear assumption to extrapolate the data. But if there is a threshold, i.e. a level of exposure below which arsenic-laced water is harmless, or if the dose-response relationship is non-linear, that modeling technique could overestimate the risk. Also, with other factors such as different genetics, diet and health status between the U.S. and Taiwan populations, there are doubts as to whether it is reasonable to simply extrapolate the data across populations. Therefore, there are issues with the extrapolation of the dose-response relationship from the observed range of exposures in Taiwan to estimate U.S. cancer risk below the observed data range.

Traditionally, EPA has used the default assumption that "risk is linearly related to dose and that any dose, no matter how small, poses some level of risk" (Clewell et al., 1999). The EPA used the "cancer slope factor" (CSF) or the "cancer potency factor", which assumes a linear dose-response relationship for cancer, as an estimation of carcinogenic potency for arsenic (USEPA, 1988; Brown, 1998). However, Brown (1998) argued, 'This "EPA approach" is poorly suited to the available information and data on arsenic' (Brown, 1998). Also, there is other evidence from pharmacokinetic studies indicating either a threshold for

the carcinogenic effects of arsenic or a sub-linear dose-response relationship at low doses of arsenic. In addition, it is found that "in humans, inorganic arsenic can be metabolized into less toxic organic forms". This mechanism may be more effective at low doses, and thus it may be reasonable to assume the dose-response curve is not linear in the low-dose region (Carlson-Lynch et al., 1994; Guo and Valberg, 1997). Moreover, "an indirect effect of arsenic on DNA repair is consistent with the expectation of a nonlinear dose-response rather than the linear dose-response traditionally assumed for mutagenic carcinogens". Clewell et al. (1999) proposed that to improve the current cancer risk assessment for arsenic would require: (1) the development of clearly articulated hypotheses of the mode-of-action of arsenic as a human carcinogen, (2) specific experimentation in appropriate animal species to bolster the evidence for the proposed mechanisms and to rule out competing mechanisms, and (3) a quantitative risk model to integrate pharmacokinetic and mechanistic experimental results and provide expectations of the low-dose risk consistent with the proposed mechanism (Clewell et al., 1999).

In a word, the uncertainty of model choice in the dose-response analysis of arsenic is due to the lack of knowledge of arsenic pharmacokinetics and pharmacodynamic mechanisms in humans, and the inconsistency of current epidemiological evidence (Pontius et al., 1994). While the traditional default linear assumption has been used in regulatory risk assessments to date, a threshold for arsenic carcinogenicity or a non-linear dose-response relationship at low doses may be the case (Clewell et al., 1999).

2.3.3.2. Data Limitations

There are several advantages to the database from Taiwan (USEPA, 2001):

- Mortality data were drawn from a cancer registry;
- Arsenic well water concentrations were measured for each of the 42 villages;
- There was a large, relatively stable study population that had life-time exposures to arsenic;
- There are limited measured data for the food intake of arsenic in this population;
- Age- and dose-dependent responses with respect to arsenic in the drinking water were demonstrated;
- The collection of pathology data was unusually through;
- The population was quite homogeneous in terms of lifestyle.

However, the EPA (2001) also recognized that there are some problems with the Taiwan studies that introduce uncertainties into the risk analysis, such as:

- The Taiwan data on exposure were uncertain due to use of median exposure data at the village level and the possible errors in assigning persons to exposure. The researchers investigated the association of individuals with contaminated wells by assigning all villagers to a single median arsenic concentration for exposure and assuming they all had a lifetime of exposure to the wells serving that village. However, wells within each village had varying arsenic levels so that people also had varying exposure to arsenic concentration according to the real wells they used. The median concentration was also questionable since not all wells serving all villages were measured. In addition, moves made from village to village were not accounted for.
- Most available studies from Taiwan are ecological studies.

- Confounding factors that may have contributed to risk may not be adequately accounted for.
- There were many differences between the Taiwan and U.S. populations, such as genetics, lifestyles, nutrition status, making the use of Taiwanese data for the U.S. population doubtful. The Taiwanese study population was a rural population, mostly low income, relatively poorly nourished and having deficits of selenium, possibly methionine or choline (methyl donors), zinc and other essential nutrients. Deficits (particularly in selenium) in the diet may be a risk factor for cancer. Since this malnourishment is not typical of the U.S. population, risk may be overestimated when the Taiwan data are applied. The Taiwanese population may also have some genetic differences from the general U.S. population. However, these issues cannot be quantitatively accounted for.
- There was high exposure of the Taiwan population to arsenic via contaminated food and cooking water. This is because the staples of the Taiwan diet were rice and sweet potatoes. Rice and sweet potatoes are high in arsenic and both staples absorb water upon cooking.

The first three problems, which involve the flaws in original data collection and research design in epidemiology, contribute a lot to uncertainty in the quantitative dose-response analysis. Other problems, such as possible dietary deficiencies and intake of arsenic from other sources, may contribute little uncertainty. This is because studies of skin and possible internal cancers from arsenic in drinking water have been done in many different countries, where the diet and many other factors vary, and the additional information in these factors seems unlikely to change the dose-response curve greatly (Abernathy et al., 1996).

2.3.4. Conclusion

The risk assessment of arsenic in drinking water has been mostly based on the epidemiological studies. The unit risks[1] calculated by different risk assessors are ranged around 10^{-5} (per µg/L) for internal cancers. However, several variability and uncertainty issues make cancer risk assessment controversial for arsenic. This research focuses on these two issues to improve the risk assessment methodology.

[1] **The unit risk is the quantitative estimate in terms of either risk per µg/L drinking water taken.**

CHAPTER 3 METHODOLOGIES AND RESULTS

Four methodologies have been developed in this study. They are (i) Using meta-analysis in dose-response assessment; (ii) Quantification of margin of safety; (iii) The alternate method of quantification of margin of safety with meta-analysis results; and (iv) Price of confidence. Figure 3-1 is the influence diagram shown the steps of these methodologies, and they are introduced separately in the following sections.

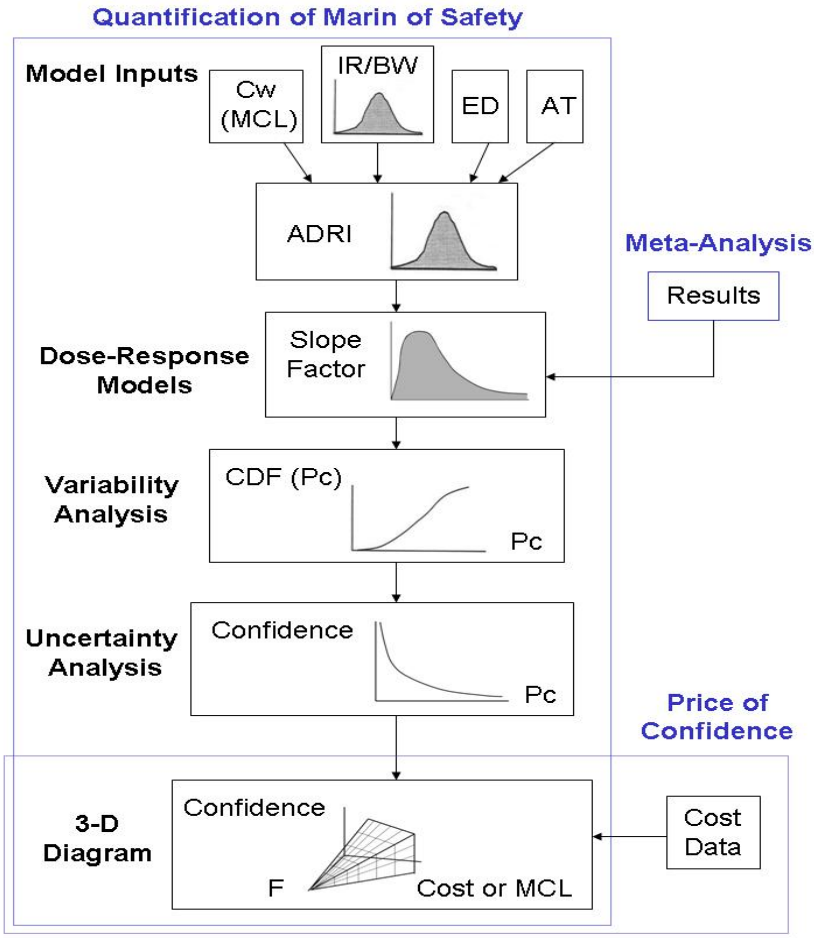

Figure 3-1. The influence diagram of steps of methodologies (in blue color).

3.1. Using Meta-Analysis in Dose-Response Assessment

3.1.1. Introduction of Meta-Analysis of Observational Studies

The dose-response assessment usually proceeds in two steps. The first step is the assessment of the data in the range of empirical observation, followed by the step of extrapolation to lower dose levels, if needed (USEPA, 2003). This methodology focuses on the first step by applying meta-analysis.

In risk-based regulation, data are needed to characterize the dose-response relationship for risk calculations. The accuracy of the data and the ability to fit them by an appropriate model in turn determine the scientific validity of a risk assessment (NRC, 1999). Usually, human data are scant and animal data are used. But in the case of arsenic risk assessment, there are inadequate data and models from animal experiments, while there are relatively plentiful human data from observational studies[2] (Abernathy et al., 1996). Therefore, arsenic cancer risk assessments have been mostly based on observational studies in epidemiology.

There are many advantages to using epidemiological studies as a source of data for dose-response analysis in risk assessment, including development of direct evidence of carcinogenic or other health effects in humans, thereby avoiding the uncertainty associated with inter-species extrapolation. However, current epidemiological evidence is highly

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[2] **Observational studies and clinical trials are two main types of research design in epidemiology. Different from clinical trials, which are relative consistency of study designs and similarity of outcome measures, group of subjects cannot be randomly assigned to one or another exposure group in observational studies. This is why meta-analysis has been facilitated in the area of clinical trials but still have controversial in the area of observational studies (Morris, 1994; Stroup, et al., 2000)**

variable and at times conflicting. So it is not appropriate to draw a firm conclusion about the shape or magnitude of the dose-response relationship based on an individual study.

Meta-analysis is a statistical tool for integrating and analyzing data from related but independent studies. Applying a set of statistical procedures, which quantitatively aggregate the results of multiple primary studies, an overall conclusion or summary of average properties such as risk coefficients across these studies may be reached (Arthur et al., 2001). If conducted appropriately, the overall conclusion or summary measure could be a more objective appraisal of the evidence, and uncertainty and disagreement among studies can also be characterized (Egger and Smith, 1997). Moreover, meta-analysis assists in the exploration and evaluation of results, including the heterogeneity between results of individual studies and among subgroups, such as genders, ages, or ethnic groups. This additional information helps in characterizing uncertainty and locating sources of inter-subject variability (Egger and Smith, 1997).

The quantitatively-aggregating ability of meta-analysis allows it to examine relationships not investigated in the original primary studies (Arthur et al., 2001), and to test hypotheses about sources and magnitudes of heterogeneity and bias (Greenland, 1994). Therefore, meta-analysis can be an alternative to a single large, expensive, and logistically problematic study (Egger and Smith, 1997); the use of a single study as the basis for risk assessments; or the use of purely subjective summary judgments in weight-of-evidence determinations. Meta-analysis can be especially advantageous when research is well-established and a large number of primary studies are available.

In a word, meta-analysis, if appropriately conducted, is a tool to quantitatively analyze a collection of epidemiological study results, and can be used in risk assessment to

combine results across studies with the goal of estimating measures of association with improved precision. In practice, meta-analysis has been used in the steps of hazard identification and dose-response assessment (Steenland and Savitz, 1997).

The research goal in this methodology is to use meta-analysis to combine several epidemiological datasets to produce an aggregated dose-response function for the relationship between bladder cancer risk and arsenic intake from drinking water.

3.1.2. Statistical Theory

The underlying statistical theory of meta-analysis is "Sample Error Theory". The sample error stems from the variation of characteristics between samples and the original population, given that a sample typically can't represent the whole population (Arthur et al., 2001). There are two major sources of variation to be considered when conducting a meta-analysis: (i) ***within-study variation***, resulting from different random sampling errors within each study; and (ii) ***inter-study variation***, resulting from the heterogeneity between studies (Normand, 1999). Because of different assumptions about the existence of variations, the statistical methods used for meta-analysis then can be broadly classified into two models: (i) ***fixed-effects models***, and (ii) ***random-effects models*** (Egger et al., 1997).

3.1.2.1. Fixed-effect model

The fixed-effects model assumes there is only within-study variation in the mean outcomes of a study, and inter-study variation can be excluded. It also assumes that the underlying population from which studies are generated is the same and has identical

characteristics and study effect for all studies considered in the meta-analysis (Normand, 1999). This is called the homogeneity assumption.

A fixed-effects model can be expressed as follows (Normand, 1999):

$$Y_i \overset{indep.}{\sim} N(\theta, s_i^2) \quad \text{for } i = 1,2,\ldots,k \tag{3.1}$$

Where *Yi* is the summary statistic of each study, which is drawn from the same population of study estimates with common mean θ but independent of each other. Therefore, the expected mean of Y_i should be equal to the population mean, i.e. E(Yi)= θ. And s_i^2 = var(Yi) is the variance of the summary statistic in the *i*th study, representing how well each study sample mean (Y_i) estimates θ. (Figure 3-2)

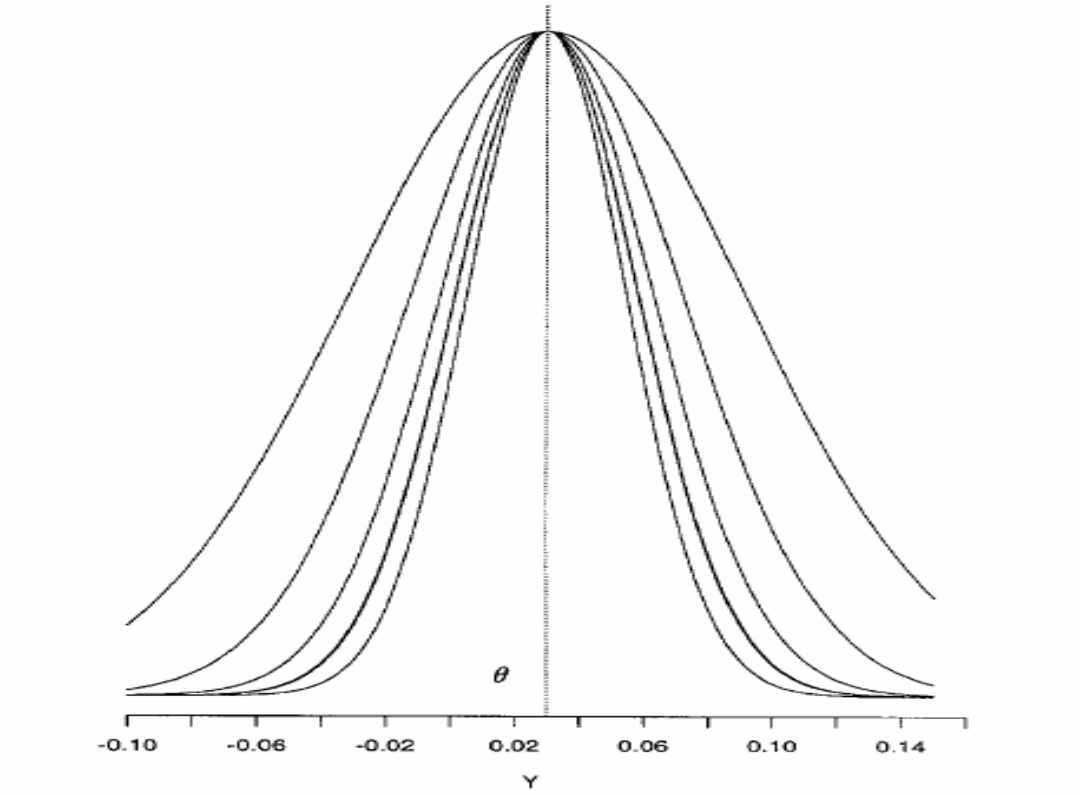


Figure 3-2. Fixed-effects model. Under the assumptions of the fixed-effects model, the expected mean of each study specific statistics, *Yi,* should be equal to the population mean, *i.e.* E (Yi) = θ. And the difference among these studies only rest on s_i^2 = var(Yi) (Normand, 1999).

3.1.2.2. Random-effects model

The random-effects model assumes both within-study and between-study variations exist. The population from which studies are generated may have different characteristics and study effect. This assumption leads to wider and more conservative confidence intervals than the fixed effects model (Normand, 1999).

A random-effects model can be expressed as follows (Normand, 1999):

$$Yi \overset{indep.}{\sim} N(\theta, s_i^2 + \tau^2) \tag{3.2}$$

This model can be further deconstructed. First, the study summary statistic (Y_i), drawn from a distribution with study-specific mean θ_i and variance s_i^2, is normally distributed, shown as follows:

$$Y_i \Big|_{\theta_I, S_i^2} \overset{indep.}{\sim} N(\theta_i, s_i^2) \tag{3.3}$$

Then, each study-specific mean, θ_i is further assumed to be a draw from some superpopulation of effects with mean θ and variance τ^2, where θ is the average treatment effect and τ^2 is the inter-study variation, shown as follows:

$$\theta_i \Big|_{\theta, \tau^2} \overset{indep.}{\sim} N(\theta, \tau^2) \tag{3.4}$$

Therefore, after averaging over the study-specific effects, the distribution of each study summary statistic, Y_i, is normal distributed with mean θ and variance $s_i^2 + \tau^2$, as shown before. (Figure 3-3)

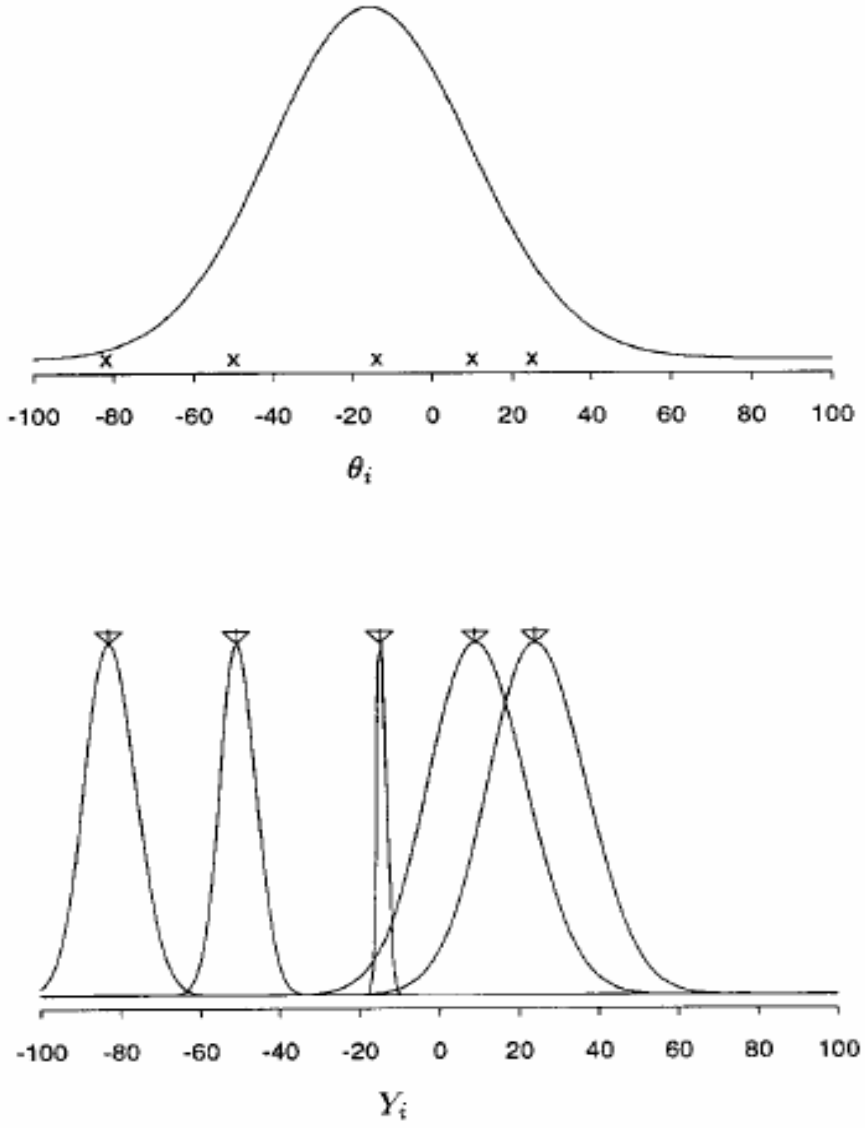


Figure 3-3. Random-effect model. Each effect, θ_i, is drawn from a superpopulation with mean θ and variance τ^2 (upper plot). The study-specific summary statistics, Y_i, are then generated from a distribution with mean determined by θ_i (denoted by $\times$ in the upper plot) and variance s_i^2 (lower plot) (Normand, 1999).

3.1.2.3. Calculating the Summary Estimator

Meta-analysis uses a weighted average of the results from the individual studies. Any method must follow the general equations for a simple, weighted average of results.

$$\overline{y_w} = \sum w_i y_i \Big/ \sum w_i \tag{3.5}$$

Where w_i is the weight of each study, y_i is the parameter being estimated of each study (here, the slope factor), and $\overline{y_w}$ is the weighted average of the parameter being estimated.

The weight usually is the inverse of the variance of the result for each study. The larger studies have more influence than the smaller ones (Egger et al., 1997; Steenland and Savitz, 1997). The weight used for a fixed-effects model is $w_i = \frac{1}{s_i^2}$ and for random effects model is $w_i = \frac{1}{s_i^2 + \tau_i^2}$, where s_i^2 is the within-study variation and τ_i^2 is the inter-study variation. Normand (1999) summarized some estimators for fixed-effects and random-effects models, listed in Table 3-1 (Normand, 1999).

Table 3-1. Summary of estimators for fixed-effects and random-effects models.

Method	Parameter	Estimator	Variance
Fixed-effects model: $Y_i \sim \mathrm{N}(\theta, s_i^2)$			
MLE	θ	$\hat{\theta}_{\mathrm{MLE}} = \frac{\sum_i W_i Y_i}{\sum_i W_i}$	$(\sum_i W_i)^{-1}$
		$W_i = 1/s_i^2$ assumed known	
Bayesian	θ	$\tilde{\theta}_{\mathrm{B}} = [\sum_i W_i + \sigma_0^{-2}]^{-1}(\sum_i W_i Y_i)$	$[\sum_i W_i + \sigma_0^{-2}]^{-1}$
		$W_i = 1/s_i^2$, σ_0^2 assumed known	
Random-effects model $Y_i \mid \theta_i \sim \mathrm{N}(\theta_i, s_i^2)$; $\theta_i \mid \theta, \tau^2 \sim \mathrm{N}(\theta, \tau^2)$			
DerSimonian and Laird	τ^2	$\hat{\tau}^2_{\mathrm{DL}} = \max\left\{0, \frac{Q_W-(k-1)}{\sum W_i - \frac{\sum W_i^2}{\sum W_i}}\right\}$	None proposed
(Method of moments)	θ	$\hat{\theta}_{\mathrm{DL}} = \frac{\sum_i w_i(\hat{\tau}_{\mathrm{DL}}) Y_i}{\sum_i w_i(\hat{\tau}_{\mathrm{DL}})}$	$(\sum_i w_i(\hat{\tau}_{\mathrm{DL}}))^{-1}$
		$W_i = 1/s_i^2$, $w_i(\hat{\tau}_{\mathrm{DL}}) = \frac{1}{s_i^2+\hat{\tau}^2_{\mathrm{DL}}}$ assumed known	
REML	τ^2	$\hat{\tau}^2_{\mathrm{R}} = \frac{\sum_i w_i^2(\hat{\tau})(\frac{k}{k-1}(Y_i-\hat{\theta}_{\mathrm{R}})^2 - s_i^2)}{\sum_i w_i^2(\hat{\tau})}$	Observed Fisher information
	θ	$\hat{\theta}_{\mathrm{R}} = \frac{\sum_i w_i(\hat{\tau}_{\mathrm{R}}) Y_i}{\sum_i w_i(\hat{\tau}_{\mathrm{R}})}$	$(\sum_i w_i(\hat{\tau}_{\mathrm{R}}))^{-1}$
Empirical Bayes	θ_i	$\hat{\theta}_i^{\mathrm{R}} = \hat{B}_i^{\mathrm{R}}\hat{\theta}_{\mathrm{R}} + (1-\hat{B}_i^{\mathrm{R}})Y_i$	$s_i^2(1-\hat{B}_i^{\mathrm{R}})$
		$w_i(\hat{\tau}_{\mathrm{R}}) = \frac{1}{s_i^2+\hat{\tau}^2_{\mathrm{R}}}, \hat{B}_i^{\mathrm{R}} = \frac{s_i^2}{s_i^2+\hat{\tau}^2_{\mathrm{R}}}$ assumed known	
Bayesian	τ^2	$\hat{\tau}^2_{\mathrm{B}} = \int \tau^2 \hat{p}(V \mid \mathbf{y}, \mathbf{s}) \mathrm{d}\theta_i \, \mathrm{d}\theta \, \mathrm{d}\tau^2$	From empirical distribution
	θ	$\hat{\theta}_{\mathrm{B}} = \int \theta \hat{p}(V \mid \mathbf{y}, \mathbf{s}) \, \mathrm{d}\theta_i \, \mathrm{d}\tau^2 \, \mathrm{d}\theta$	From empirical distribution
	θ_i	$\hat{\theta}_i^{\mathrm{B}} = \int \theta_i \hat{p}(V \mid \mathbf{y}, \mathbf{s}) \, \mathrm{d}\theta_j \, \mathrm{d}\theta \, \mathrm{d}\tau^2 \, \mathrm{d}\theta_i$	From empirical distribution
	g(V)	$\hat{g}(V) = \int g(V) \hat{p}(V \mid \mathbf{y}, \mathbf{s}) \mathrm{d}V$	From empirical distribution
		Prior distribution for hyperparameters assumed known	

Table Source: (Normand, 1999)

3.1.2.4. Test of Homogeneity

The fixed-effects model assumes that all studies are sampled from the same population, so the *k* study-specific summary statistics share a common mean θ. A statistical test for the homogeneity of study means is equivalent to testing (Normand, 1999).

H_0: $\theta = \theta_1 = \theta_2 = ... = \theta_k$ against

H_1: At least one θ_i different.

The chi-square test can be employed as a basic statistical test of the homogeneity assumptions (Wang et al., 1999):

$$\chi^2 = \sum_i^k w_i (Y_i - \bar{Y})^2 \sim \chi^2_{k-1} \quad (3.6)$$

Where w (weight) = $1/s_i^2$, $\bar{Y} = \sum w_i Y_i / \sum w_i$, and n = number of studies.

If H_0 cannot be rejected, we have to accept the null hypotheses; *i.e.* the *k* studies share a common mean θ and are homogeneous. Otherwise, if H_0 is rejected, it may be concluded that these study means arose from different populations and are not homogeneous. Under this condition, Normand (1999) suggested to "…continue proceeding by either attempting to identify covariates that stratify studies into the homogeneous populations or estimating a random-effects model" (Normand, 1999). Another option is to use a random-effect model instead of fix-effect model.

3.1.3. Conducting Steps

The first step in conducting a meta-analysis is formulating the problem to be addressed. This step includes clearly stating the objectives, the hypotheses to be tested, and the subgroups of interest. The study variables (outcome and exposure) and parameters are

also defined in this step. The potential confounders should also be identified (Egger et al., 1997).

The second step is collection and analysis of the data. It involves a thorough literature search to gather all relevant published and unpublished data. After using the proposed methods and criteria for identifying and selecting relevant studies, one will extract and analyze information, and finally perform a statistical meta-analysis and calculate the overall effect by combining the data. A heterogeneity test and sensitivity analysis may also be conducted if necessary (Egger et al., 1997).

The final step is reporting the results. Besides the result of a statistical combination of data, the result of the sensitivity analysis is presented. A good way to present the result is by graphical display, together with the confidence intervals of the results (Egger et al., 1997).

3.1.4. Inorganic Arsenic in Drinking Water and Bladder Cancer: A Meta-Analysis for Dose-Response Assessment

3.1.4.1. Introduction

Several epidemiological studies have shown a positive association between arsenic in drinking water and bladder cancer, with a dose-response relationship being evident between the amount of arsenic intake and the probability of getting cancer, while other studies have shown no association. Meta-analysis was used here to combine the epidemiological datasets from different regions, such as Taiwan, US, Bangladesh, India, Chile and Finland, accounting as much as possible for the methodological differences in these studies and the population differences. The research product is an aggregated dose-response function for risk calculation.

3.1.4.2. Material and Methods

Search methods

The criteria for inclusion of epidemiological studies in the present meta-analysis are: (i) all studies are of a case-control or cohort studies, and evaluate the relationship between arsenic concentration in drinking water and bladder cancer; (ii) studies are of males, females or in both genders combined; studies examine incidence or mortality as the study outcome; studies provide information required for the statistical analysis; (iii) studies are published in English between 1970 and 2005; and (vi) studies are referenced in the U.S. EPA IRIS (Integrated Risk Information System), NRC's (National Research Council) Reports (NRC, 1999; NRC, 2001) or Medline database. Besides these searches, the list of references in the identified articles was also systematically examined for additional studies.

The study outcomes varied among studies. In cohort studies, relative risks were used as the study outcome; in case-control studies, odds ratios were the outcomes. Considering that bladder cancer is a rare disease, the odds ratio was assumed approximately the same as relative risk, and relative risk was used as the study outcome. Only one cohort mortality study (Lewis et al., 1999) used SMR (standardized mortality rate) as the study outcome. But this study was criticized because "the comparison of the study population to all of Utah is not appropriate for estimating excess risks" and "the study is not powerful enough to estimate excess risks with enough precision to be useful for arsenic risk analysis" (USEPA, 2001). Hence it was excluded in this meta-analysis.

Seven studies were included in the meta-analysis since they satisfied the criteria mentioned above. They were from different regions, including Taiwan, U.S., Argentina,

Chile and Finland (Bates et al., 1995; Chiou et al., 1995; Kurttio et al., 1999; Chiou et al., 2001; Moore et al., 2003; Steinmaus et al., 2003; Bates et al., 2004). Most of the study outcomes were adjusted by factors of age, gender and cigarette smoking. The details of these studies are listed in Table 3-2.

Rescaling of Exposure

As for deciding the exposure midpoint assigned to a subpopulation, if the highest category of arsenic exposure was open-ended, its interval was set to equal to the width between 0 and the lower bound of the open-ended boundary. For example, in the study of Chiou et al. (2001), the highest category of arsenic exposure was open-ended (>100); this open-ended interval was set to equal the width between 0 and 100, and its midpoint was 150. If the lowest category was open-ended, the lowest boundary was considered as zero. The upper- and lower-bound values of arsenic concentration in each category were then used to calculate the mid-point of exposure for that subpopulation (Norat et al., 2002). Also, the definition of arsenic exposure varied among studies. In most of the articles, "arsenic exposure" means the annual average concentration of arsenic in drinking water (in units of μg/L or ppb). Studies using another exposure index (i.e. lifetime exposure) were rescaled to concentration assuming population-average rates of water ingestion.

Dose-response Model

For each study, using the information on RR (relative risk) and average arsenic concentration (X) for each subpopulation, the hazard as a function of exposure can be modeled as (Greenland and Longnecker, 1992):

$$\ln RR = b \Delta X \text{ or } \ln RR = b(X - X_0) \quad (3.7)$$

where X is the exposure (in μg/L), ΔX is the difference in arsenic concentration intake between each category of exposure (X) and the reference category in each study (X_0). The coefficient b is the fitted slope factor in the linear-logistic regression model. This linear-logistic model estimates the logarithm of the observed relative risks (estimated as the odds ratio in some studies), and accounts for the correlation between risk estimates for separate exposure levels depending on the same reference group.

After finding the coefficient (b_i) of each study, the summary estimate is the pooled coefficient ($\bar{b}$). The individual slopes of each study were combined by weighted average, using the inverse of their variances as weights. The 95% confidence intervals (CI) were calculated for the common regression slopes. The fixed-effect model was first used and the homogeneity test was conducted. The random-effect model was applied when the homogeneity test provided evidence of heterogeneity.

Table 3-2. Studies of Bladder Cancer (188)

Study	Study Type	Location	Arsenic Exposure (µg/L)	Exposure Midpoint (µg/L)	Study Outcome	Adjustment
Chiou et al., 1995	Cohort	SW Taiwan	<=50 50-70 71+	25 60 100	**Relative Risk** 1.0 1.8 3.3	Age, sex, cigarette smoking
Bates et al., 1995	Case-Control	Utah, US	<440 440-<707 707-<987 >=987	220 600 850 1200	**Odds Ratio** 1.0 0.69 0.54 1.0	Age, sex, cigarette smoking
Kurttio et al., 1999	Case-Control	Finland	<0.1 0.1-0.5 >=0.5	0.05 0.3 5	**Odds Ratio** 1.0 1.53 2.44	Age, sex, cigarette smoking
Chiou et al., 2001	Cohort	NE Taiwan	<=10 10.1-50 50.1-100 >100	5 30 75 150	**Relative Risk** 1.0 1.5 2.2 4.8	Age, sex, cigarette smoking, and duration of well water drinking
Steinmaus et al., 2003	Case-Control	Westen US Californi a & Nevada)	<10 10-80 >80	5 45 120	**Odds Ratio** 1.0 1.04 0.94	Age, gender, occupatio n, smoking history
Moore et al., 2003	Case-Control	Argentina & Chile	<10 10-99 100-299 >300	5 55 200 400	**Odds Ratio** 1.0 1.46 2.26 1.36	Tumor stage and grade
Bates et al., 2004	Case-Control	Argentina	0-50 51-100 101-200 >200	25 75 150 300	**Odds Ratio** 1.0 0.88 1.02 0.6	Multivari ate-adjusted

3.1.4.3. Results

Dose-Response Slope of Each Study

From Figure 3-4, we can see that the results of observational studies of arsenic in drinking waster are quite dispersed. In three studies (Bates et al. 1995, Steinmaus et al. 2003, and Bates et al. 2004), a dose-response relationship is not evident between the exposure to arsenic and the relative risk of bladder cancer, or is negative. In the study of Kurttio et al. 1999, a much stronger relationship is noted from the limited and lower range of arsenic exposure. Although two studies done by Chioe et al. (1995 and 2001) are different study designs from two different regions in Taiwan, their dose-response relationships are quite similar.

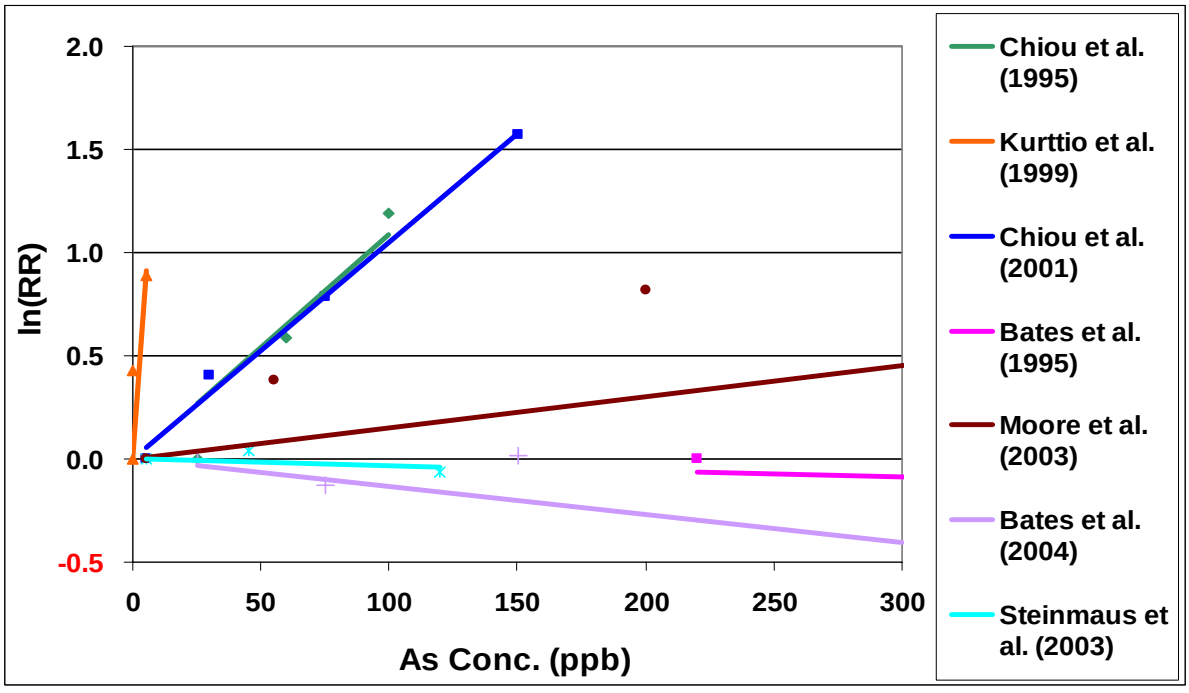


Figure 3-4. Dose-response analysis of relative risk of bladder cancer for arsenic intake from Drinking water.

Calculating the Summary Estimator and Test of Homogeneity

The fixed-effect model was first used, with the weight calculated by the inverse of variance of each study, i.e. $w_i = \frac{1}{s_i^2}$. By using the statistical software of Stata, the pooled estimate of slopes from seven studies was 0.00615 (95% CI: 0.00588, 0.00642), with the unit of lnRR per unit increase of exposure (i.e. per μg/L). But the chi-square statistic was quite large (i.e. Q= 3197.110 on 6 degrees of freedom, p= 0.00), which rejects the null hypothesis of homogeneity and means there was evidence of heterogeneity.

The fitted slope (with the unit of lnRR per unit increase of exposure) of each study and the combined estimate of slope by using fixed-effect model are presented as box plots in Figure 3-5. The horizontal line of each study corresponds to its 95% confidence interval, and the size of the square reflects the weight of each study. From Figure 3-5, it is clear that the Finland study done by Kurttio et al. (1999) has a much wider horizontal line and no box, showing that its 95% confidence interval is much wider than other studies but with very little weight. We then concluded that this study might be an outlier for its far lower arsenic exposure. This study was then excluded to solve the problem of heterogeneity. A sensitivity analysis was conducted to make sure the exclusion of the Finland study done by Kurttio et al. (1999) doesn't cause significant effect on the result, which will be discussed later. But this didn't lower the value of the chi-square statistic sufficiently, showing that heterogeneity still exists even in the remaining subset of six studies. Therefore, a random-effect model was used next.

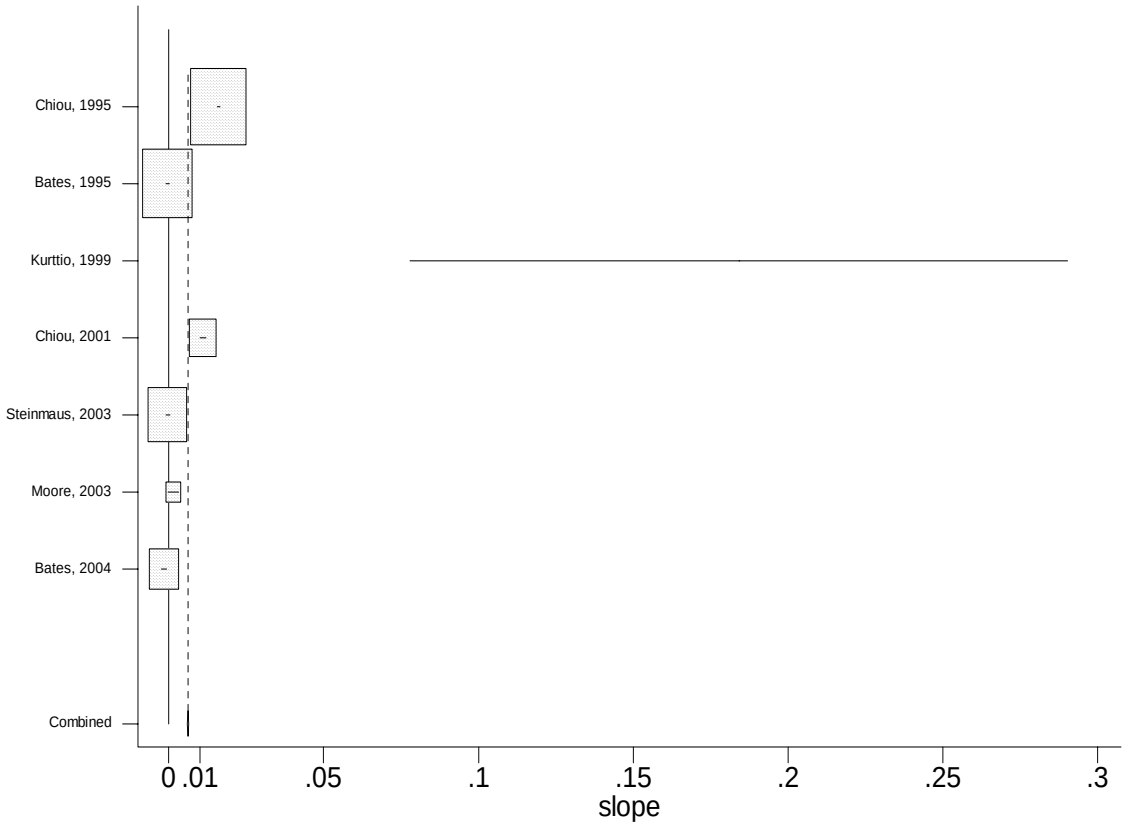


Figure 3-5. Slope (with the unit of lnRR per unit increase of exposure) of each study and the combined estimate of slope by using fix-effect model. The horizontal line of each study corresponds to its 95% confidence interval, and the size of the square reflects the weight of each study.

By using the random-effect model, the pooled estimate of the slopes from six studies was found to be 0.004 (lifetime excess probability of bladder cancer per μg/L) (95% CI: -0.003, 0.012). The results are shown in Figure 3-6.

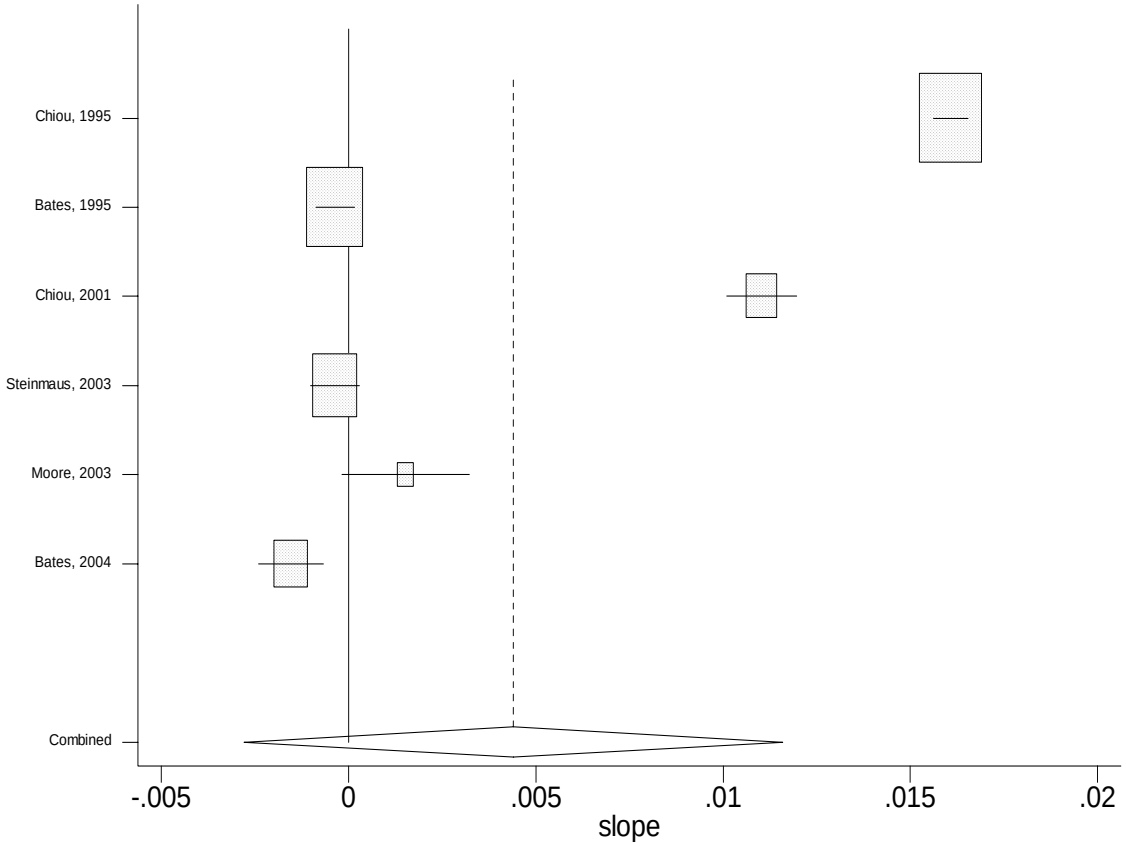


Figure 3-6. Slope (with the unit of lnRR per unit increase of exposure) of each study and the combined estimate of slope by using random-effect model.

Sensitivity Analysis

To make sure the exclusion of the Finland study done by Kurttio et al. (1999) doesn't cause significant effect on the result, another meta-analysis of using random-effect model and including all seven studies was also conducted. The average of the slopes is 0.005 (95% C.I.: -0.002, 0.012). Comparing this result with the previous one using the random-effect model but excluding the Finland study, their best-estimates are only slightly different (0.004 vs. 0.005), and the difference between them will be even slighter when exponential functions are applied to these two values. Also, their upper-bound estimates are the same (i.e. 0.012).

Therefore, it is appropriate to exclude the Finland study. The comparison of these results is shown in Table 3-3. Figure 3-7 shows both the summary estimators from the fixed-effect model (including all seven studies) and random-effect model (including six studies).

Table 3-3. Comparison of the Results by using Different Models and including Different Studies.

STUDIES INCLUDED	MODEL	BEST-ESTIMATE	LOWER	UPPER
7	Fixed-effect	0.006	0.006	0.006
	Random-effect	0.005	-0.002	0.012
6	Fixed	0.006	0.006	0.006
	Random	0.004	-0.003	0.012

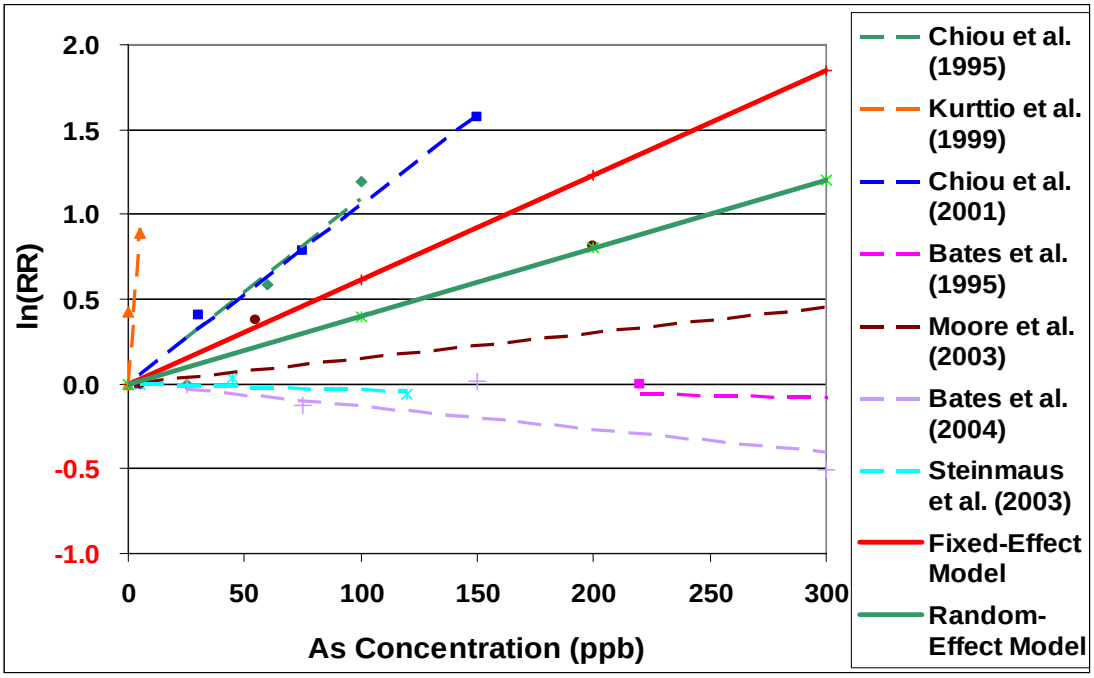


Figure 3-7. Dose-response relationship of relative risk of bladder cancer for arsenic intake from Drinking water by using fixed-effect and random-effect model.

Risk Calculation

The result of meta-analysis supports the claim that there is a positive dose-response relationship between exposure to arsenic in drinking water and bladder cancer. Using the results presented above, the best estimate of the relative risk associated with an increase of arsenic exposure can be estimated as lnRR = 0.004X, or RR= EXP (0.004X), were X is the waterborne arsenic concentration in units of μg/L. Using the upper 95% confidence limit, the plausible upper limit of the relative risk associated with an increase of arsenic exposure can be estimated as lnRR = 0.012X, or RR= EXP (0.012X).

The absolute risk (AR) of bladder cancer is calculated by multiplying the excessive relative risk (ERR) by the natural rate (NR) of bladder cancer. Excess relative risk equals to the relative risk minus one (i.e. ERR=RR-1). Therefore, AR can be calculated as:

$$AR= NR\times ERR = NR\times (RR-1)= NR\times \{EXP\ (0.012X)-1\} \quad (3.8)$$

Table 3-4 and Figure 3-8 show the results of the AR calculation for bladder cancer associated with a variety of proposed MCLs (maximum contaminant levels) by using the different estimates from the meta-analysis: the best estimate, the upper and lower bound estimates of the slope factors. At the most recent arsenic MCL (i.e. 10μg/L), the associated bladder cancer risk (lifetime excess probability) is 2.29×10^{-5} by using the upper bound estimation of slope factor.

From the upper bound result of the meta-analysis, the arsenic concentration corresponding to a lifetime excess probability of 10^{-3} is approximately 160 μg/L; the concentration corresponding to 10^{-4} is approximately 40 μg/L; and the concentration corresponding to 10^{-5} is 4.5 μg/L.

Table 3-4. Risk of Bladder Cancer at different MCLs

MCL (ppb)	AR (U_95)	AR (Mean)	AR (L_95)
0	0	0	0
1	2.17E-06	7.21E-07	-5.47E-06
3	6.60E-06	2.17E-06	-1.59E-05
5	1.11E-05	3.64E-06	-2.57E-05
10	2.29E-05	7.35E-06	-4.78E-05
20	4.88E-05	1.50E-05	-8.29E-05
50	1.48E-04	3.98E-05	-1.41E-04

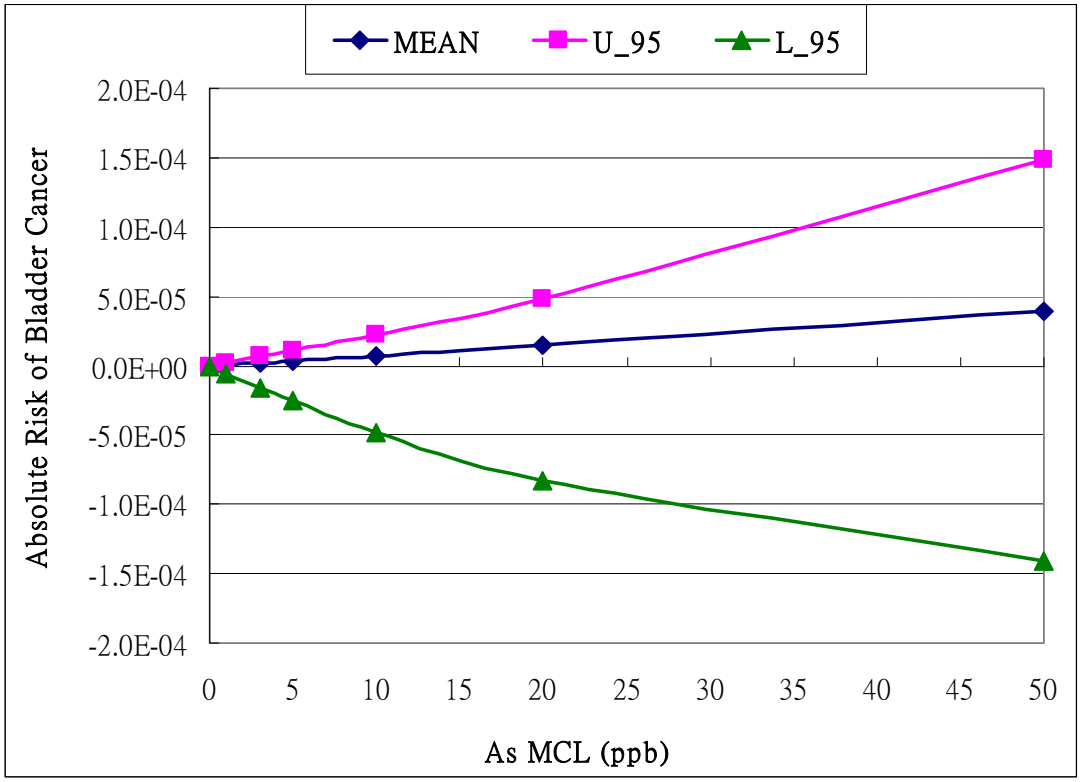


Figure 3-8. Absolute Risk of Bladder Cancer at different proposed MCLs (Maximum Contaminant Levels) from meta-analysis. (Mean: the best estimation of slope factor, U_95: the upper bound estimation of slope factor)

Aggregated slope factors for dose-response relationship.

The slope factor was fitted using the equation of Pc = SF×ADRI, where Pc is the mean probability of cancer, SF is the slope factor, and ADRI is average daily rate of intake of arsenic (µg/kg/day). ADRI (µg/kg/day) was transformed from arsenic MCL (µg/L or ppb) by assuming a tap water ingestion rate of 0.023 L/kg-day. A linear function (characterized by a slope factor) was then fitted as an approximation to the dose-response curve for the meta-analysis results. Figure 3-9 shows the regression results of slope factors. The best estimate of the slope factor from the meta-analysis is 3.0×10^{-5} (with unit of probability per µg//kg/day), with the upper bound of 1.27×10^{-4}. These slope factors from the meta-analysis are lower than the ones from the EPA (1.15×10^{-3}) and NRC (8.85×10^{-4}).

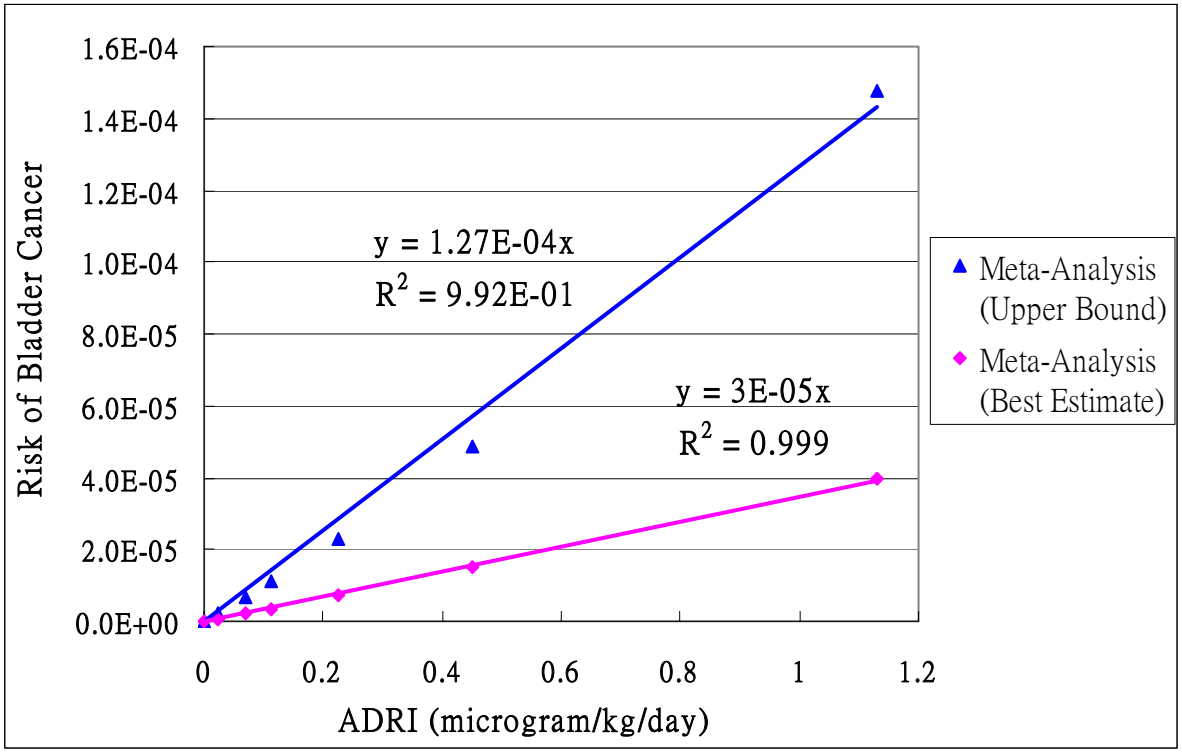


Figure 3-9. Slope Factors of Bladder Cancer generated from Meta-analysis Results.

3.1.5. Conclusion and Discussions

In this study, a meta-analysis of arsenic studies was conducted by combining several epidemiological studies from different regions (such as Taiwan, US, Argentina, Chile and Finland) to produce a composite dose-response relationship between the amount of arsenic exposure and the excess probability of cancer. Both the fixed-effect and random-effect models were used to calculate the averaged coefficient of the linear-logistic regression model. A homogeneity test was conducted first to check the heterogeneity among these studies. Because the heterogeneity was found to be high, a random-effect model had to be used. This results in a wider confidence interval of slopes and a more conservative upper bound quantitative summary of risk. The high heterogeneity shows that there are large differences between studies, which suggests it may not be appropriate to simply extrapolate from Taiwanese studies to the U.S.

The final product is an aggregated dose-response model in the range of empirical observation of arsenic. The best estimate of the slope factor from the meta-analysis is 3.0×10^{-5} (with unit of probability per microgram/kg/day), with the upper bound of 1.27×10^{-4}. These slope factors from the meta-analysis are lower than the ones from the EPA (1.15×10^{-3}) and NRC (8.85×10^{-4}). There clearly are large differences between the current study and the EPA/NRC results. The possible reason for the difference is because EPA/NRC conducted their study mainly based on data from Taiwan, while we used meta-analysis to combine data from several different regions.

Considering the most recent arsenic MCL (i.e. 10 μg/L), the associated bladder cancer risk (lifetime excess probability) conducted using the upper bound result of the meta-analysis is 2.29×10^{-5} (7.35×10^{-6} if the best estimate is used), which is much lower than NRC's

theoretical lifetime excess risk of bladder cancer for U.S. Populations (1.2×10^{-3} for female and 2.3×10^{-3} for male). These results show that the existing estimates of risk of bladder cancer provided by the EPA and NRC may be overestimates.

One shortcoming of this study is that there are only seven observational studies available for meta-analysis. The available data make it difficult to do further investigation, such as meta-regression to check whether an overall study result varies among subgroups (e.g. study type or location), or a sensitivity analysis to detect the robustness of the findings to different assumptions. New observational studies of arsenic, especially ones involving a case-control or cohort design, need the investment of large amounts of money and time. Even given that requirement, meta-analysis can be an appropriate tool to resolve the discrepancies among existing epidemiological data, and to produce a reasonable generalized dose-response model and its distribution of parameter values.

3.2. The Quantification of Margin of Safety

3.2.1. Margin of Safety and Regulatory Rationality

Maximum Contaminant Levels (MCLs) are selected to provide a margin of safety for the protection of public health in the face of inter-subject variability and uncertainty. The margin of safety is not quantitatively defined yet, but is known to be related to variability and uncertainty. The margin of safety generally increases as the fraction of a population predicted to be below a target risk is increased and as the confidence in this claim increases. Therefore, the goal of this research is to better quantify the margin of safety by probabilistic risk assessment, dealing with variability and uncertainty issues, and to relate this margin of safety to compliance costs. This will help to develop regulatory limits on a contaminant concentration that adequately protects human health with an ample margin of safety at a more reasonable cost than currently is the case.

In this study, a key assumption is that lower MCLs associated with increasing margins of safety come at increased cost of compliance, and that decision-makers must understand the price of any such increased margin of safety. A central idea here is that the increased cost of a lower MCL must be viewed in part as purchasing a larger margin of safety, rather than purchasing some established reduction in health effects (the magnitude of which remains uncertain).

The rationality of this research can also be understood through the following figures. Figure 3-10 shows one example of the traditional approach in risk-based decision making. In that figure, the best estimate of the risk (i.e. probability of getting cancer, Pc) is obtained for a representative individual in the exposed population. As the MCL is lowered, this reduces

the risk to this representative individual, and so the increased cost associated with a lower MCL may be viewed as producing a reduction in the risk. Since the individual risk is reduced, so is the total burden of effects in the exposed population. As a result, the increased cost associated with a lower MCL may be viewed as "purchasing" a reduction in health effects in the affected population.

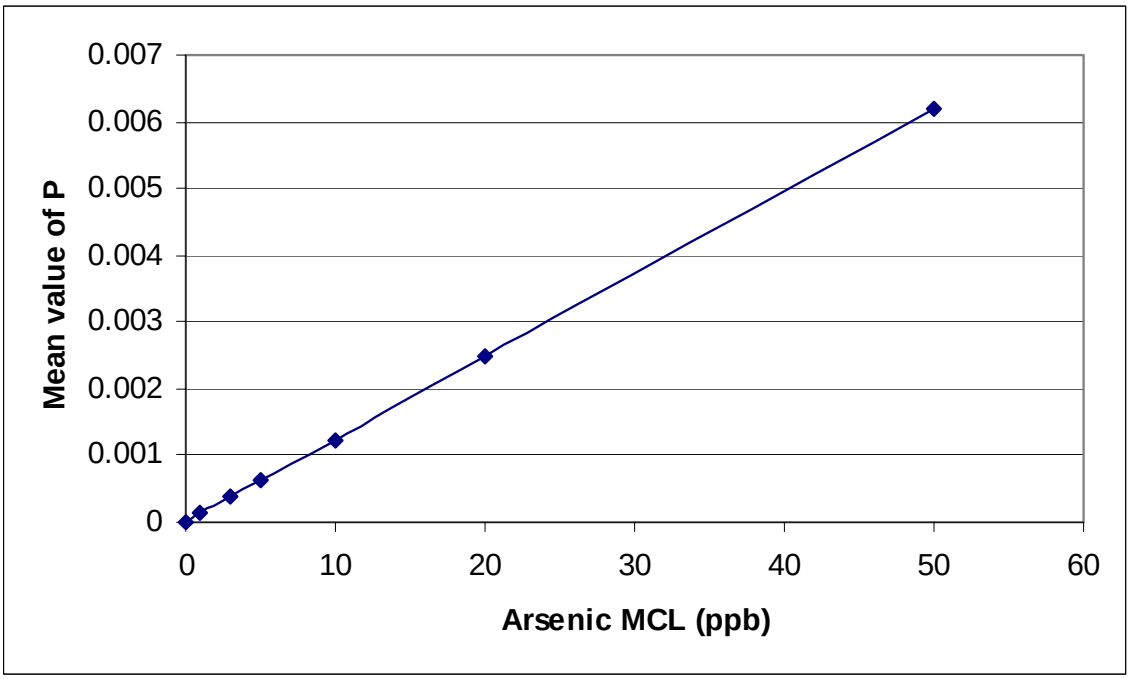


Figure 3-10. A hypothetical relationship between MCL and the "best estimate" of risk (P) to a representative individual in the exposed population (using a linear dose-response model).

Consider, however, the variability of risk across the population. This is shown in Figure 3-11. Note that lowering the MCL increases the fraction of the population whose risk is below a certain target risk, such as a value of Pc equal to 10^{-4}. The increased cost associated with a lower MCL may be viewed as "purchasing" an addition in the fraction of individuals whose risk is below the target level of risk we have established.

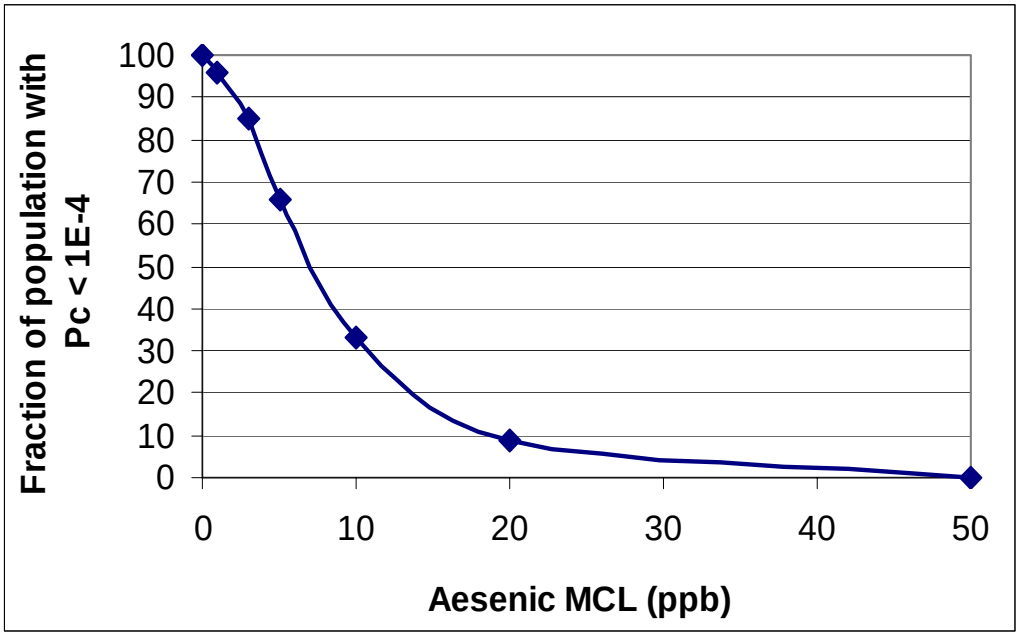


Figure 3-11. A hypothetical relationship between arsenic MCL and the fraction of a population whose risk below 10^{-4} (using a linear dose-response model).

Then the issue of uncertainty is considered by asking: "*With what confidence can we state that at least some target fraction of the population (e.g. 90%) is below the target risk (e.g.*10^{-4}*)?* This is shown in Figure 3-12 as an example. Note that lowering the MCL raises the confidence that at least 90% of the population is below the target risk of 10^{-4}. The increased cost associated with a lower MCL may be viewed as "purchasing" increased confidence that the fraction of individuals whose risk is below the target risk is acceptable.

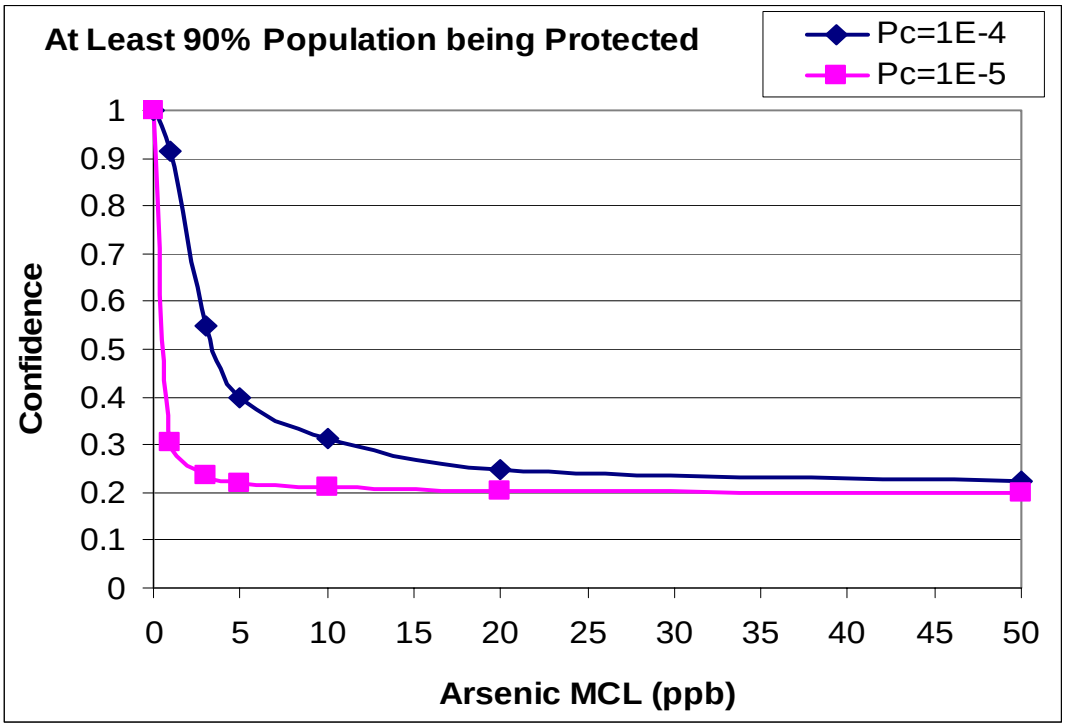


Figure 3-12. A hypothetical relationship between MCL and the confidence that at least 90% of the population whose risk is below 10^{-4} or 10^{-5} (in other words, no more than 10% of the population whose risk is above 10^{-4} or 10^{-5}).

The above discussion suggests that each potential MCL can be described by a three dimensional volume containing points described by a triplet of values: (Pc, F, C), where Pc is the probability of getting cancer, F is the fraction of the population whose risk is below this value of Pc, and C is the confidence with which the assessor can state that at least this fraction of the population is protected from a risk with the value of Pc. For example, suppose the MCL is fixed (e.g. 5 ppb). Figure 3-13 shows the surface of confidence (C) associated with this MCL, where the X and Y axes are F (fraction of the population with a risk below a given value of Pc) and Pc, respectively. Note that as the value of Pc is reduced at a given value of F, the surface height decreases, since the confidence that AT LEAST this fraction of the population experiences a risk below Pc decreases. Similarly, as the target fraction

increases at a given value of Pc, the confidence that this target fraction is not exceeded (protected) decreases also.

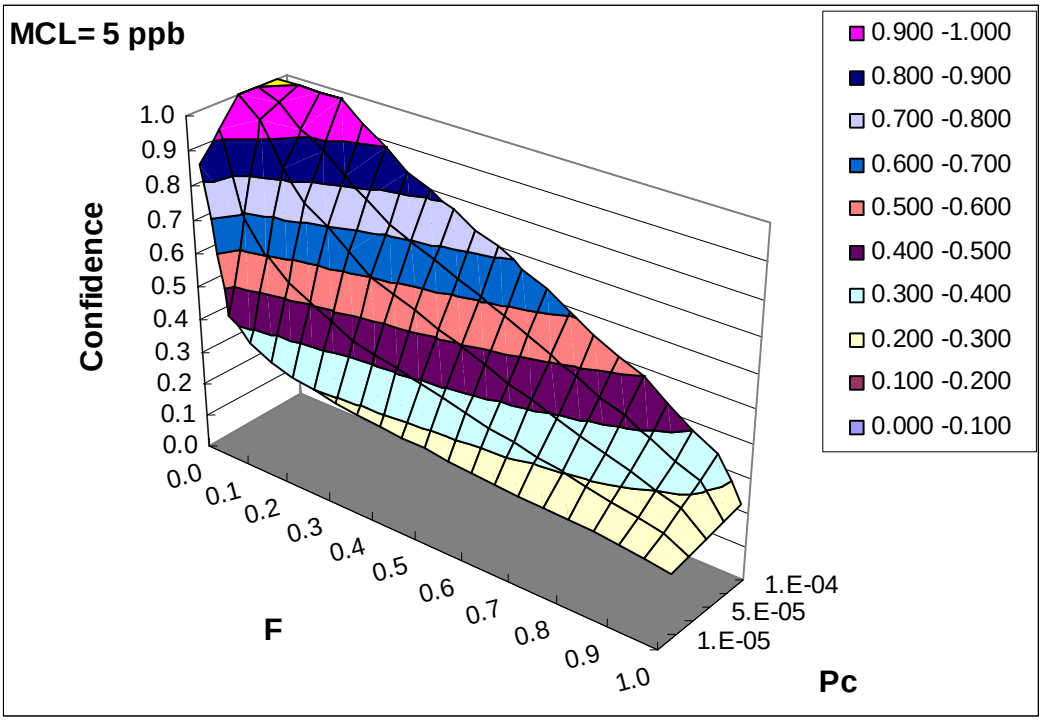


Figure 3-13. A hypothetical surface showing the confidence (C) with which it can be stated that at least certain fraction (F) of the population experience a risk below a target risk (Pc).

From a policy perspective, the existence of this surface suggests that the desirability of an MCL will depend on where Pc, F and C are set as targets. Clearly, this desirability increases as the target values of Pc are decreased and F are increased, but this is offset by decreased confidence that at least these values are achieved. If one imagines a series of these surfaces, one for each potential MCL, one can imagine that reducing the MCL (with its associated increase in cost) may be viewed in three ways: (i) it reduces the mean, or expectation, value of Pc in the population, and hence the expectation value of the total burden of effects; (ii) it increases the fraction F, conditional on target values of Pc and C; or

(iii) it increases the confidence, C, in protection conditional on target values of Pc and F. As a result, the goal of this research is three-fold:

- to develop the methodologies needed to generate these surfaces,
- to develop a decision methodology for choosing an appropriate MCL given multiple surfaces at potential MCLs, and
- to test the methodologies in the case of arsenic in drinking water using the results of the meta-analysis performed in last section.

3.2.2. Reasoning for the Arsenic Case

Applying the previous regulatory reasoning to the arsenic case, a regulator should be able to identify an MCL that provides some pre-specified level of confidence that at least a prescribed or target fraction of the population will be protected against a risk that exceeds Pc after the regulatory limit is in place. Lowering or tightening the allowed concentration limit (i.e. MCL) then increases the confidence that this action has purchased protection of some specified fraction of the population against some specific risk. In a very real sense, the cost of the regulatory action may be justified by the increased confidence that a desired state of health has been reached. Therefore, the central question facing a decision-maker can be stated as: "*What is the MCL for which it can be said with at least C (%) confidence that no more than F (%) of the population will be exposed to target risks of Pc or greater?*" And the auxiliary research question is: "*What is the incremental cost associated with an incremental increase in the margin of safety, characterized by an increase in C (confidence) and decrease in F (fraction of population above a risk of Pc)*?"

More specifically, my step-by-step reasoning is listed in Table 3-5.

Table 3-5. Steps of Reasoning

STEP	REASONING
1	EPA's old limit was 50 µg/L.
2	New information in the 1990's suggested 50 µg/L was not protecting health (Pc was above 10^{-4}).
3	EPA proposed 10 µg/L based on these data. This level was determined to be feasible technologically and economically.
4	The new NAS analysis of epidemiological data shows significant risk at 10 µg/L (Pc > 10^{-4}) if linear model is used. (Linear model might not be the best model to estimate dose-response relationship.)
5	This suggests that the MCL should be below 10 µg/L to prevent the lifetime risk of getting cancer above from exceeding 10^{-4}.
6	The cost of lowering the MCL to below 10 µg/L is high. (Gurian and Small, 2001)
7	However, the risk estimate contains a margin of safety (e.g. linear model).
8	A "reasonable" margin of safety might still be associated with an MCL of 10 µg/L or above.
9	Therefore, the MCL might be chosen by establishing a target level of health risk and an appropriate margin of safety, and then locating a concentration that meets these goals.
10	Performing the analysis in step 9 requires answering several questions: (1) What are the uncertainty and variability probability density functions (PDFs) or cumulative density functions (CDFs) of cancer risk for different MCLs? (2) How much confidence can we have that an MCL of 1, 3, 5, 10 etc. will still produce acceptable risk, which is defined as some combination of target risk and fraction of population protected? (3) What is meant by a "reasonable margin of safety" for SDWA decisions taking into account variability and uncertainty?
11	For each MCL, one can then calculate the margin of safety and the cost, producing a curve relating these two quantities, which in turn can be used to select an MCL that produces a "reasonable margin of safety" at acceptable cost.

3.2.3. Nested Variability/Uncertainty Analysis by Monte Carlo Simulation

Monte Carlo simulation is popularly used to address variability and/or uncertainty in probabilistic risk assessment. In the nested Monte Carlo methodology, the variability of each parameter is specified as a probability distribution. Then, a set of parameter values needed

for modeling is drawn from these distributions and the risk is calculated. This process is repeated numerous times over multiple draws from the distributions, accounting for correlations (Greenland, 2001). The result is a realization of the variability distribution. Using uncertainty distribution, the above process is repeated to generate a new realization of the variability distribution. The procedure of applying Monte Carlo analysis in exposure assessment is shown in Figure 3-14. Some computer software, such as Crystal Ball, can easily do the Monte Carlo simulation, assuming the underlying model is sufficiently simple so it can be executed in Excel.

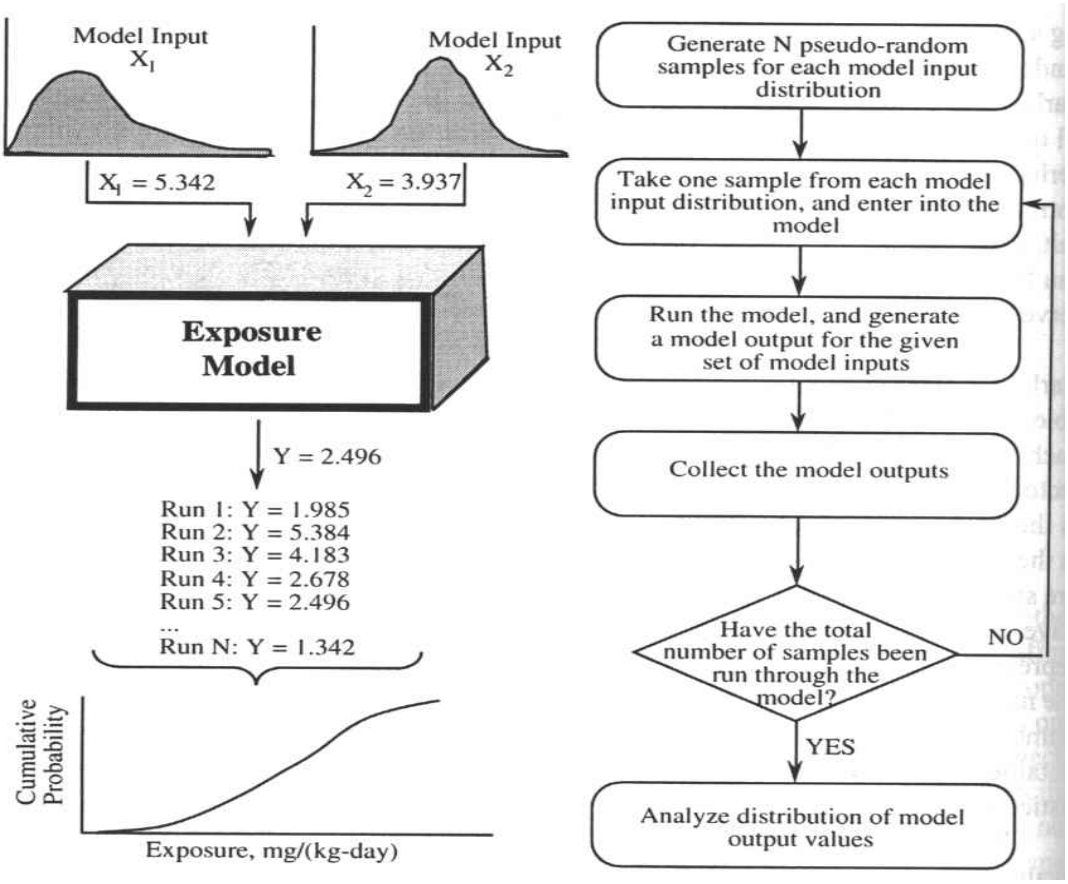


Figure 3-14. Schematic and flowchart illustrating the application of Monte Carlo analysis to a model (Cullen and Frey, 1999).

The influence diagram in Figure 3-15 illustrates the steps of risk calculation taken in the present study on arsenic. Crystal Ball software was used to do the simulation. The result

of the simulation is a quantitative assessment of the uncertainty in estimates of the percentile of the inter-subject variability distribution associated with a given level of risk. Using nested variability /uncertainty methods, the simulation can be used to place an uncertainty distribution (PDF or CDF) on the estimate of the fraction of exposed individuals with a probability of cancer below 10^{-4} (or any other target value of Pc). By generating such distributions, one can produce a 3-D surface with one axis being probability of cancer (Pc), another being fraction of people below that probability of cancer, and a third being confidence that this fraction is not exceeded at the MCL considered.

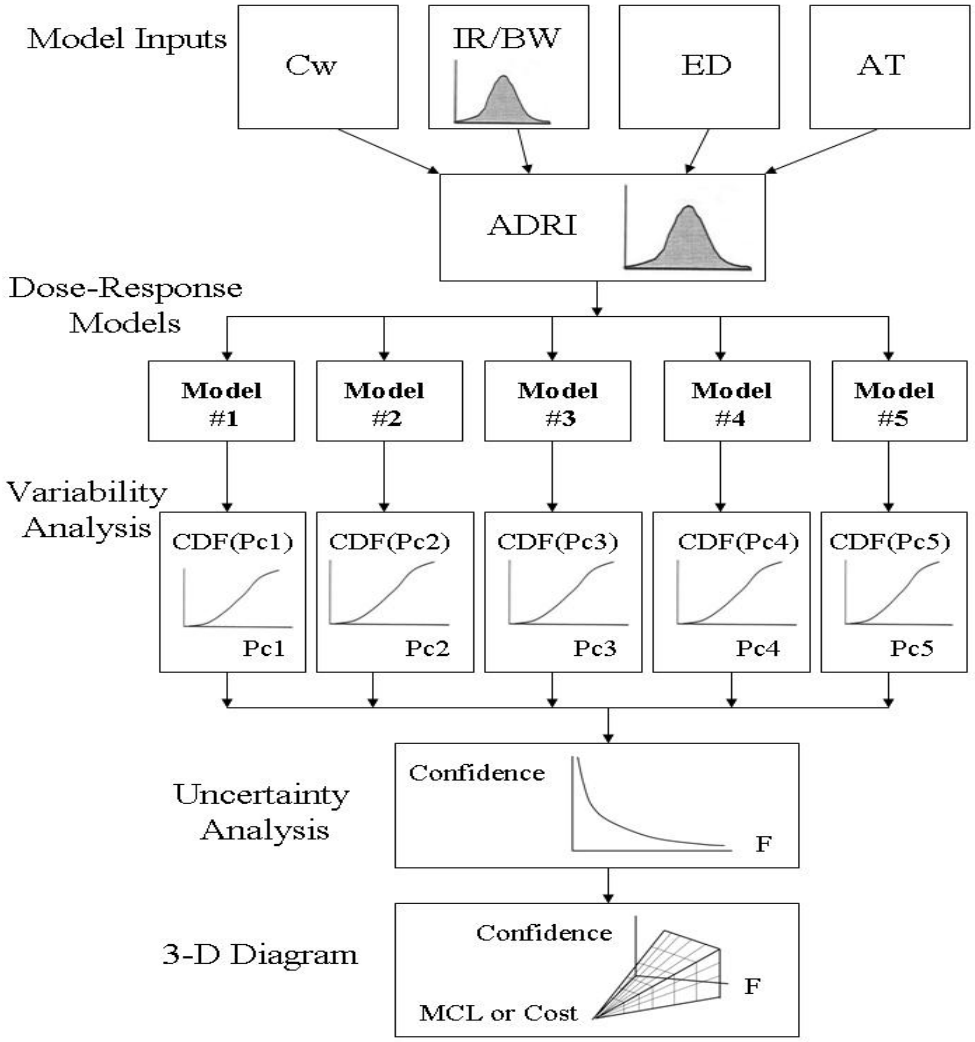


Figure 3-15. Influence Diagram for Steps of Risk Calculation employed in the study.

3.2.4. Methods

The margin of safety is related to inter-subject variability of risk and to uncertainty. Several model inputs were considered for contributing inter-subjective variability (in parameter values, activity patterns, etc) or uncertainty (in modeling, parameter values and low-dose extrapolation, etc). They are listed as follows. How to incorporate them into risk characterization will be discussed in the following sections.

(1) ***Variability*** between individuals (Inter-subject variability)

- Intake rate per unit body weight *(IR/BW).*
- Variability of secondary pathway parameters.
- Susceptibility (*e.g.* retention times; bioactivation fractions).
- No variability in water concentration was assumed since exposure at the MCL is examined.
- No variability in exposure duration was assumed (a lifetime exposure of 75 years is assumed).

(2) ***Uncertainty*** (in modeling, parameter values and extrapolations between species and/or subpopulations)

- Median values of variability Probability Density Functions (PDFs).
- Dose-response relationships.

3.2.4.1. Variability Analysis

The model inputs needed to establish the magnitude of exposure for an individual include Cw, IR/BW, ED and AT. Cw is the arsenic concentration to which a person is exposed; here this is the regulatory levels we are interested in assessing: 1, 3, 5, 10 and 20

μg/L. IR/BW is total tap water intake per unit body weight (L/kg-day) for an individual in a given age group. Information on IR/BW was obtained from Table 3-7 of the EPA's 1997 Exposure Factors Handbook (USEPA, 1997). ED (duration of exposure) is assumed equal to the length of time represented by an age category, and AT (averaging time) is assumed to be the average years of life (75 years). The Average Daily Rate of Intake (ADRI, the unit of exposure used in this study) was calculated by the following formula:

$$ADRI = Cw \times (\frac{IR}{BW}) \times (\frac{ED}{AT}) \tag{3.9}$$

The age-weighted ADRI was calculated considering the changes in the above parameters with age, classified into the following groups: <0.5, 0.5-0.9, 1-3, 4-6, 7-10, 11-14, 15-19, 20-44, 45-64, 65-74, and 75+ years. The age-weighted value of ADRI then is:

$$\begin{aligned} ADRI = {} & Cw \times (\frac{IRw}{BW})_{<0.5} \times \frac{0.5}{75} + Cw \times (\frac{IRw}{BW})_{0.5-0.9} \times \frac{0.5}{75} + Cw \times (\frac{IRw}{BW})_{1-3} \times \frac{3}{75} \\ & + Cw \times (\frac{IRw}{BW})_{4-6} \times \frac{3}{75} + Cw \times (\frac{IRw}{BW})_{7-10} \times \frac{4}{75} + Cw \times (\frac{IRw}{BW})_{11-14} \times \frac{4}{75} \\ & + Cw \times (\frac{IRw}{BW})_{15-19} \times \frac{5}{75} + Cw \times (\frac{IRw}{BW})_{20-44} \times \frac{25}{75} + Cw \times (\frac{IRw}{BW})_{45-64} \times \frac{20}{75} \\ & + Cw \times (\frac{IRw}{BW})_{65-74} \times \frac{10}{75} + Cw \times (\frac{IRw}{BW})_{75+} \times \frac{0}{75} \end{aligned} \tag{3.10}$$

In using an age-weighted value for ADRI, it is implicit that the health effects are independent of the time-history of exposure; data and models needed to correct for this assumption are not available at present (Cullen and Frey, 1999). The age-weighted ADRI was assumed to have a lognormal distribution in the population when everyone is exposed at the same concentration (at the proposed MCL). Inter-subject variability in ADRI is dominated by inter-subject variability in IR/BW for each age category, which in turn was determined from the cumulative distribution function percentiles represented by the data in Table 3-7 of the 1997 Exposure Factors Handbook cited previously. A lognormal

distribution was fit to these data in each age category, with best fits resulting from a GSD of approximately 1.75 in each category (it varied between 1.6 and 1.9 across the age categories, with a mean of 1.75). It then was assumed that an individual's z-statistic for a given parameter is invariant with age. With this assumption, the age-weighted value of ADRI (Equation 3.10) will also be distributed lognormally with a GSD of 1.75. The median value of the age-weighted ADRI was calculated as the product of the mean age-weighted ADRI (from Equation 3.10) and EXP{-[LN^2(GSD)]/2} (the ratio of median over mean for lognormal distributions). Uncertainty is negligible compared to that introduced by dose-response models (described below), and so is not considered further here. Appendix A shows the details of calculation steps.

3.2.4.2. Uncertainty analysis

Five dose-response models, shown in Table 3-6, were considered to reflect uncertainty in the dose-response equation. These models are Mitosis (Crawford-Brown, 2001), Repair (Crawford-Brown, 2001), NAS (NRC, 1999), Linear New (Morales et al., 2000) and Upper Morales (Morales et al., 2000). They were fit to the data on bladder and lung cancer of Morales *et al* .(Morales et al., 2000), ignoring liver cancer since, as detailed in the NAS reports, the particular forms of liver cancer noted in the Taiwanese population do not correspond to those expected within the U.S. population (NRC, 1999; NRC, 2001). The Agency report also indicates that non-cancer effects are likely to be significant only at concentrations well above those considered here, so cancer risk is likely to be the driving effect in regulatory decisions (USEPA, 2001). Total fatal and non-fatal cancers are combined here.

Morales and her colleagues (Morales et al., 2000) utilized 10 separate models in interpreting the dose-response data, including variations of the generalized linear and multistage-Weibull models. Their results indicated little ability to distinguish between the model fits, although the generalized linear models provided marginally more robust and stable results. Available scientific evidence suggests that arsenic does not act as a direct carcinogen through interaction with DNA (USEPA, 2001). The limited evidence available points towards a mode of action in which arsenic either is toxic, inducing some form of proliferative response, or interfering with repair of DNA damage. In light of this evidence, the data of Morales *et al.* were fit in the current study with an alternative set of models based on multistage theories of carcinogenesis. In particular, the Moolgavkar model (Moolgavkar et al., 1990), involving transitions between normal cells, initiated cells and a full tumor, was employed after modification for repair following the state-vector models of Crawford-Brown and Hofmann (Crawford-Brown and Hofmann, 1993; Crawford-Brown and Hofmann, 1996). In these models, background transitions occur between normal, initiated and tumor states, with proliferation in the initiated state and repair from initiated back to normal calls. The mitosis model presupposes that arsenic primarily increases the mitotic rate in the initiated pool of cells, while the repair model presupposes that arsenic primarily reduces the repair rate constant. The differential equations for the mitosis and repair models are as follows:

$$\frac{dN_n(t)}{dt} = -k_{ni}N_n(t) + k_r N_i(t) \tag{3.11}$$

$$\frac{dN_i(t)}{dt} = k_{ni}N_n(t) - k_r N_i(t) + MN_i(t) \tag{3.12}$$

$$\frac{dN_t(t)}{dt} = k_{it}N_i(t) \tag{3.13}$$

where k_{ni} is the transition rate constant from normal to initiated cells (probability per unit time); k_{it} is the transition rate constant from initiated to tumor cells (probability per unit time); k_r is the repair rate constant from initiated to normal cells cells (probability per unit time); M is the net growth rate constant for the pool of initiated cells (probability per unit time); $N_n(t)$ is the number of normal cells; $N_i(t)$ is the number of initiated cells; $N_t(t)$ is the number of tumor cells. It is assumed that the probability of cancer is proportional to the number of tumor cells generated over a lifetime of 73 years. For arsenic exposure, either the repair rate constant (for the repair model) or the net mitotic rate (for the mitosis model) was assumed a function of arsenic concentration in water. For the repair model, this function was linear in concentration (i.e. the repair rate constant declined linearly with concentration). For the mitotic model, this function was quadratic in concentration (Crawford-Brown et al., 2002).

The biologically-based models were solved through numerical integration of the underlying differential equations, with the initial values in the normal, initiated and tumor states being 1, 0 and 0, respectively. The best-fitting value of k_{it} was 6×10^{-7} per day. The best fitting ratio of values of k_{ni}/k_r at background was 0.075. The value of M was 0.002 per day at background. For the repair model, the best-fitting equation for the relationship between k_r and arsenic concentration was:

$$k_r = 0.01 - (1.3\times10^{-6} \times C) \quad (3.14)$$

where C is the concentration of arsenic in units of μg/L and k_r is in units of probability of repair per day. For the mitotic model, the best-fitting equation for the relationship between M and arsenic concentration was:

$$M = 0.002 + (1.8\times10^{-10}\times C^2) \quad (3.15)$$

where C is the concentration of arsenic in units of μg/L and M is in units of net probability of mitosis per initiated cell per day (i.e. the difference between the mitotic and apoptotic/cell death rates).

Results of the model fits are shown in Table 3-6. Pc in the table is the mean probability of cancer at a benchmark concentration of 10 μg/L of arsenic, assuming a tap water ingestion rate of 0.0226 L/kg-day. A benchmark dose approach was adopted in which (i) a best fit of each separate model to the data was obtained; (ii) the model was used to estimate the value of Pc at 10 μg/L; and (iii) a linear function (characterized by a slope factor) was fitted between the origin and this benchmark as an approximation to the dose-response curve for that model. The sum of confidence over all models was set equal to unity, and it was assumed that all five models are equally likely, giving each one the same confidence (p = 0.2). This latter assumption was made because the mode of action of arsenic has not been well established.

Table 3-6. Results of Different Dose-response Models for Arsenic Used in the Current Study (Showing the Difference in Predicted Values of Pc at 10 μg/L)

MODELS	Pc ([As]= 10 μg/L)	EQUIVALENT SLOPE FACTORS	SUBJECTIVE CONFIDENCE
Mitosis	1.00E-06	4.42E-06	0.2
Repair	9.60E-05	4.25E-04	0.2
NAS	2.00E-04	8.85E-04	0.2
Linear New	3.50E-04	1.55E-03	0.2
Upper Morales	6.00E-04	2.65E-03	0.2

3.2.5. Results

3.2.5.1. Cumulative Distribution Functions (CDFs) of Pc

By running the Monte Carlo simulation using the PDF for ADRI, the variability of risk (probability of cancer, Pc) at each MCL under each different model was estimated. The resulting variability cumulative distribution functions (CDFs) for each examined MCL and model are shown in Figures 3-16 (A through E). The y-axis, CDF(Pc), represents the fraction of population with risk at or below the value of Pc on the x-axis. As expected, the figures demonstrate that more stringent MCLs yield a larger proportion of population protected at each target value of Pc for each model.

3.2.5.2. Fraction of Population below a Target Risk Level

The fractions of population at or below a given risk level were extracted from the five CDFs of Pc (Figure 3-16). The extracted results for each model are provided in Table 3-7 and shown in Figure 3-17, which shows that this fraction increases as the MCL is reduced, conditional on each of several target values of Pc (10^{-4} and 10^{-5}).

Using MCL=1 µg/L as an example, we can say that by using the Upper Morales model, there will be at least 84% of the population protected from a cancer risk of 10^{-4} at this MCL, but only 2% of the population is protected from a cancer risk of 10^{-5} at the same MCL.

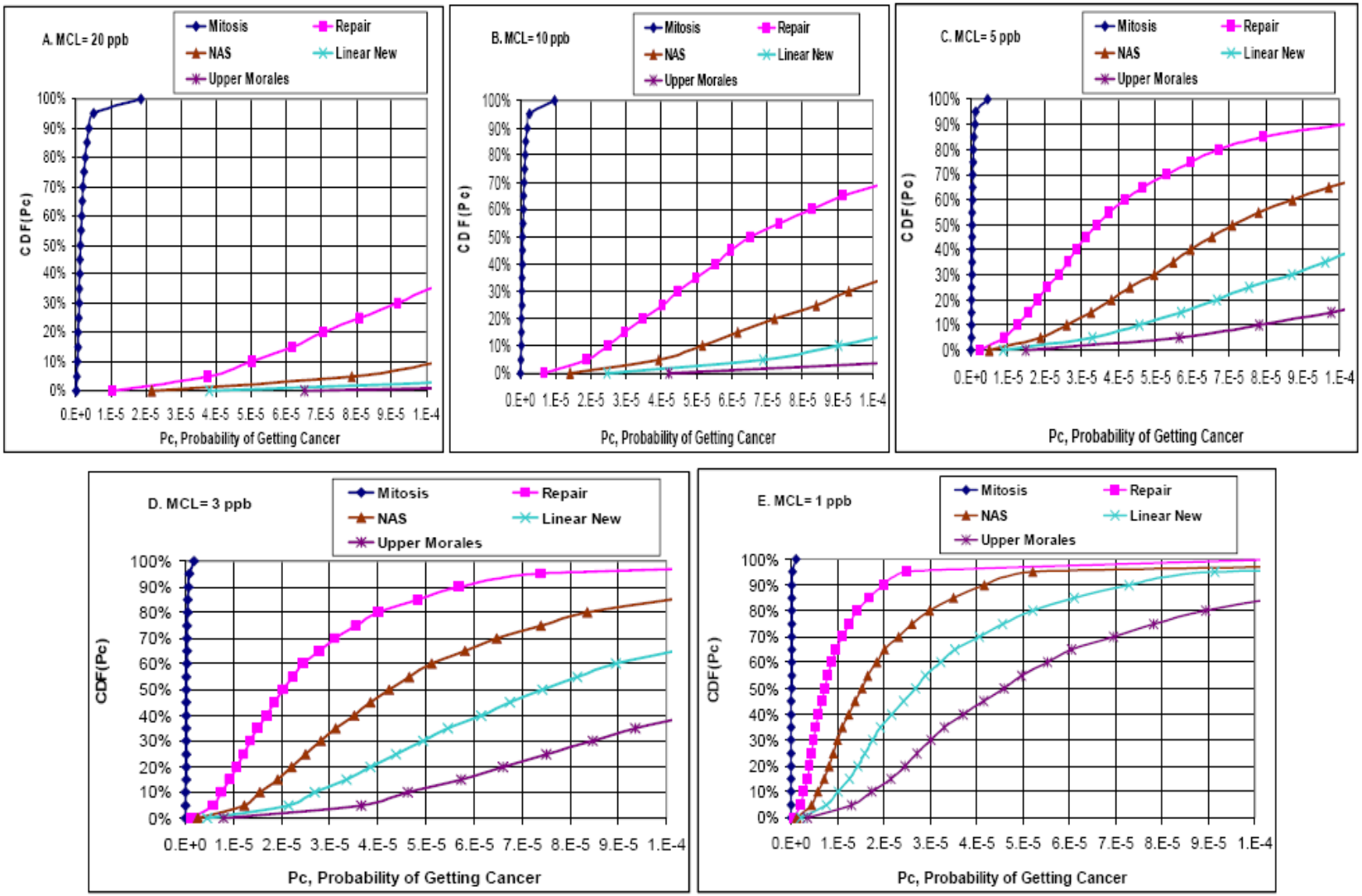


Figure 3-16. Relationship between probability of cancer (x-axis) and fraction of population below this value of Pc (F, or CDF(Pc)) under different models and MCLs.

Table 3-7. Fraction of Population whose Value of Pc Exceeds the Target Value of Pc (10^{-4} or 10^{-5}).

Models	F (%), Fraction of Population Exposed to Target Risk (Pc)									
	MCL=1 (µg/L)		MCL=3 (µg/L)		MCL=5 (µg/L)		MCL=10 (µg/L)		MCL=20 (µg/L)	
	Pc= 10^{-4}	Pc= 10^{-5}	Pc= 10^{-4}	Pc= 10^{-5}	Pc= 10^{-4}	Pc= 10^{-5}	Pc= 10^{-4}	Pc= 10^{-5}	Pc= 10^{-4}	Pc= 10^{-5}
Mitosis	100	100	100	100	100	100	100	100	100	100
Repair	99	66	97	18	90	6	68	2	35	0
NAS	96	30	85	4	66	2	33	0	9	0
Linear New	95	10	64	2	37	1	13	0	3	0
Upper Morales	84	2	38	1	16	0	4	0	0	0

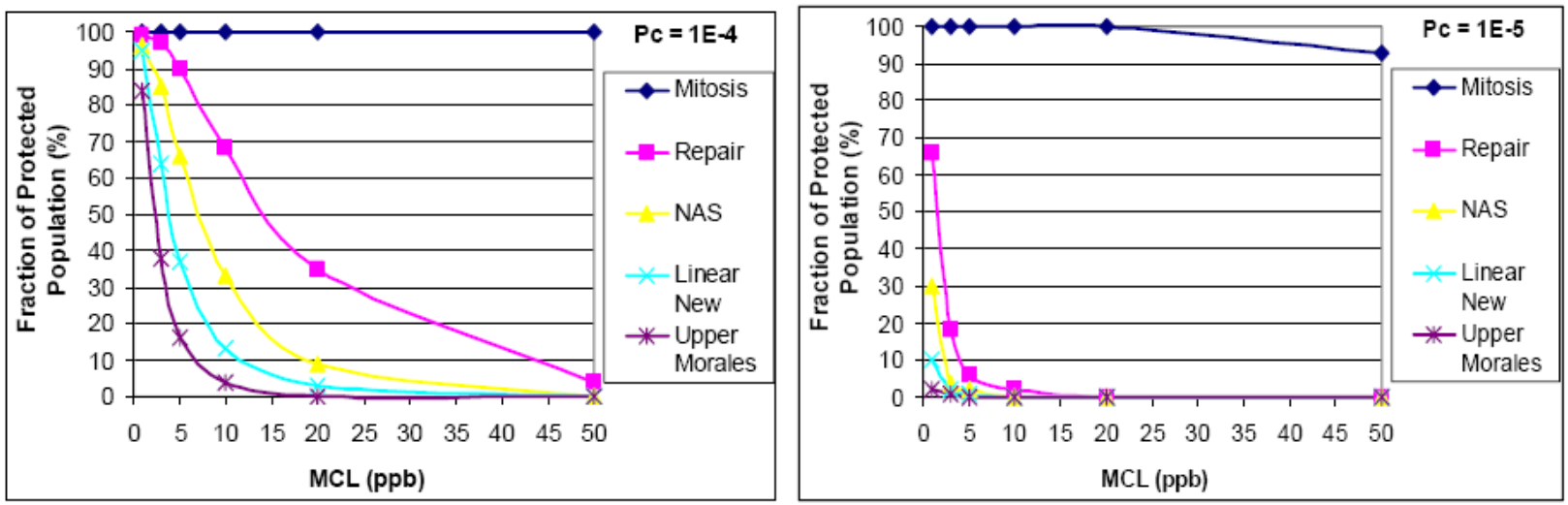


Figure 3-17. Relationships between Arsenic MCLs and the fraction of population protected from the target risk.

3.2.5.3. Confidence Analysis

As described in the previous sections, there are several alternative models for calculating the probability of cancer from arsenic in drinking water. The differences among the predictions of these models cause uncertainty in determining the true risk to the population. In order to account for this uncertainty, 5 dose-response models listed in Table 3-6 were considered and a confidence analysis to address the uncertainty was conducted.

The sum of confidences (over all models) is bounded by unity, and it was assumed that each model is equally likely in terms of prediction power, i.e. each model was assigned a confidence of 0.2. Extracted from the results of the Monte Carlo simulation in the previous section (the variability distributions for the five alternative dose-response models, shown in Figure 3-16 previously), new information can be obtained on the confidence that a given fraction of population (F) is protected at each value of Pc at each MCL. Table 3-8 and Figure 3-18 are examples, assuming the target value of F is 90%.

Table 3-8. The Calculated Pc from Monte Carlo Simulation at different MCLs by using different models and their confidence, assuming the target value of F is 90%.

Models	Mitosis	Repair	NAS	Linear New	Upper Morales
MCL (ppb)	Pc	Pc	Pc	Pc	Pc
1	2.08E-07	2.00E-05	4.16E-05	7.28E-05	1.25E-04
3	5.92E-07	5.69E-05	1.18E-04	2.07E-04	3.55E-04
5	1.05E-06	1.01E-04	2.11E-04	3.68E-04	6.32E-04
10	1.90E-06	1.82E-04	3.80E-04	6.65E-04	1.14E-03
20	3.77E-06	3.62E-04	7.55E-04	1.32E-03	2.26E-03
50	9.10E-06	8.74E-04	1.82E-03	3.19E-03	5.46E-03
Confidence	0.2	0.2	0.2	0.2	0.2
CDF(Confidence)	0.2	0.4	0.6	0.8	1

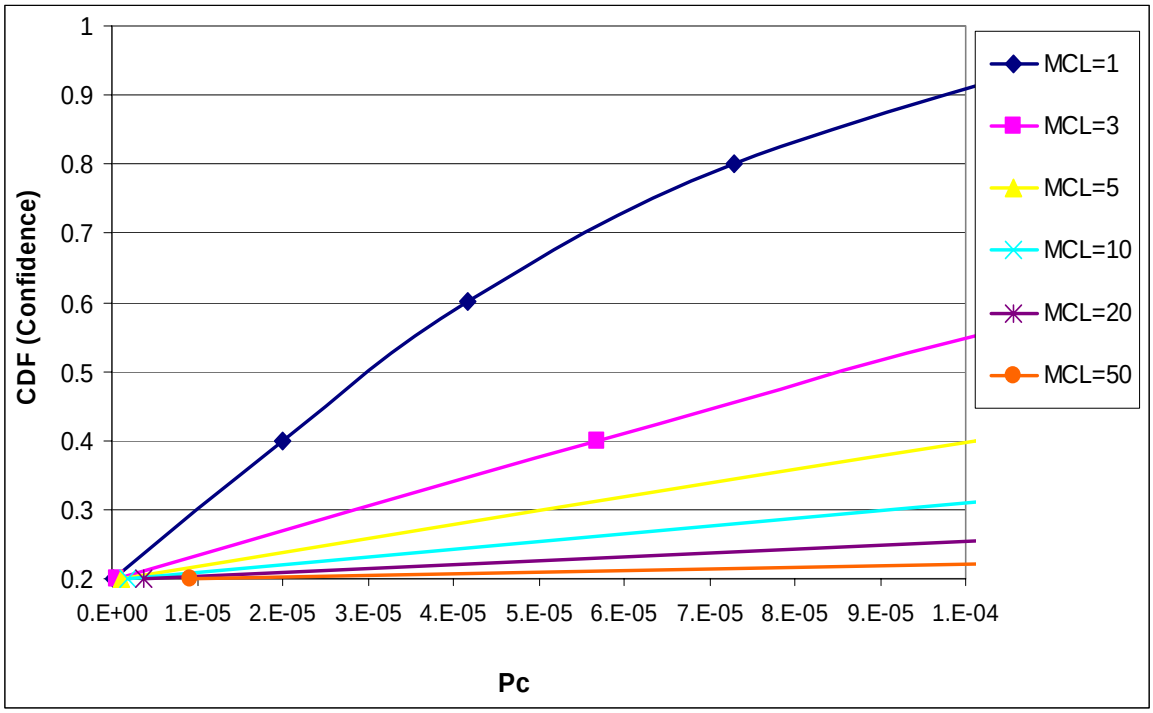


Figure 3-18. CDF (Confidence) of protecting 90% of population at risk less than given Pc and at different MCLs.

Table 3-9 summarizes the results for a variety of MCLs and values of F, and for two values of Pc (10^{-4} and 10^{-5}). Bear in mind that these results used the five dose-response models described previously, all were fitted to the data of Morales *et al.*, and all were equally weighted with respect to confidence.

Table 3-9. Confidence in the Claim that At Least a Fraction of the population (F) will have Risk below the Target Value of Pc (10^{-4} or 10^{-5}).

MCL(µg/L)	1	3	5	10	20	50	1	3	5	10	20	50
F	Pc=10-4						Pc=1E-5					
0%	1.000	1.000	1.000	1.000	1.000	0.526	1.000	1.000	0.850	0.490	0.380	0.227
5%	1.000	1.000	1.000	0.930	0.680	0.325	0.910	0.550	0.425	0.305	0.250	0.210
10%	1.000	1.000	1.000	0.830	0.585	0.300	0.800	0.475	0.365	0.280	0.240	0.210
15%	1.000	1.000	1.000	0.775	0.525	0.280	0.750	0.425	0.330	0.270	0.230	0.210
20%	1.000	1.000	0.945	0.720	0.480	0.275	0.675	0.390	0.310	0.260	0.225	0.210
25%	1.000	1.000	0.900	0.660	0.450	0.275	0.650	0.375	0.300	0.250	0.225	0.205
30%	1.000	1.000	0.850	0.625	0.420	0.265	0.600	0.350	0.285	0.245	0.220	0.205
35%	1.000	1.000	0.820	0.590	0.400	0.260	0.580	0.340	0.275	0.240	0.220	0.205
40%	1.000	0.980	0.785	0.560	0.375	0.250	0.550	0.320	0.270	0.235	0.217	0.204
45%	1.000	0.940	0.750	0.530	0.370	0.250	0.520	0.310	0.265	0.233	0.215	0.203
50%	1.000	0.910	0.725	0.505	0.350	0.250	0.490	0.300	0.260	0.230	0.214	0.203
55%	1.000	0.875	0.685	0.475	0.340	0.245	0.455	0.290	0.252	0.227	0.212	0.202
60%	1.000	0.840	0.650	0.440	0.325	0.240	0.440	0.285	0.248	0.223	0.210	0.202
65%	1.000	0.800	0.610	0.420	0.310	0.235	0.425	0.275	0.242	0.220	0.210	0.202
70%	1.000	0.760	0.570	0.395	0.300	0.230	0.390	0.265	0.235	0.218	0.209	0.201
75%	1.000	0.710	0.530	0.375	0.290	0.230	0.370	0.258	0.232	0.216	0.207	0.201
80%	1.000	0.670	0.500	0.355	0.275	0.225	0.348	0.250	0.228	0.213	0.206	0.201
85%	0.980	0.600	0.450	0.330	0.270	0.225	0.330	0.242	0.225	0.212	0.205	0.201
90%	0.915	0.550	0.400	0.315	0.250	0.225	0.305	0.235	0.218	0.210	0.204	0.200
95%	0.830	0.475	0.365	0.275	0.240	0.220	0.280	0.226	0.215	0.206	0.202	0.200
100%	0.387	0.322	0.244	0.220	0.217	0.216	0.216	0.210	0.203	0.200	0.200	0.200

3.2.6. Conclusions

Using the framework above, several distinct questions can be answered. The primary question in this research is about the MCL of arsenic that may be allowed by the U.S. EPA if the Agency wishes to claim that a reasonable fraction of the population (F%) is protected below any given value of lifetime cancer risk (Pc) at any selected level of confidence (C). Obtaining a graphical representation of the relationship between Pc, F, C and MCL to answer this question was the focus of this section; since there are multiple variables (MCL, F%, Pc and C), it is not possible to display them at once in a single graph.

This issue can be considered from different perspectives by slicing through these four dimensional volumes. First, we can fix the factor of the protected population (F) by asking the question: "*With what confidence can we state that at least some target fraction of the population (e.g. 90%) is below the target risk (e.g.10^{-4} or 10^{-5})?* This is shown in Figure 3-19 as an example. It is easy to compare the confidence at different MCLs and risk targets under a fixed protected fraction of the population. For example, at an MCL of 5µg/L, the confidence that at least 90% of the population is being protected from a risk of 10^{-4} is 0.4, while the confidence for a risk target of 10^{-5} is only around 0.2. Also, note that for both of the risk targets, lowering the MCL raises the confidence that at least 90% of the population is below the target risk of either 10^{-4} or 10^{-5}.

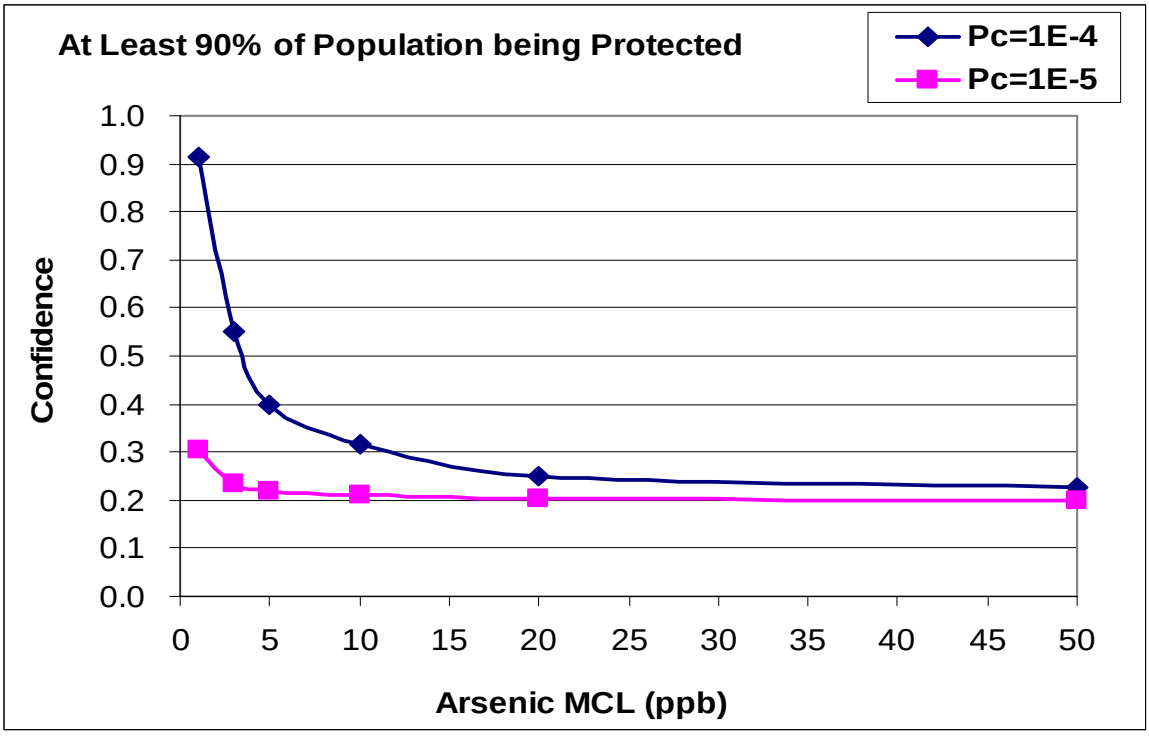


Figure 3-19. The Confidence that at least 90% of the population whose risk is below to the risk level (10^{-4} or 10^{-5}) at different MCLs.

Figure 3-20 is another way of considering the same issue, but the fixed factor is changed to target risk (or Pc). The figure illustrates the confidence associated with the fraction of the population below a constraining target risk level (10^{-4}) at different MCLs. From this graph, it is easy to check how much confidence one can have if the goal is to protect a given fraction of the population from a target risk of 10^{-4} at each MCL. For example, if the regulatory target is that at least 90% of the population witch have a risk lower than 10^{-4}, from Figure 3-20, it can be seen that at an MCL equal to 50 µg/L, there is only a confidence of 0.2 that this goal will be met. The confidence increases to 0.55 when the MCL is set to 3 µg/L, and increases to 0.9 when the MCL is set more stringently to 1 µg/L. Also, note that increasing the fraction of the population being protected decreases the confidence at all MCLs.

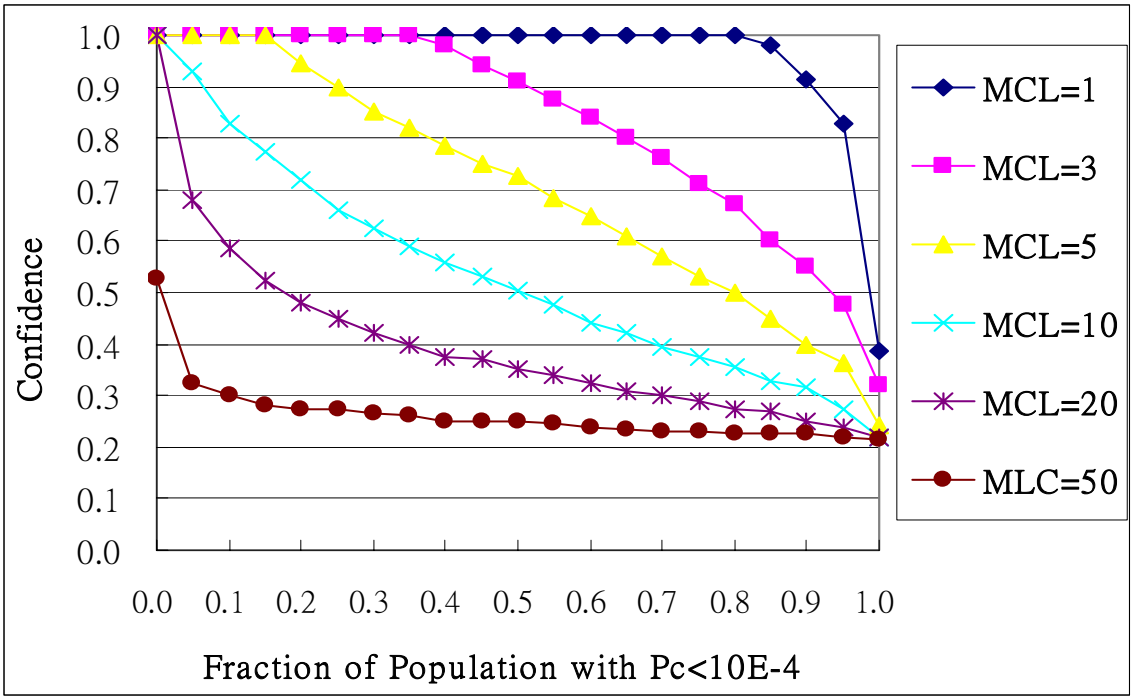


Figure 3-20. The relationship between Confidence and with the fraction of population whose risk below to the target risk level (10^{-4}) at different MCLs.

3.2.6.1. Risk Surfaces

Figure 3-21 is the other way to graphically present the relationships between Pc, F, C and MCL. They are a series of "risk surface", one for each potential MCL. Note that reducing the MCL can be viewed in three ways from these surfaces: (i) it reduces the mean, or expectation, value of Pc in the population, and hence the expectation value of the total burden of effects; (ii) it increases the fraction F, conditional on target values of Pc and C; or (iii) it increases the confidence, C, in protection conditional on target values of Pc and F.

3.2.6.2. MCL Tables

The relationships among Pc, F, C and MCL can also be presented in a series of table (Tables 3-10 and 3-11) to clearly show what the decision (i.e. MCL) would be at given target risk and policy goal (i.e. a given confidence that a certain fraction of the population is being protected from this target risk). For example, when the target risk is set to be 10^{-5} (Table 3-10), and the values of F and C are set to 90% and 0.8 respectively, the MCL should be set 1 µg/L to meet this policy goal; when the target risk is set to be 10^{-4} (Table 3-11), and F and C are retained at 90% and 0.8, the MCL should be set 3 µg/L to meet this policy goal. By using these tables, policy makers can choose a desirable MCL based on different policy goals.

From these MCL tables, it is evident that the current arsenic MCL of 10 µg/L may still be too high at a target risk of 10^{-5} (Table 3-10). At a target risk of 10^{-4} (Table 3-11), an arsenic MCL of 10 µg/L becomes more reasonable if the policy maker is willing accept values of F and C that are in the neighborhood of 60% and 0.6 (or 70% and 0.5). Otherwise, an MCL on the other of 3 would be required.

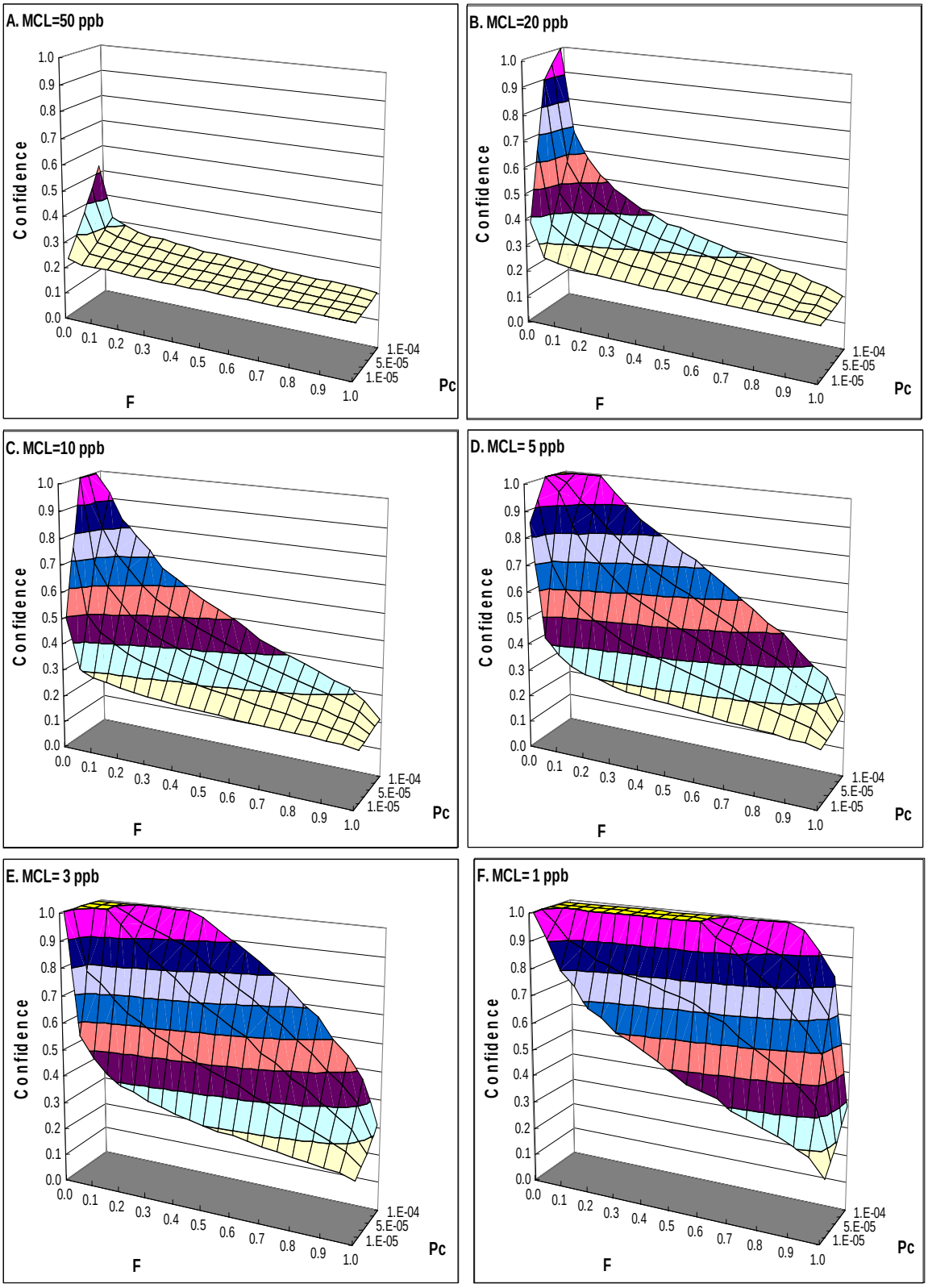


Figure 3-21. The "risk surface" showing the relationship between confidence, risk, and the fraction of protected population to the target risk level at a given MCL.

Table 3-10. MCL (µg/L) at target risk of 10^{-5}

	Fraction (F) of the Population with Pc< 10^{-5} (%)					
	100	**90**	**80**	**70**	**60**	**50**
1	1	1	1	1	1	1
0.9	1	1	1	1	1	1
0.8	1	**1**	1	1	1	1
0.7	1	1	1	1	1	1
0.6	1	1	1	1	1	1
0.5	1	1	1	1	1	1

Confidence (C)

Table 3-11. MCL (µg/L) at target risk of 10^{-4}

	Fraction (F) of the Population with Pc< 10^{-4} (%)					
	100	**90**	**80**	**70**	**60**	**50**
1	1	1	3	3	3	3
0.9	1	3	3	3	3	5
0.8	1	**3**	3	3	5	5
0.7	1	3	3	5	5	10
0.6	1	3	5	5	10	10
0.5	1	5	5	10	10	20

Confidence (C)

3.3. The Alternate Method of Quantification of Margin of Safety with Meta-Analysis Results

In previous section (section 3.1), meta-analysis was performed to combine results from several epidemiological studies to get aggregated slope factors, which are shown in Figure 3-9. In another previous section, five best available models for calculating the arsenic risk from drinking water and its variability and uncertainty were considered. The comparisons of these models and the results from meta-analysis are in Table 3-12 and Figure 3-22. From Figure 3-22, it is clear that the slope factors resulting from meta-analysis are located at the lower values from the fits to the Morales data, which will result in lower risk. Considering the uncertainty in choice of dose-response model, it was assumed here that the slope factor itself has a lognormal distribution, with a median value at the best estimate from the meta-analysis (i.e. 3×10^{-5}).

Table 3-12. Arsenic Slope Factors calculated from Meta-Analysis and of other Dose-response Models (also Showing the Difference in Predicted Values of Pc at 10 µg/L)

MODELS	Pc ([As]= 10 µg/L)	EQUIVALENT SLOPE FACTORS
Meta-analysis (Upper-Bound)	2.29E-05	1.27E-04
Meta-Analysis (Best-Estimate)	7.35E-06	3.00E-05
Mitosis	1.00E-06	4.42E-06
Repair	9.60E-05	4.25E-04
NAS	2.00E-04	8.85E-04
Linear New	3.50E-04	1.55E-03
Upper Morales	6.00E-04	2.65E-03

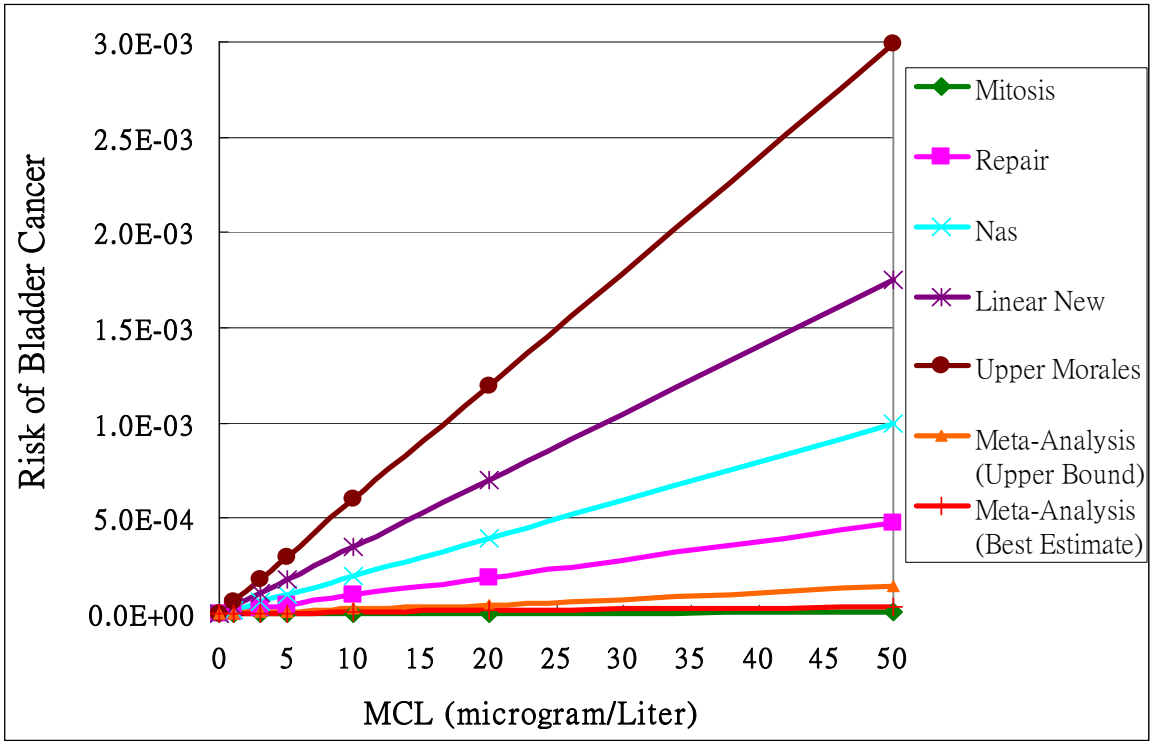


Figure 3-22. Risk of Bladder Cancer calculated from Different Slope Factors.

3.3.1. Methods

The variation between models (or GSD for a lognormal distribution), was determined as follows:

(1) It was assumed that the uncertainty distribution was lognormal, and so is characterized by a median and GSD.

(2) It was further assumed that the sole difference between the results in Section 5 and the results using the meta-analysis is the employment of the meta-analysis slope factor as the best estimate, rather than the "Linear New" analysis. Both of these used the linear models.

(3) It was further assumed that the effect of using the meta-analysis rather than the individual dataset used in Section 5, is to "shift" the dose-response curve for a given model

downwards, and that the magnitude of this shift will be identical (which would be the case here, given the procedure by which the dose-response curves were fit to the original dataset).

(4) As a result, if a given model (e.g. the Mitosis model) predicted a low-exposure risk a factor of X above or below the predictions of the "Linear New" model, it would similarly predict a factor of X above or below the linear fit of the meta-analysis.

(5) As a further result, the GSD value obtained from the variation of predictions in Section 5 would be the same as GSD value when these five models are "re-normalized" to the meta-analysis results.

(6) The GSD for the variation in model predictions in Section 5 is approximately 2.2 (the preponderance of the models falling with a factor of 2.2 x 2.2 = 4.84 of the median value, which is the Linear New model. So, this GSD is assumed to apply to the variation between model predictions obtained using the meta-analysis results).

(7) The resulting uncertainty distribution for the slope factor, taking into account the meta-analysis result and the variation between models, is lognormal with median of $3x10^{-5}$ and GSD of 2.2.

With this uncertainty distribution on the slope factors, a nested variability-uncertainty analysis was conducted. By using Crystal Ball, twenty different slope factors were sampled from the lognormal distribution with a median value of 3×10^{-5} and a GSD of 2.2. Then we repeated the same variability analysis mentioned previously for each of these twenty sampled slope factors (p=0.05). Twenty risk variability distributions at different MCLs then were generated. The confidence that a given MCL produces at least F% of the population with a risk below Pc is the fraction of the sampled values of slope factor for which the resulting

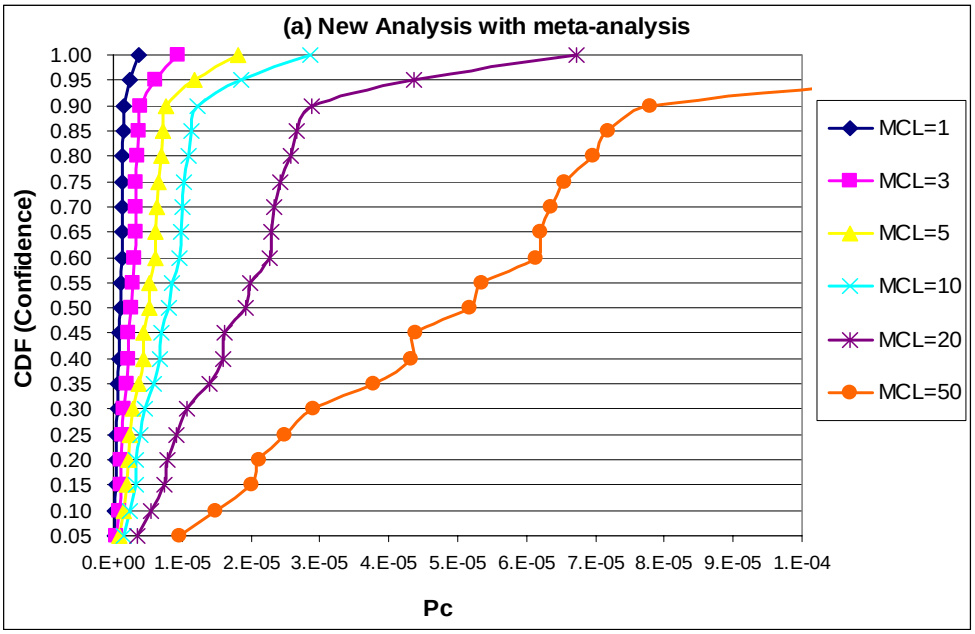
variability distribution satisfies those criteria (i.e. the fraction of sampled slope factors for which at least F% of the population has a risk below the target Pc). Appendix B shows the details of calculation steps.

3.3.2. Results and Conclusions

3.3.2.1. Confidence Analysis

Figure 3-23(a) is the new cumulative distribution function of confidence, and Figure 3-23(b) is the same as the old one (identical to Figure 3-18), put here for comparison. Note the CDF at each MCL is shifted toward the upper left under these new results. This is because the slope factors used in the new analysis (which used the slope factor from the meta-analysis as the median of an uncertainty PDF) are lower than the ones used in the previous analysis (which used only the Morales data). Therefore, the confidence in protection increases under the same assumptions of MCL, F% and Pc.

Figure 3-24 was generated by extraction from Figure 3-23(a). Assume the policy goal is to protect at least 90% of the population from a given risk level (10^{-4}, 10^{-5}, or 10^{-6}). Using curves in Figure 3-24, it is easy to compare the confidence at different MCLs. For example, at an MCL of 10 µg/L, the confidence is 1, 0.7, and 0 at risk levels of 10^{-4}, 10^{-5}, and10^{-6}, respectively. The confidence increases to 1, 0.95, 0.05 (at risk levels of 10^{-4}, 10^{-5}, and10^{-6}, respectively) if the MCL is tightened to 5µg/L.



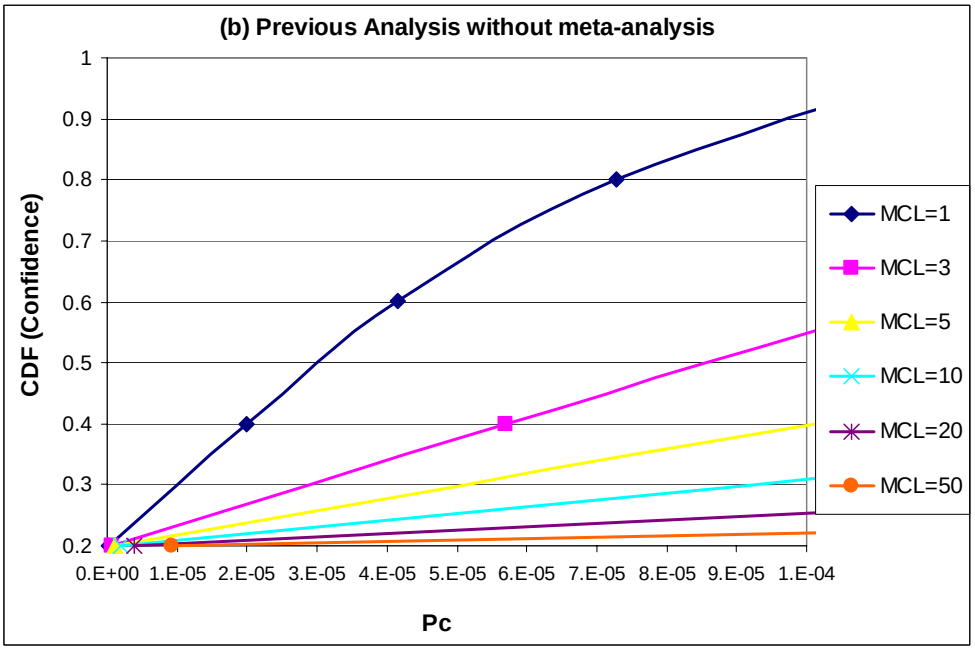


Figure 3-23. CDF (Confidence) of protecting 90% of the population at risk less than given Pc and at different MCLs by previous analysis and new analysis.

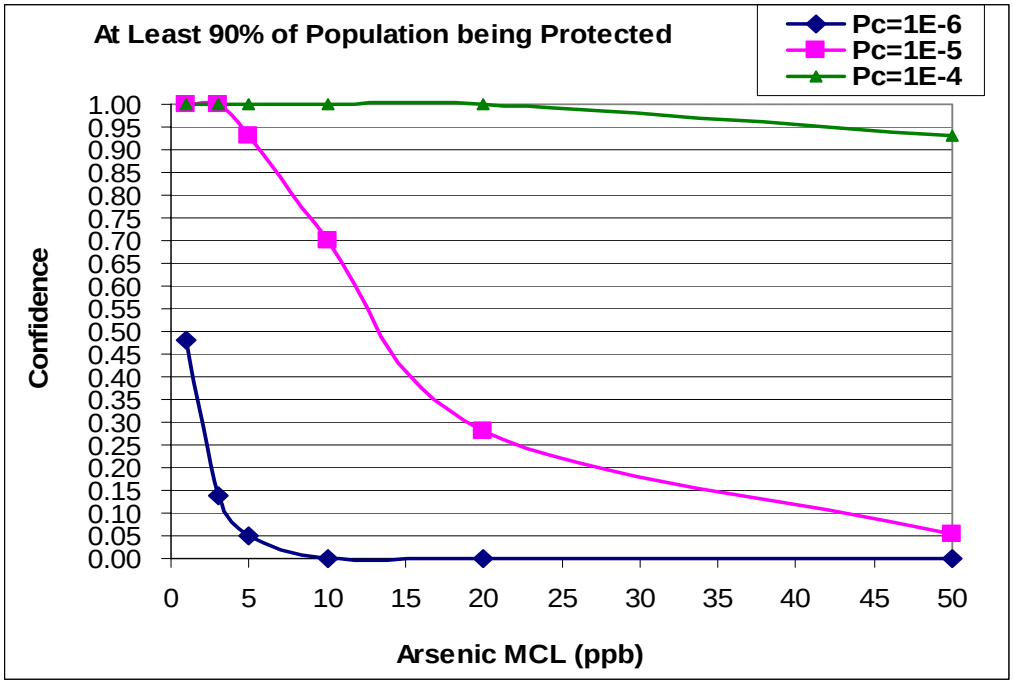


Figure 3-24. The Confidence that at least 90% of the population whose risk is below to the risk level (10^{-4}, 10^{-5}, or 10^{-6}) at different MCLs (using meta-analysis).

Figures 3-25 and 3-26 were generated by extraction from Figure 3-23(a), too. They are presenting the same information as in Figure 3-24 from another perspective. They illustrate the new confidence associated with fraction of the population below various target risk levels at different MCLs. The figures generated from the previous analysis (using only Morales) are also put here for comparison.

The graphs shown in Figures 3-25 illustrate the confidence associated with the claim that the fraction of the population below the target risk level at different MCLs is at least F%. The curves are shown in the situation of constraining target risk (or Pc) to 10^{-6}. From these graphs, if the regulation target is that at least 90% of the population has a risk lower than 10^{-6}, it can be seen that at MCLs from 50 to 10 µg/L, we have only a confidence of 0 that this goal will be met, but that the confidence increases to 0.05 when the MCL is set to 5 µg/L,

increases to 0.15 when the MCL is set more stringently to 3 µg/L, and increases to 0.5 at MCL of 1 µg/L.

Given the same policy goal (i.e., to protect 90% of the population), we can also compare the results of the new analysis (using meta-analysis) and the previous one (using Morales data). At a risk level of 10^{-5}, from Figure 3-26(b), we can see that the confidence ranges from 0.2 to 0.3 at MCLs varied from 50 to 1µg/L. However, when the meta-analysis results are applied (see Figure 3-26(a)), an MCL equal to 50 µg/L produces a confidence of 0.05 that this goal will be met, but the confidence increases to 0.7 when the MCL is set to 10 µg/L and increases to almost 1 when the MCL is set more stringently to 1 µg/L.

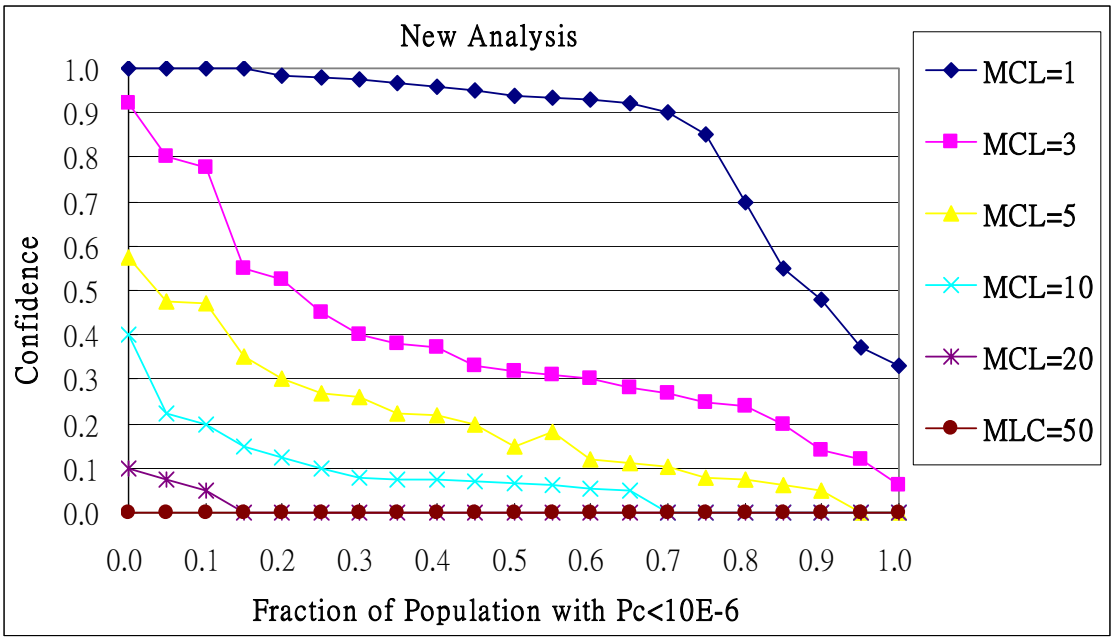


Figure 3-25. The Relationship between Confidence and with the fraction of the population whose risk below to the risk level (10^{-6}) at different MCLs.

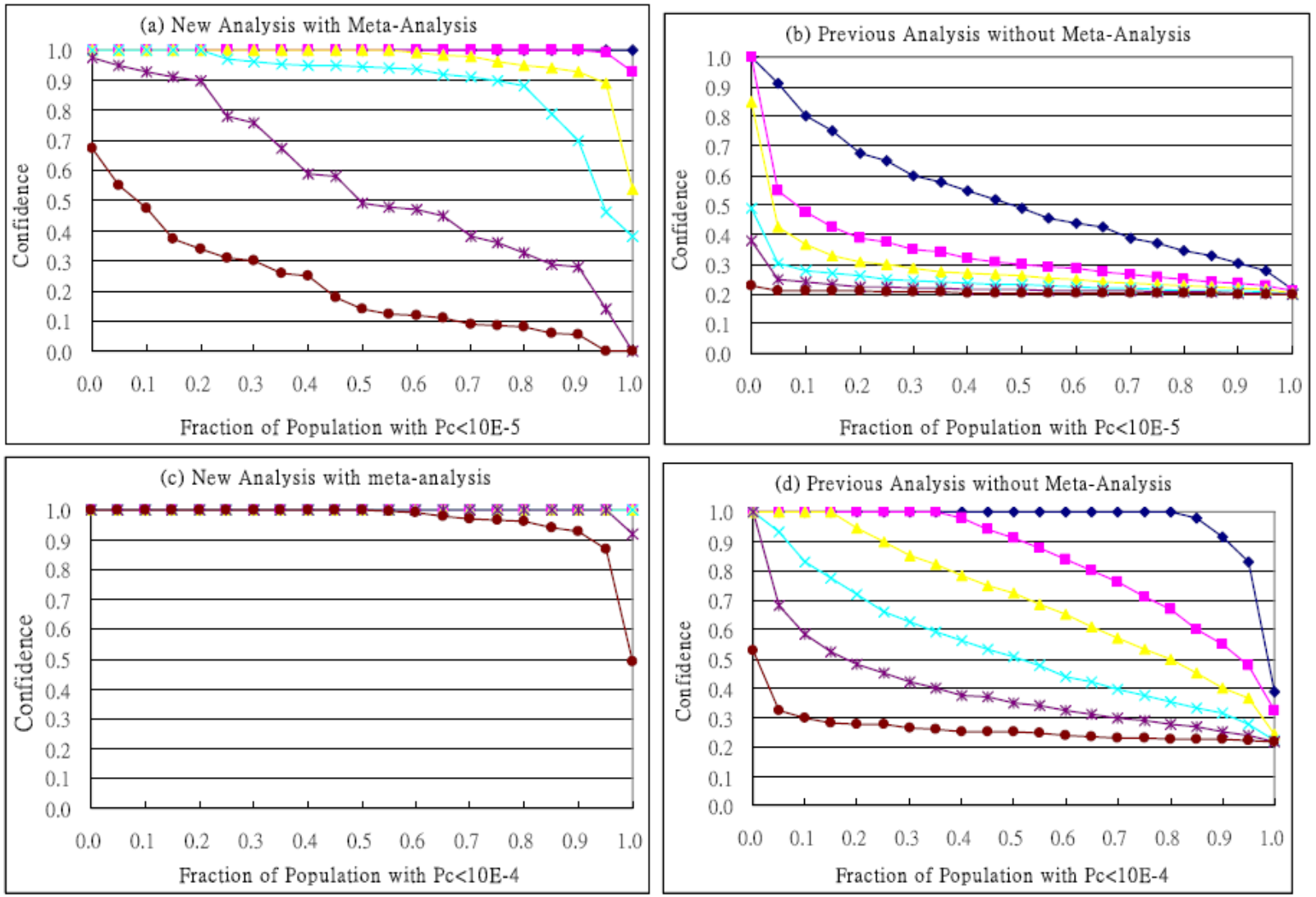


Figure 3-26. The relationship between Confidence and with the fraction of population whose risk below to various risk level (10^{-4} and 10^{-5}) at different MCL.

3.3.2.2. Risk Surfaces

Figure 3-27 is the new series of “risk surface” to graphically present the relationships between Pc, F, C and MCL, one for each potential MCL. As mentioned in section 3.2.6.1., reducing the MCL can be viewed in three ways from these surfaces: (i) it reduces the mean, or expectation, value of Pc in the population, and hence the expectation value of the total burden of effects; (ii) it increases the fraction F, conditional on target values of Pc and C; or (iii) it increases the confidence, C, in protection conditional on target values of Pc and F. Comparing with Figure 3-21, the new confidence associated with the fraction of the population below various target risk levels at different MCLs are higher. Clearly, the effect of the meta-analysis is to greatly increase the confidence given the same fraction of protected population and risk target.

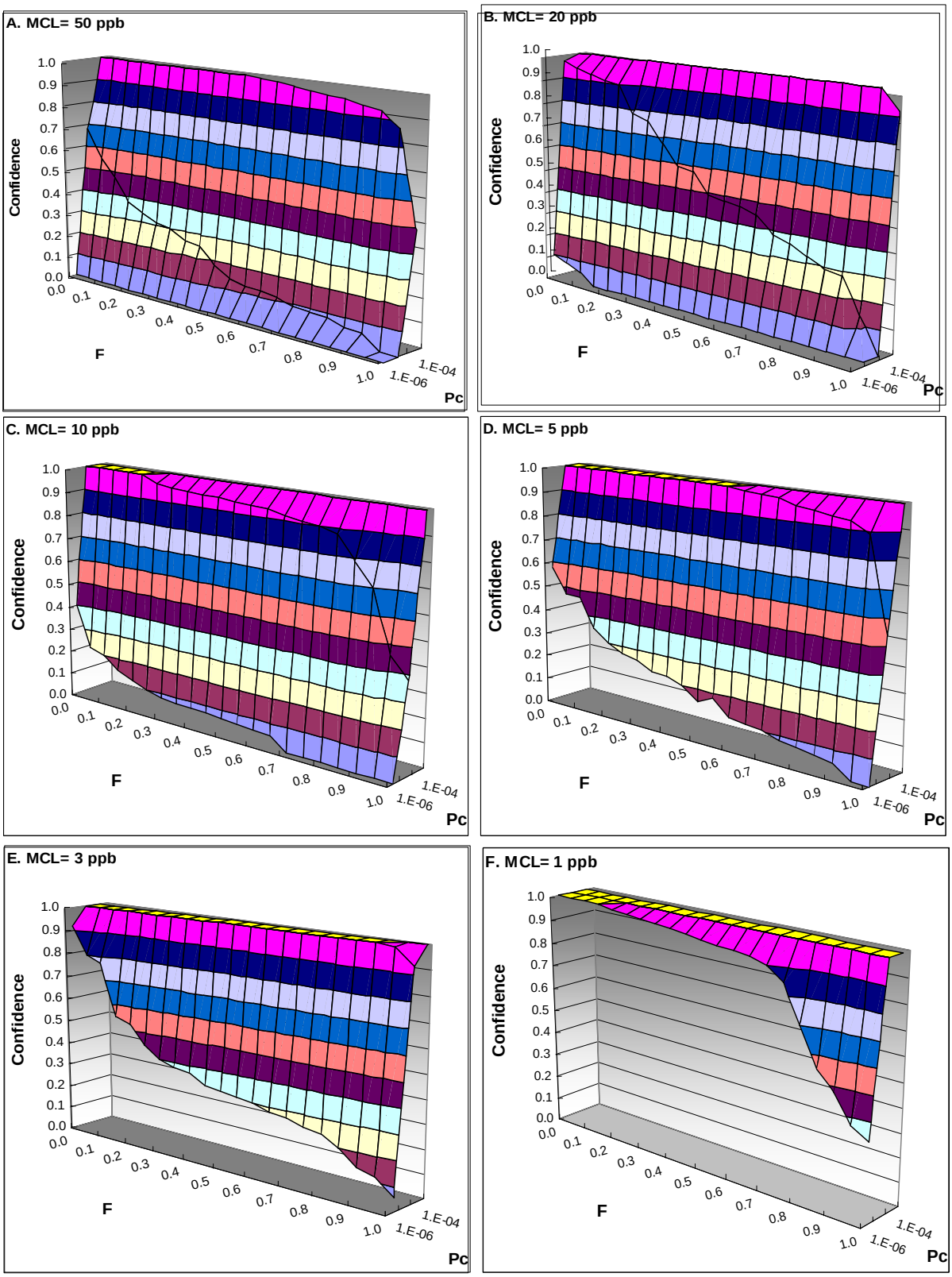


Figure 3-27. The "risk surface" showing the relationship between confidence, risk, and the fraction of protected population to the target risk level at a given MCL (by the new analysis with meta-analysis).

3.3.2.3. MCL Tables

The relationships among Pc, F, C and MCL can also be presented in a series of table (Table 3-13, 3-14, and 3-15) to clearly show what the decision (i.e. MCL) would be at given target risk and policy goal (i.e. a given confidence that a certain fraction of the population is being protected from this target risk).

Considering that the policy goal is having confidence of 0.8 that at least 90% of the population is protected from the target risk (10^{-4}, 10^{-5}, and 10^{-6}), the policy maker may ask: "***What would decisions be like under this new framework employing fully probabilistic methods?***" For example, when the target risk is set to be 10^{-6} (Table 3-13), the MCL should be set 1μg/L to meet this policy goal; when the target risk is set to be 10^{-5} (Table 3-14), the MCL should be set 10μg/L to meet this policy goal; and when the target risk is set to be 10^{-4} (Table 3-15), the MCL can be set higher than 50μg/L to meet this policy goal. By using these tables, policy makers can choose a desirable MCL based on different policy goals.

Comparing with the previous results of section 3.2.6.2, given the policy goal that having confidence of 0.8 that at least 90% of the population is protected from the target risk (10^{-4} and 10^{-5}), when the target risk is set to be 10^{-5}, the MCL should be set 1 μg/L to meet this policy goal by previous analysis (Table 3-10), while the MCL should be set 10 g/L to meet this policy goal by new analysis considering the result of meta-analysis (Table 3-14). When the target risk is set to be 10^{-4} the MCL should be set 3 g/L to meet this policy goal by previous analysis (Table 3-10), while the MCL doesn't need to be change from 50 μg/L to meet this policy goal by new analysis considering the result of meta-analysis (Table 3-15). It is clear to see that by considering the result of meta-analysis, the arsenic MCLs are set to be less stringent by using MCL tables.

From these new MCL tables, if the target risk is 10^{-6} (Table 3-13), it indicates that the current arsenic MCL of 10 µg/L may still be too high. And at target risk of 10^{-5} (Table 3-14), arsenic MCL of 10 µg/L is reasonable when the policy maker wants to have confidence of 0.9 that 90% of the population is protected from this target risk, or have confidence of 0.5 that 100% of the population is protected from this target risk. If the policy maker is willing to have less confidence that less fraction of the population is protected from the target risk, then the arsenic MCL can be set less stringent. Moreover, at target risk of 10^{-4} (Table 3-15), it indicates that the current arsenic MCL of 10 µg/L is too stringent.

Therefore, from these MCL tables, it is possible for a policy maker to select a regulatory limit (MCL) that will provide a desired level of confidence that at least some pre-specified fraction of the population (F) is below the pre-specified lifetime risk (Pc). If an MCL fails to meet the desired confidence, the MCL may be lowered in order to gain the desired confidence. This more stringent MCL then could be defended by referring to an increased confidence in meeting the goal of public health protection (although it does so at increased compliance cost). (Crawford-Brown, 2001)

Table 3-13. MCL (µg/L) at target risk of 10^{-6}

	Fraction (F) of the Population with Pc< 10^{-6} (%)						
		100	**90**	**80**	**70**	**60**	**50**
Confidence (C)	**1**	1	1	1	1	1	1
	0.9	1	1	1	1	3	3
	0.8	1	**1**	1	3	3	3
	0.7	1	1	1	3	3	3
	0.6	1	1	3	3	3	3
	0.5	1	1	3	3	3	3

Table 3-14. MCL (µg/L) at target risk of 10^{-5}

	Fraction (F) of the Population with Pc< 10^{-5} (%)					
	100	**90**	**80**	**70**	**60**	**50**
1	1	3	3	3	3	5
0.9	5	10	10	20	20	20
0.8	5	**10**	20	20	20	20
0.7	5	10	20	20	20	20
0.6	5	20	20	20	20	20
0.5	10	20	20	20	20	20

Confidence (C)

Table 3-15. MCL (µg/L) at target risk of 10^{-4}

	Fraction (F) of the Population with Pc< 10^{-4} (%)					
	100	**90**	**80**	**70**	**60**	**50**
1	20	20	20	20	20	50
0.9	50	>50	>50	>50	>50	>50
0.8	50	**>50**	>50	>50	>50	>50
0.7	50	>50	>50	>50	>50	>50
0.6	50	>50	>50	>50	>50	>50
0.5	50	>50	>50	>50	>50	>50

Confidence (C)

3.4. Price of Confidence

3.4.1. Introduction

Traditional approaches to establishing regulatory limits on exposure to water-borne pollutants examine the predicted number of health benefits under a variety of scenarios that are judged to include a margin of safety in estimating risk. While this approach, rooted in the precautionary principle, has merit, it does not allow the analyst to understand the increased cost of compliance that can be associated with a given margin of safety. This can lead, in turn, to inconsistent degrees of protectiveness across different regulatory limits and, more troubling, to economic inefficiency in allocating limited resources to bring about improvements in the public health. Therefore, the purpose of this methodology is to understand the increased cost of compliance that can be associated with a given margin of safety, and to developed to assess the relationship between different degrees of protectiveness and the cost of compliance. This methodology can help the policy makers know whether the increased confidence, given a target fraction of the population protected against an unacceptable level of risk, is worth the cost.

3.4.2. Methods

By linking with MCL, The annual compliance cost data were added as the third axis in Figures 3-25, 3-26(a) and 3-26(c). They then became the 3-D graphs in Figures 3-28 (A, B and C). These new graphs make it easier to see the relationships among Pc, F (presented by using Y here), C and cost. The annual compliance cost data from the study of Gurian and Small (Gurian and Small, 2001) and other two alternate cost estimates from different resources are summarized in Table 3-16.

Table 3-16. Cost (per year) Associated with MCLs.

MCL (ppb)	Cost (M$/year)		
	EPA	Independent Researcher (Gurian and Small, 2001)	AWWARF
1	1000.0	2000.0	4500.0
3	650.0	1050.0	3000.0
5	400.0	700.0	1050.0
10	200.0	300.0	600.0
20	60.0	10.2	4.5

Table Source: (Gurian and Small, 2001)

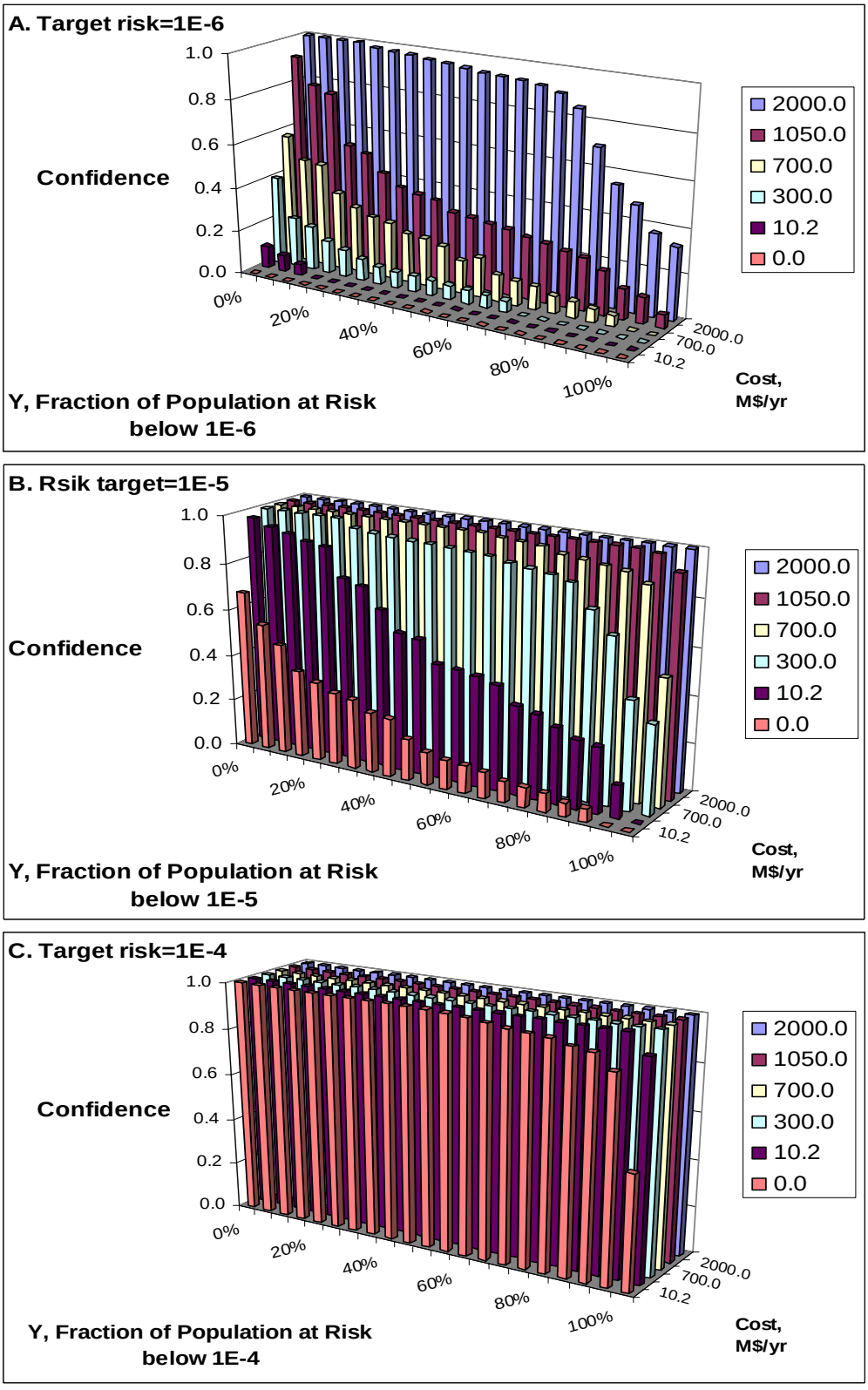


Figure 3-28. 3-D graphical presentations of the relationships among confidence, the fraction of the population being protected at the target risk levels of 10^{-6}(A), 10^{-5}(B) and 10^{-4}(C), and Costs.

3.4.3. Results and Conclusions

A new research question can be addressed by linking the previous analyses to cost data: ***What is the incremental cost associated with an incremental increase in the margin of safety, characterized by an increase in C (confidence) and increase in F (fraction of the population protected from a risk of Pc)?*** The results are presented by an example of a regulatory scenario to see if the cost associated with the stricter MCL can be justified by increased confidence. Assume a regulator wishes that at least 90% of population is below a risk of 10^{-5}. By using the cost data of Gurian et al. (2001), the result is shown in Table 3-17.

In Table 3-17, the third column is the incremental change in confidence derived from the Confidence column, and the fifth column is the incremental change in cost derived from the Cost column. They are also shown in Figure 3-29. Dividing incremental Cost by incremental Confidence, we can get the price of confidence, which is the sixth column. This column exhibits the incremental annual cost required in order to increase confidence by 1%. The price of confidence is also shown in Figure 3-30. Decision-makers can use the price of confidence as a regulatory tool to select a regulatory limit (MCL) that characterizes the increases in F and C, and the decrease in Pc (and hence increase in total health benefits), "purchased" by the cost of a given MCL.

Table 3-17. Calculation of Price of Confidence (for a regulatory scenario that at least 90% of the population is below a risk of 10^{-5})

MCL (ppb)	**Confidence**	**Incremental Confidence**	**Cost** (Million $/year)	**Incremental Cost** (Million $/year)	**Price of Confidence** (Million$/year/Confidence)
50	5.5%	-	0.0		
20	28%	22.5%	10.2	10.2	45.33
10	70%	42%	300.0	289.8	690.00
5	93%	23%	700.0	400.0	1739.13
3	100%	7%	1050.0	350.0	5000.00
1	100%	0%	2000.0	950.0	Infinite

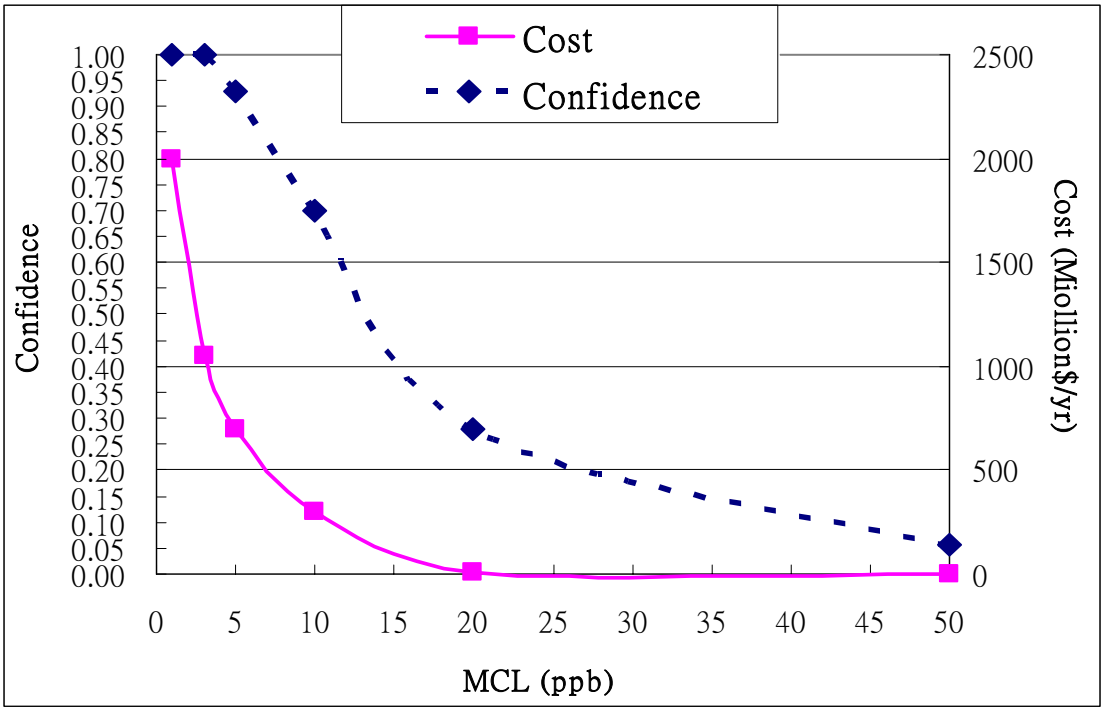


Figure 3-29. The Confidence of protecting 90% of population below risk of 10^{-5} and its cost.

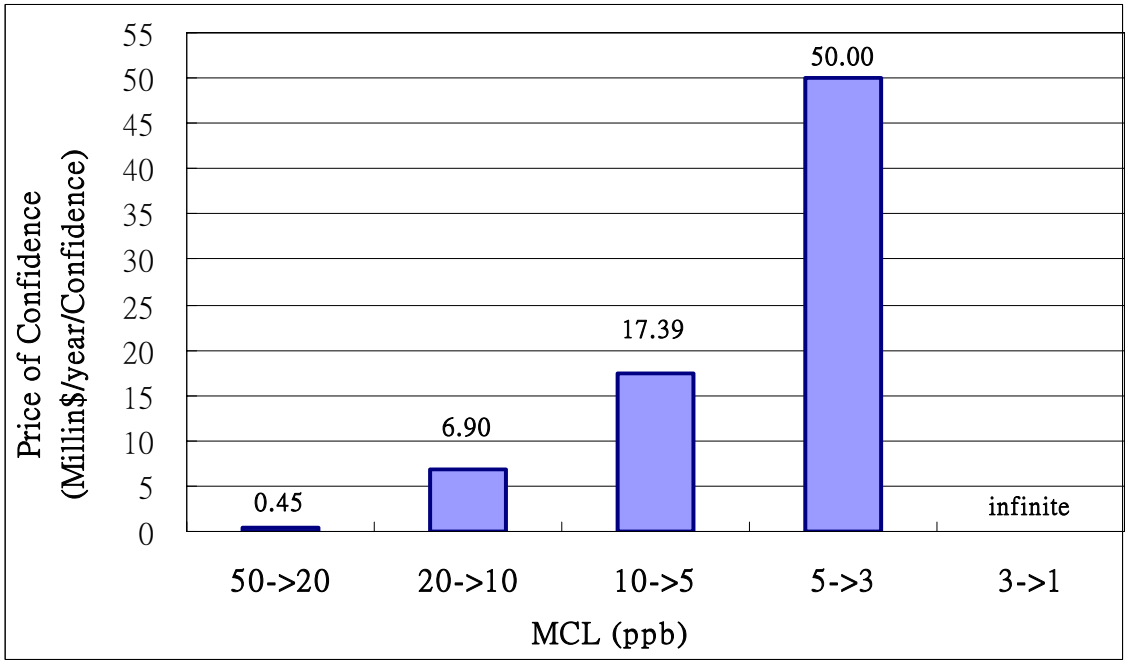


Figure 3-30. Price of Confidence (for a regulatory scenario that at least 90% of population is below a risk of 10^{-5})

The implication of this result is that we can compare the price of confidence among different MCL policies. Assume a regulator wishes that at least 90% of population is below a risk of 10^{-5}. From Figure 3-30 we can clearly see the price of confidence of lowering arsenic from one MCL to another MCL. Since there is no difference in confidence at MCLs from 3 to 1 μg/L, the incremental change in confidence is 0, making the price of confidence infinite. Therefore, this suggests that the cost of lowering the MCL from 3 to 1 could not be justified by a confidence increase. The lowest price of confidence falls into the range of lowering the MCL from 50 to 20 μg/L (0.45 million dollars per year per percent increase in confidence), while the one from 5 to 3 μg/L increases to 50 million dollars per year per percent increase in confidence.

Figure 3-31 is another way of interpret the price of confidence. Instead of calculating the incremental confidence and cost, it simply calculates the increase of confidence and cost associated with lowing the MCL from the original 50 μg/L. Then the increased cost is divided by increased confidence, resulting in the increased annual cost required in order to increase confidence by 1%. From Figure 3-31, we can see that the highest price of confidence is associated with the policy of lowering arsenic MCL from 50 to 1 μg/L, while the lowest one is the policy of lowering arsenic MCL from 50 to 20 μg/L. If the policy goal falls into this range of MCLs, these two different ways of illustrating the price of confidence offers a quantitatively useful reasoning tool to make decisions.

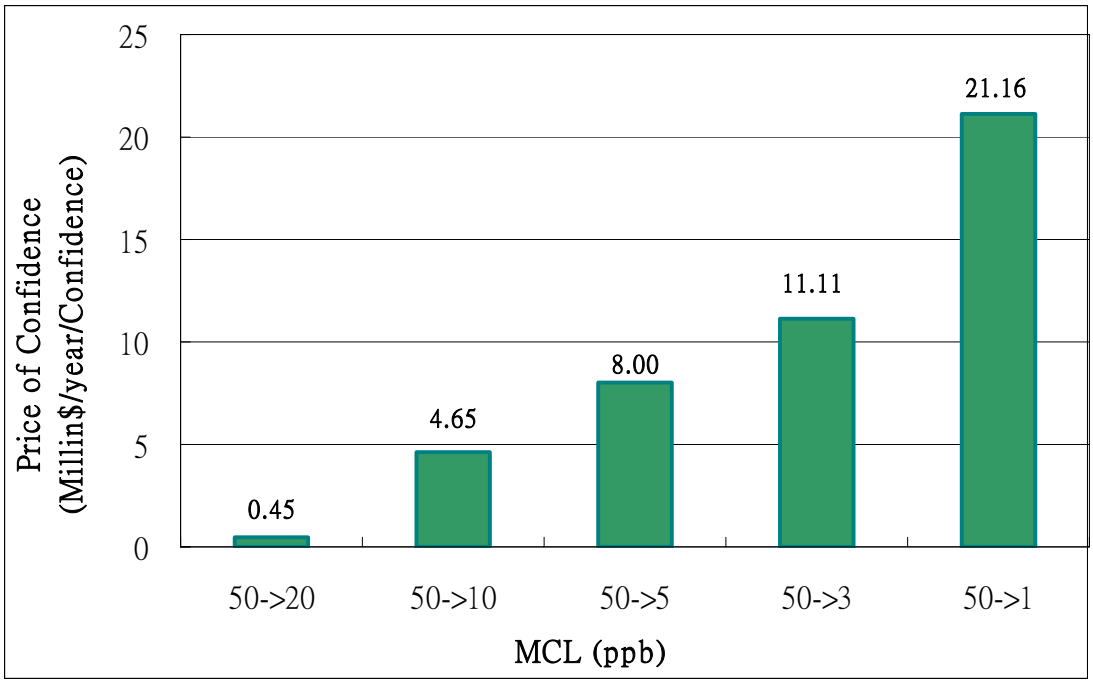


Figure 3-31. Price of Confidence of each policy (for a regulatory scenario that at least 90% of population is below a risk of 10^{-5})

CHAPTER 4 DISCUSSIONS

4.1. Conclusions

Ingestion of drinking water containing inorganic arsenic has become a matter of great public health concern, both in the United States and globally. Inorganic arsenic in drinking water can exert both cancerous and non-cancer effects after acute or chronic exposures. The US EPA reconsidered the exposure limits for arsenic in both community water systems and non-transit non-community water systems, and established a health-based, non-enforceable Maximum Contaminant Level Goal (MCLG) of zero μg/L and an enforceable Maximum Contaminant Level (MCL) of 10 μg/L based on data in NRC reports in 1999 and 2001.

The purposes of this study were (1) to improve the current dose-response assessment for arsenic by performing and incorporating the results of a meta-analysis, (2) to understand margin of safety as it relates to uncertainty and variability, and to understand how an increasing margin of safety relates to the cost of a regulation, and (3) to develop a new framework of risk-based decision-making by characterizing probabilistically the variability and uncertainty in risk assessment, using arsenic as an example.

The primary question in this research concerns the MCL of arsenic that may be allowed if a decision-maker wishes to claim that a reasonable fraction of the population (F) is protected below any given value of excess lifetime cancer risk (Pc) at any selected level of confidence (C). The graphical and tabular presentations of the relationship among Pc, F, C and MCL provided here help to address this issue. The price of confidence also offers a

quantitatively useful reasoning tool to make decisions. Finally, this study incorporates these methodologies into the traditional risk assessment framework to develop a new framework of fully probabilistic risk assessment to explicitly incorporate variability and uncertainty into the assignment of margins of safety in risk assessment, and to help further decision-making.

4.1.1. Using Meta-Analysis in Dose-Response Assessment

A meta-analysis of arsenic studies was conducted by combining several epidemiological studies from different regions (such as Taiwan, US, Argentina, Chile and Finland) to produce a composite dose-response relationship between the amount of arsenic exposure and the excess probability of cancer. Both the fixed-effect and random-effect models were used to calculate the averaged coefficient of the linear-logistic regression model. A homogeneity test was conducted first to check the heterogeneity among these studies. Because the heterogeneity was found to be high, a random-effect model had to be used. This results in a wider confidence interval of slopes and a more conservative upper bound quantitative summary of risk. **The high heterogeneity shows that there are large differences between studies, which tells us it may not be appropriate to simply extrapolate from Taiwanese studies to the U.S.** The final product is an aggregated dose-response model in the range of empirical observation of arsenic. **The best estimate of the slope factor from the meta-analysis is 3.0×10^{-5} (with unit of probability per microgram/kg/day), with the upper bound of 1.27×10^{-4}.** These slope factors from the meta-analysis are lower than the ones from the EPA (1.15×10^{-3}) and NRC (8.85×10^{-4}). There clearly are large differences between the current study and the EPA/NRC results. The possible reason for the difference is because EPA/NRC conducted their study mainly based

on data from Taiwan, while in this study, meta-analysis was used to combine data from several different regions.

Considering the most recent arsenic MCL (i.e. 10μg/L), the associated bladder cancer risk (lifetime excess probability) conducted using the upper bound result of the meta-analysis is 2.29×10^{-5} (7.35×10^{-6} if using the best estimate), which is much lower than NRC's theoretical lifetime excess risk of bladder cancer for U.S. Populations (1.2×10^{-3} for female and 2.3×10^{-3} for male). This result shows that the existing estimates of risk of bladder cancer provided by the EPA and NRC may be overestimates. From the upper bound result of meta-analysis, the arsenic concentration corresponding to a lifetime excess probability of 10^{-3} is approximately 160 μg/L; the concentration corresponding to 10^{-4} is approximately 40 μg/L; and the concentration corresponding to 10^{-5} is 4.5 μg/L.

4.1.2. The Quantification of Margin of Safety

Due to variability and uncertainty issues surrounding even the best method for estimating risks from arsenic, an arsenic MCL should be selected to provide a margin of safety. The regulatory rationality employed in this research is to identify an MCL that provides some pre-specified level of confidence that at least a certain fraction of the population will be protected against a target level probability of cancer by a proposed regulatory action.

In this study, five best available linear dose-response models were first used for variability and uncertainty analysis. Then the results of the meta-analysis were incorporated into this probabilistic framework for considering the uncertainty of dose-response models;

the new relationships among Pc, F, C and MCL are provided (see Figure 3-23, 3-24, 3-25 and 3-26).

The relationships among Pc, F, C and MCL are significantly different without the meta-analysis (previous analysis) and with the meta-analysis (new analysis). As for the cumulative distribution functions (CDF) of confidence, the new CDFs at each MCL are shifted toward the upper left when the meta-analysis results are used. This is because the slope factors used in the new analysis (which used the slope factor from the meta-analysis as the median of an uncertainty PDF) are lower than the ones used in the previous analysis (which used only the Morales data). **Therefore, the confidence in protection increases under the same assumptions of MCL, F% and Pc when the meta-analysis results are incorporated** (see Figure 3-23).

For example, assume a regulator wishes that at least 90% of the population is below a risk of 10^{-5}. In the previous analysis without meta-analysis, the confidence ranged from 0.2 to 0.3 at MCLs varied from 50 to 1 µg/L. However, when the meta-analysis results are applied, an MCL equal to 50 µg/L produces a confidence of 0.05 that this goal will be met, but the confidence increases to 0.7 when the MCL is set to 10 µg/L and increases to almost 1 when the MCL is set more stringently to 1 µg/L. At the risk target of 10^{-4}, in the previous analysis without meta-analysis, an MCL equal to 50 µg/L produces a confidence of 0.2 that this goal will be met, and the confidence gradually increases to 0.4 when the MCL is set to 5 µg/L and increases to almost 0.9 when the MCL is set more stringently to 1 µg/L. In the new analysis with meta-analysis, the confidence ranged from 0.9 to 1 at MCLs from 50 µg/L to 1 µg/L (see Figure 3-19, Figure 3-24, and Figure 3-26). **Clearly, the effect of the meta-**

analysis is to greatly increase the confidence that MCLs of between 1 and 50 μg/L will be protective at arsenic level of 10^{-5} or 10^{-4}.

This research then generated two policy tools that can be applied in selecting an MCL: (1) risk surfaces and (2) MCL tables.

(1) Risk Surfaces

The primary policy question concerns the MCL of arsenic that may be allowed if a decision-maker wishes to claim that a reasonable fraction of the population (F) is protected below any given value of excess lifetime cancer risk (Pc) at any selected level of confidence (C). The graphical and tabular presentations of the relationships among Pc, F, C and MCL provided here help to address this issue.

Using arsenic in drinking water as an example, a methodology of probabilistic risk assessment was developed to depict "risk surfaces" relating candidate MCLs to the excess lifetime probability of cancer following exposure (Pc), the fraction (F) of the exposed population at or below this probability, and the confidence (C) that this fraction does not exceed any pre-specified target fraction. From a series of surfaces (see Figure 3-21), one for each potential MCL, reducing the MCL can be viewed in three ways: (i) it reduces the mean, or expectation, value of Pc in the population, and hence the expectation value of the total burden of effects; (ii) it increases the fraction F, conditional on target values of Pc and C; or (iii) it increases the confidence, C, in protection conditional on target values of Pc and F. Also, this probabilistic framework for assessing the risk surfaces associated with different MCLs provides decision-makers a regulatory tool to select a regulatory limit (MCL) that

characterizes the increases in F and C, and the decrease in Pc (and hence increase in total health benefits), "purchased" by the cost of a given MCL.

Comparing Figure 3-21 (without meta-analysis) with Figure 3-27 (with meta-analysis), the new confidence associated with the fraction of population below various target risk levels at different MCLs are higher. **Clearly, the effect of the meta-analysis is to greatly increase the confidence given the same fraction of protected population and risk target.**

(2) MCL Tables

The relationships among Pc, F, C and MCL can be presented in a series of table (Table 3-10 and 3-11 without meta-analysis, or Table 3-31, 3-14, and 3-15 with meta-analysis) to clearly show what the MCL would be at given target risk and policy goal (i.e. a given confidence that a certain fraction of population is being protected from this target risk). If consider the MCL tables with meta-analysis and assuming the policy maker sets the policy goal of having confidence of 0.8 that at least 90% of the population is protected from the target risk: when the target risk is set to be 10^{-6}, the MCL should be set 1μg/L to meet this policy goal; when the target risk is set to be 10^{-5}, the MCL should be set 10μg/L to meet this policy goal; and when the target risk is set to be 10^{-4}, the MCL can be set higher than 50μg/L to meet this policy goal (Table 3-13, 3-14, and 3-15). **By using these tables, policy makers can choose a desirable MCL based on different policy goals.**

Table 4-1 shows the comparison of difference choices in MCLs by study without meta-analysis and study with meta-analysis. Given the policy goal that having confidence of 0.8 that at least 90% of the population is protected from the target risk (10^{-4} and 10^{-5}), when

the target risk is set to be 10^{-5}, the MCL should be set 1 μg/L to meet this policy goal by previous analysis (Table 3-10), while the MCL should be set 10 g/L to meet this policy goal by new analysis considering the result of meta-analysis (Table 3-14). When the target risk is set to be 10^{-4} the MCL should be set 3 g/L to meet this policy goal by previous analysis (Table 3-11), while the MCL doesn't need to be change from 50 μg/L to meet this policy goal by new analysis considering the result of meta-analysis (Table 3-15). **It is clear to see that by considering the result of meta-analysis, the arsenic MCLs are set to be less stringent by using MCL tables.**

Table 4-1 Comparison of MCLs (μg/L) (Given the Policy Goal that having Confidence of 0.8 that at least 90% of the Population is Protected from the Target Risk)

	Without Meta-Analysis	**With Meta-Analysis**
Target Risk (Pc)	**MCL (μg/L)**	**MCL (μg/L)**
10^{-6}	-	1
10^{-5}	1	10
10^{-4}	3	>50

4.1.3. Price of Confidence

Another policy question concerns whether the increased confidence that a target fraction of the population is protected against an unacceptable level of risk is worth the cost. The price of confidence was developed here to offer a quantitatively useful reasoning tool to answer the question: What is the incremental cost associated with an incremental increase in

the margin of safety, characterized by an increase in C (confidence) and increase in F (fraction of population protected from a risk of Pc)?

Assuming a regulator wishes that at least 90% of the population is below a risk of 10^{-5}, and using the cost data of Gurian et al. (2001), the price of confidence offers a quantitatively useful reasoning tool to make decisions (see Table 3-17, Figure 3-30 and 3-31). By using the marginal method, the lowest price of confidence is found when the MCL is lowered from 50 to 20 µg/L (0.45 million dollars per year per percent increase in confidence), while the price of moving from 5 to 3 µg/L increases to 50 million dollars per year per percent increase in confidence, and the price per percent increase in confidence of lowering the MCL from 3 to 1 was essentially infinite. If we would like to compare different policies (i.e. lowering the MCL from 50 µg/L to another MCL), the lowest price of confidence is associated with a policy that lowers the arsenic MCL from 50 to 20 µg/L, while the highest price of confidence is associated with lowering the arsenic MCL from 50 to 1 µg/L. Both of these methods suggest that the lowest price of confidence, i.e. the lowest incremental cost associated with an incremental increase in the confidence of public health protection, is associated with the policy of lowering the arsenic MCL from 50 to 20 µg/L. Therefore, according to the results of the price of confidence analysis here, lowering the arsenic MCL from 50 to 20 µg/L is the optimal policy.

By applying the concept of the price of confidence, decision-makers should be able to understand the costs associated with MCLs aimed at protecting against unacceptable residual health risks with some margin of safety. They may first characterize the degree to which a regulatory decision produces reasonable confidence that a reasonable majority of the population will be below a target risk. Then, the cost associated with each MCL may be

taken into account in striving for greater protection of health both by providing an ample margin of safety and by requiring the least cost to produce an increase in this margin of safety. Within these broad constraints, there remains a wide degree of flexibility in interpreting whether a particular decision is rational and justified.

The results generated from Price of Confidence may look different with the ones generated from the Quantification of Margin of Safety. This is because they are illustrated by different perspectives in which the policy goals are stated. Separately, these two methodologies can be policy tools, while putting them together, it can be a framework for risk-based decision making.

4.2. Limitations, Contributions and Future Research

4.2.1. Using Meta-Analysis in Dose-Response Assessment

One limitation of this study is that there are only seven observational studies available for meta-analysis. The very few available data make it difficult to do further investigation, such as meta-regression to check whether an overall study result varies among subgroups (e.g. study type or location), or a sensitivity analysis to detect the robustness of the findings to different assumptions. New observational studies of arsenic, especially ones involving a case-control or cohort design, are critical but require the investment of large amounts of money and time. Still, meta-analysis has proven here to be an appropriate tool to resolve the discrepancies among existing epidemiological data, and to produce a reasonable generalized

dose-response model and its distribution of parameters. The precision of meta-analysis can be improved when more observational studies in various regions of the world are done in the future.

This methodology can also be applied to other internal cancers from arsenic or other contaminants. However, considering that bladder cancer is the controlling effect for arsenic regulation and that there are fewer observational studies available for other internal cancers, it is unlikely that the results developed here would change significantly if other cancers were considered.

4.2.2. The Quantification of Margin of Safety

To incorporate several model inputs contributing inter-subjective variability (in parameter values, activity patterns, etc) or uncertainty (in modeling, parameter values and low-dose extrapolation, etc) in characterizing margin of safety, several assumptions had to be made. Some of these assumptions are not yet fully supported as described below and will require future research to improve on them.

(1) Inter-subjective variability

No inter-subject variations in water concentration (Cw) and in exposure duration were assumed (a lifetime exposure of 75 years is assumed). The first assumption was made because only exposure at the MCL was examined; the latter one was made because data on which alternative associations might be based were unavailable.

(2) Uncertainty

A benchmark dose approach was adopted in which (1) a best fit of each separate model to the data was obtained; (2) the model was used to estimate the value of Pc at 10 μg/L; and (3) a linear function (characterized by a slope factor) was fit between the origin and this benchmark as an approximation to the low-dose behavior of the dose-response curve for that model. However, some uncertainty problems can still not be eliminated by using this benchmark dose approach. First, linear models characterized by slope factors were the only dose-response models considered in this study at low levels of exposure. This may overestimate the risk, especially at low doses for the Mitosis and Repair models. Other kinds of dose-response shapes should also be considered in the future. Also, in the analysis without meta-analysis, only five best available models were chosen for the consideration of model uncertainty. These five models may not be able to represent fully the distribution of models, and the approximated GSD derived from these five models may be changed if additional models were considered. More kinds of models should be incorporated in further studies, at least until the mechanism of action for arsenic is better understood.

With some limitations in mind, this new framework of risk-based decision-making does improve understanding of variability and uncertainty issues in risk assessment, provides a useful way to quantify the margin of safety, and helps to select optimal regulatory limits under given constraints. This new framework of risk-based decision-making provides a useful policy tool which can be applied coherently across the regulation decisions for different contaminants. It can also provide a consistent scientific application of the human health risk assessment, including the calculation of risk, the characterization of inter-subjective variability and the characterization of uncertainty.

APPENDIX A. Risk Calculation

	A	B	C	D	E	F	G	H	I	J	K	L	M	N
1	Intersubject Variability in ADRI and Risk													
2														
3		Enter the proposed MCL:			50	microgram/L								
4														
5														
6						Age		IR/BW						
7		Mean value of IR/BW for age group:				<0.5	months	0.0524	L/kg-day					
8						0.5-0.9	months	0.0362	L/kg-day					
9		(Source: EPA Exposure Factor Handbook)				1-3	years	0.0468	L/kg-day					
10		pp.3-6				4-6	years	0.0379	L/kg-day					
11						7-10	years	0.0269	L/kg-day					
12						11-14	years	0.0202	L/kg-day					
13						15-19	years	0.0164	L/kg-day					
14						20-44	years	0.0186	L/kg-day					
15						45-64	years	0.0220	L/kg-day					
16						65-74	years	0.0219	L/kg-day					
17						75+	years	0.0216	L/kg-day					
18														
19														
20						Age		ADRI						
21		ADRI by age group:				<0.5	months	2.62	microgram/kg-day					
22						0.5-0.9	months	1.81	microgram/kg-day					
23						1-3	years	2.34	microgram/kg-day					
24						4-6	years	1.895	microgram/kg-day					
25						7-10	years	1.345	microgram/kg-day					
26						11-14	years	1.01	microgram/kg-day					
27						15-19	years	0.82	microgram/kg-day					
28						20-44	years	0.93	microgram/kg-day					
29						45-64	years	1.1	microgram/kg-day					
30						65-74	years	1.095	microgram/kg-day					
31						75+	years	1.08	microgram/kg-day					
32														
33														
34						Age		Length	Fraction of 75 year lifetime					
35		Age weighted ADRI:				<0.5	months	0.5	0.01					
36						0.5-0.9	months	0.5	0.01					
37						1-3	years	3	0.04					
38						4-6	years	3	0.04					
39						7-10	years	4	0.05					
40						11-14	years	4	0.05					
41						15-19	years	5	0.07					
42						20-44	years	25	0.33					
43						45-64	years	20	0.27					
44						65-74	years	10	0.13					
45						75+	years	0	0.00					
46														
47														
48		Mean age-weighted ADRI =			1.129	microgram/kg-day								
49														
50														
51		Assume this ADRI is distributed lognormally in a population, all exposed at the proposed MCL												
52														
53			The mean of this lognormal distribution is Cell E48 =					1.129						
54			The GSD of this lognormal distribution is				1.75							
55														
56														
57		We will multiply the mean value in Cell E48 by a "variability factor" which has a mean of 1 and a GSD equal to Cell G54												
58			The median of this lognormal distribution is mean * exp(-LN(GSD)/2) =							0.86				
59														
60			This "variability factor" has a sampled value of:					6.21						
61														
62		We then sample for the value of ADRI for an individual, multiplying the sampled "variability factor" in Cell H60												
63			by the mean age-weighted ADRI value in Cell E48:											
64														
65				Sampled ADRI =		7.01								
66														
67														
68		The slope factor for this compound is:				4.42E-06	per microgram/kg-day			Mitosis				
69						4.25E-04				Repair				
70						8.85E-04				NAS				
71						1.55E-03				Linear new				
72						2.65E-03				Upper Morales				
73														
74														
75														
76											Pc			
77		The sampled value of the lifetime risk then equals the sampled ADRI times the slope factor =									3.10E-05		Mitosis	
78											2.98E-03		Repair	
79											6.20E-03		NAS	
80											1.09E-02		Linear new	
81											1.86E-02		Upper Morales	

	A	B	C	D	E	F	G	H	I	J	K	L	M	N
1	**Intersubject Variability in ADRI and Risk**													
2														
3		Enter the proposed MCL:			20	microgram/L								
4														
5														
6						**Age**		**IR/BW**						
7		Mean value of IR/BW for age group:				<0.5	months	0.0524	L/kg-day					
8						0.5-0.9	months	0.0362	L/kg-day					
9						1-3	years	0.0468	L/kg-day					
10						4-6	years	0.0379	L/kg-day					
11						7-10	years	0.0269	L/kg-day					
12						11-14	years	0.0202	L/kg-day					
13						15-19	years	0.0164	L/kg-day					
14						20-44	years	0.0186	L/kg-day					
15						45-64	years	0.0220	L/kg-day					
16						65-74	years	0.0219	L/kg-day					
17						75+	years	0.0216	L/kg-day					
18														
19														
20						**Age**		**ADRI**						
21		ADRI by age group:				<0.5	months	1.048	microgram/kg-day					
22						0.5-0.9	months	0.724	microgram/kg-day					
23						1-3	years	0.936	microgram/kg-day					
24						4-6	years	0.758	microgram/kg-day					
25						7-10	years	0.538	microgram/kg-day					
26						11-14	years	0.404	microgram/kg-day					
27						15-19	years	0.328	microgram/kg-day					
28						20-44	years	0.372	microgram/kg-day					
29						45-64	years	0.44	microgram/kg-day					
30						65-74	years	0.438	microgram/kg-day					
31						75+	years	0.432	microgram/kg-day					
32														
33														
34						**Age**		**Length**	**Fraction of 75 year lifetime**					
35		Age weighted ADRI:				<0.5	months	0.5	0.01					
36						0.5-0.9	months	0.5	0.01					
37						1-3	years	3	0.04					
38						4-6	years	3	0.04					
39						7-10	years	4	0.05					
40						11-14	years	4	0.05					
41						15-19	years	5	0.07					
42						20-44	years	25	0.33					
43						45-64	years	20	0.27					
44						65-74	years	10	0.13					
45						75+	years	0	0.00					
46														
47														
48		Mean age-weighted ADRI =			0.451	microgram/kg-day								
49														
50														
51		Assume this ADRI is distributed lognormally in a population, all exposed at the proposed MCL												
52														
53			The mean of this lognormal distribution is Cell E48 =					0.451						
54			The GSD of this lognormal distribution is				1.75							
55														
56														
57		We will multiply the mean value in Cell E48 by a "variability factor" which has a mean of 1 and a GSD equal to Cell G54												
58			The median of this lognormal distribution is mean * exp(-LN^2(GSD)/2) =							0.86				
59														
60			This "variability factor" has a sampled value of:					0.21						
61														
62		We then sample for the value of ADRI for an individual, multiplying the sampled "variability factor" in Cell H60												
63			by the mean age-weighted ADRI value in Cell E48:											
64														
65				Sampled ADRI =		2.80								
66														
67														
68		The slope factor for this compound is:				4.42E-06	per microgram/kg-day			**Mitosis**				
69						4.25E-04				**Repair**				
70						8.85E-04				**NAS**				
71						1.55E-03				**Linear new**				
72						2.65E-03				**Upper Morales**				
73														
74														
75														
76											Pc			
77		The sampled value of the lifetime risk then equals the sampled ADRI times the slope factor =									1.24E-05		**Mitosis**	
78											1.19E-03		**Repair**	
79											2.48E-03		**NAS**	
80											4.34E-03		**Linear new**	
81											7.45E-03		**Upper Morales**	

	A	B	C	D	E	F	G	H	I	J	K	L	M	N
1	**Intersubject Variability in ADRI and Risk**													
2														
3		Enter the proposed MCL:			10	microgram/L								
4														
5														
6						**Age**		**IR/BW**						
7		Mean value of IR/BW for age group:				<0.5	months	0.0524	L/kg-day					
8						0.5-0.9	months	0.0362	L/kg-day					
9						1-3	years	0.0468	L/kg-day					
10						4-6	years	0.0379	L/kg-day					
11						7-10	years	0.0269	L/kg-day					
12						11-14	years	0.0202	L/kg-day					
13						15-19	years	0.0164	L/kg-day					
14						20-44	years	0.0186	L/kg-day					
15						45-64	years	0.0220	L/kg-day					
16						65-74	years	0.0219	L/kg-day					
17						75+	years	0.0216	L/kg-day					
18														
19														
20						**Age**		**ADRI**						
21		ADRI by age group:				<0.5	months	0.524	microgram/kg-day					
22						0.5-0.9	months	0.362	microgram/kg-day					
23						1-3	years	0.468	microgram/kg-day					
24						4-6	years	0.379	microgram/kg-day					
25						7-10	years	0.269	microgram/kg-day					
26						11-14	years	0.202	microgram/kg-day					
27						15-19	years	0.164	microgram/kg-day					
28						20-44	years	0.186	microgram/kg-day					
29						45-64	years	0.22	microgram/kg-day					
30						65-74	years	0.219	microgram/kg-day					
31						75+	years	0.216	microgram/kg-day					
32														
33														
34						**Age**		**Length**	**Fraction of 75 year lifetime**					
35		Age weighted ADRI:				<0.5	months	0.5	0.01					
36						0.5-0.9	months	0.5	0.01					
37						1-3	years	3	0.04					
38						4-6	years	3	0.04					
39						7-10	years	4	0.05					
40						11-14	years	4	0.05					
41						15-19	years	5	0.07					
42						20-44	years	25	0.33					
43						45-64	years	20	0.27					
44						65-74	years	10	0.13					
45						75+	years	0	0.00					
46														
47														
48		Mean age-weighted ADRI =			0.226	microgram/kg-day								
49														
50														
51		Assume this ADRI is distributed lognormally in a population, all exposed at the proposed MCL												
52														
53			The mean of this lognormal distribution is Cell E48 =					0.226						
54			The GSD of this lognormal distribution is				1.75							
55														
56														
57		We will multiply the mean value in Cell E48 by a "variability factor" which has a mean of 1 and a GSD equal to Cell G54												
58			The median of this lognormal distribution is mean * exp(-LN^2(GSD)/2) =							0.86				
59														
60			This "variability factor" has a sampled value of:					0.21						
61														
62		We then sample for the value of ADRI for an individual, multiplying the sampled "variability factor" in Cell H60												
63			by the mean age-weighted ADRI value in Cell E48:											
64														
65				Sampled ADRI =		1.40								
66														
67														
68		The slope factor for this compound is:				4.42E-06	per microgram/kg-day			**Mitosis**				
69						4.25E-04				**Repair**				
70						8.85E-04				**NAS**				
71						1.55E-03				**Linear new**				
72						2.65E-03				**Upper Morales**				
73														
74														
75														
76											Pc			
77		The sampled value of the lifetime risk then equals the sampled ADRI times the slope factor =									6.20E-06		**Mitosis**	
78											5.96E-04		**Repair**	
79											1.24E-03		**NAS**	
80											2.17E-03		**Linear new**	
81											3.72E-03		**Upper Morales**	

	A	B	C	D	E	F	G	H	I	J	K	L	M	N
1	**Intersubject Variability in ADRI and Risk**													
2														
3		Enter the proposed MCL:			5	microgram/L								
4														
5														
6						**Age**		**IR/BW**						
7		Mean value of IR/BW for age group:				<0.5	months	0.0524	L/kg-day					
8						0.5-0.9	months	0.0362	L/kg-day					
9						1-3	years	0.0468	L/kg-day					
10						4-6	years	0.0379	L/kg-day					
11						7-10	years	0.0269	L/kg-day					
12						11-14	years	0.0202	L/kg-day					
13						15-19	years	0.0164	L/kg-day					
14						20-44	years	0.0186	L/kg-day					
15						45-64	years	0.0220	L/kg-day					
16						65-74	years	0.0219	L/kg-day					
17						75+	years	0.0216	L/kg-day					
18														
19														
20						**Age**		**ADRI**						
21		ADRI by age group:				<0.5	months	0.262	microgram/kg-day					
22						0.5-0.9	months	0.181	microgram/kg-day					
23						1-3	years	0.234	microgram/kg-day					
24						4-6	years	0.1895	microgram/kg-day					
25						7-10	years	0.1345	microgram/kg-day					
26						11-14	years	0.101	microgram/kg-day					
27						15-19	years	0.082	microgram/kg-day					
28						20-44	years	0.093	microgram/kg-day					
29						45-64	years	0.11	microgram/kg-day					
30						65-74	years	0.1095	microgram/kg-day					
31						75+	years	0.108	microgram/kg-day					
32														
33														
34						**Age**		**Length**	**Fraction of 75 year lifetime**					
35		Age weighted ADRI:				<0.5	months	0.5	0.01					
36						0.5-0.9	months	0.5	0.01					
37						1-3	years	3	0.04					
38						4-6	years	3	0.04					
39						7-10	years	4	0.05					
40						11-14	years	4	0.05					
41						15-19	years	5	0.07					
42						20-44	years	25	0.33					
43						45-64	years	20	0.27					
44						65-74	years	10	0.13					
45						75+	years	0	0.00					
46														
47														
48		Mean age-weighted ADRI =			0.113	microgram/kg-day								
49														
50														
51		Assume this ADRI is distributed lognormally in a population, all exposed at the proposed MCL												
52														
53			The mean of this lognormal distribution is Cell E48 =					0.113						
54			The GSD of this lognormal distribution is				1.75							
55														
56														
57		We will multiply the mean value in Cell E48 by a "variability factor" which has a mean of 1 and a GSD equal to Cell G54												
58			The median of this lognormal distribution is mean * exp(-LN(GSD)/2) =							0.86				
59														
60			This "variability factor" has a sampled value of:					6.21						
61														
62		We then sample for the value of ADRI for an individual, multiplying the sampled "variability factor" in Cell H60												
63			by the mean age-weighted ADRI value in Cell E48:											
64														
65				Sampled ADRI =		0.70								
66														
67														
68		The slope factor for this compound is:				4.42E-06	per microgram/kg-day			**Mitosis**				
69						4.25E-04				**Repair**				
70						8.85E-04				**NAS**				
71						1.55E-03				**Linear new**				
72						2.65E-03				**Upper Morales**				
73														
74														
75														
76											Pc			
77		The sampled value of the lifetime risk then equals the sampled ADRI times the slope factor =									3.10E-06		**Mitosis**	
78											2.98E-04		**Repair**	
79											6.20E-04		**NAS**	
80											1.09E-03		**Linear new**	
81											1.86E-03		**Upper Morales**	

	A	B	C	D	E	F	G	H	I	J	K	L	M	N
1	**Intersubject Variability in ADRI and Risk**													
2														
3		Enter the proposed MCL:			3	microgram/L								
4														
5														
6						**Age**		**IR/BW**						
7		Mean value of IR/BW for age group:				<0.5	months	0.0524	L/kg-day					
8						0.5-0.9	months	0.0362	L/kg-day					
9						1-3	years	0.0468	L/kg-day					
10						4-6	years	0.0379	L/kg-day					
11						7-10	years	0.0269	L/kg-day					
12						11-14	years	0.0202	L/kg-day					
13						15-19	years	0.0164	L/kg-day					
14						20-44	years	0.0186	L/kg-day					
15						45-64	years	0.0220	L/kg-day					
16						65-74	years	0.0219	L/kg-day					
17						75+	years	0.0216	L/kg-day					
18														
19														
20						**Age**		**ADRI**						
21		ADRI by age group:				<0.5	months	0.1572	microgram/kg-day					
22						0.5-0.9	months	0.1086	microgram/kg-day					
23						1-3	years	0.1404	microgram/kg-day					
24						4-6	years	0.1137	microgram/kg-day					
25						7-10	years	0.0807	microgram/kg-day					
26						11-14	years	0.0606	microgram/kg-day					
27						15-19	years	0.0492	microgram/kg-day					
28						20-44	years	0.0558	microgram/kg-day					
29						45-64	years	0.066	microgram/kg-day					
30						65-74	years	0.0657	microgram/kg-day					
31						75+	years	0.0648	microgram/kg-day					
32														
33														
34						**Age**		**Length**	**Fraction of 75 year lifetime**					
35		Age weighted ADRI:				<0.5	months	0.5	0.01					
36						0.5-0.9	months	0.5	0.01					
37						1-3	years	3	0.04					
38						4-6	years	3	0.04					
39						7-10	years	4	0.05					
40						11-14	years	4	0.05					
41						15-19	years	5	0.07					
42						20-44	years	25	0.33					
43						45-64	years	20	0.27					
44						65-74	years	10	0.13					
45						75+	years	0	0.00					
46														
47														
48		Mean age-weighted ADRI =			0.068	microgram/kg-day								
49														
50														
51		Assume this ADRI is distributed lognormally in a population, all exposed at the proposed MCL												
52														
53			The mean of this lognormal distribution is Cell E48 =					0.068						
54			The GSD of this lognormal distribution is				1.75							
55														
56														
57		We will multiply the mean value in Cell E48 by a "variability factor" which has a mean of 1 and a GSD equal to Cell G54												
58			The median of this lognormal distribution is mean * exp(-LN(GSD)/2) =							0.86				
59														
60			This "variability factor" has a sampled value of:					6.21						
61														
62		We then sample for the value of ADRI for an individual, multiplying the sampled "variability factor" in Cell H60												
63			by the mean age-weighted ADRI value in Cell E48:											
64														
65				Sampled ADRI =	0.42									
66														
67														
68		The slope factor for this compound is:				4.42E-06	per microgram/kg-day			**Mitosis**				
69						4.25E-04				**Repair**				
70						8.85E-04				**NAS**				
71						1.55E-03				**Linear new**				
72						2.65E-03				**Upper Morales**				
73														
74														
75														
76											Pc			
77		The sampled value of the lifetime risk then equals the sampled ADRI times the slope factor =									1.86E-06		**Mitosis**	
78											1.79E-04		**Repair**	
79											3.72E-04		**NAS**	
80											6.51E-04		**Linear new**	
81											1.12E-03		**Upper Morales**	

	A	B	C	D	E	F	G	H	I	J	K	L	M	N
1	**Intersubject Variability in ADRI and Risk**													
2														
3		Enter the proposed MCL:			1	microgram/L								
4														
5														
6						**Age**		**IR/BW**						
7		Mean value of IR/BW for age group:				<0.5	months	0.0524	L/kg-day					
8						0.5-0.9	months	0.0362	L/kg-day					
9						1-3	years	0.0468	L/kg-day					
10						4-6	years	0.0379	L/kg-day					
11						7-10	years	0.0269	L/kg-day					
12						11-14	years	0.0202	L/kg-day					
13						15-19	years	0.0164	L/kg-day					
14						20-44	years	0.0186	L/kg-day					
15						45-64	years	0.0220	L/kg-day					
16						65-74	years	0.0219	L/kg-day					
17						75+	years	0.0216	L/kg-day					
18														
19														
20						**Age**		**ADRI**						
21		ADRI by age group:				<0.5	months	0.0524	microgram/kg-day					
22						0.5-0.9	months	0.0362	microgram/kg-day					
23						1-3	years	0.0468	microgram/kg-day					
24						4-6	years	0.0379	microgram/kg-day					
25						7-10	years	0.0269	microgram/kg-day					
26						11-14	years	0.0202	microgram/kg-day					
27						15-19	years	0.0164	microgram/kg-day					
28						20-44	years	0.0186	microgram/kg-day					
29						45-64	years	0.022	microgram/kg-day					
30						65-74	years	0.0219	microgram/kg-day					
31						75+	years	0.0216	microgram/kg-day					
32														
33														
34						**Age**		**Length**	**Fraction of 75 year lifetime**					
35		Age weighted ADRI:				<0.5	months	0.5	0.01					
36						0.5-0.9	months	0.5	0.01					
37						1-3	years	3	0.04					
38						4-6	years	3	0.04					
39						7-10	years	4	0.05					
40						11-14	years	4	0.05					
41						15-19	years	5	0.07					
42						20-44	years	25	0.33					
43						45-64	years	20	0.27					
44						65-74	years	10	0.13					
45						75+	years	0	0.00					
46														
47														
48		Mean age-weighted ADRI =			0.023	microgram/kg-day								
49														
50														
51		Assume this ADRI is distributed lognormally in a population, all exposed at the proposed MCL												
52														
53			The mean of this lognormal distribution is Cell E48 =					0.023						
54			The GSD of this lognormal distribution is				1.75							
55														
56														
57		We will multiply the mean value in Cell E48 by a "variability factor" which has a mean of 1 and a GSD equal to Cell G54												
58			The median of this lognormal distribution is mean * exp(-LN(GSD)/2) =							0.86				
59														
60			This "variability factor" has a sampled value of:					6.21						
61														
62		We then sample for the value of ADRI for an individual, multiplying the sampled "variability factor" in Cell H60												
63			by the mean age-weighted ADRI value in Cell E48:											
64														
65				Sampled ADRI =		0.14								
66														
67														
68		The slope factor for this compound is:				4.42E-06	per microgram/kg-day			**Mitosis**				
69						4.25E-04				**Repair**				
70						8.85E-04				**NAS**				
71						1.55E-03				**Linear new**				
72						2.65E-03				**Upper Morales**				
73														
74														
75														
76											Pc			
77		The sampled value of the lifetime risk then equals the sampled ADRI times the slope factor =									6.20E-07		**Mitosis**	
78											5.96E-05		**Repair**	
79											1.24E-04		**NAS**	
80											2.17E-04		**Linear new**	
81											3.72E-04		**Upper Morales**	

APPENDIX B. Rick Calculation using Meta-Analysis Results

	A	B	C	D	E	F	G	H	I	J	K	L
1	**Intersubject Variability in ADRI and Risk**											
2												
3		Enter the proposed MCL:			50	microgram/L						
4												
5												
6						**Age**		**IR/BW**				
7		Mean value of IR/BW for age group:				<0.5	months	0.0524	L/kg-day			
8						0.5-0.9	months	0.0362	L/kg-day			
9		(Source: EPA Exposure Factor Handbook)				1-3	years	0.0468	L/kg-day			
10		pp.3-6				4-6	years	0.0379	L/kg-day			
11						7-10	years	0.0269	L/kg-day			
12						11-14	years	0.0202	L/kg-day			
13						15-19	years	0.0164	L/kg-day			
14						20-44	years	0.0186	L/kg-day			
15						45-64	years	0.0220	L/kg-day			
16						65-74	years	0.0219	L/kg-day			
17						75+	years	0.0216	L/kg-day			
18												
19												
20						**Age**		**ADRI**				
21		ADRI by age group:				<0.5	months	2.62	microgram/kg-day			
22						0.5-0.9	months	1.81	microgram/kg-day			
23						1-3	years	2.34	microgram/kg-day			
24						4-6	years	1.895	microgram/kg-day			
25						7-10	years	1.345	microgram/kg-day			
26						11-14	years	1.01	microgram/kg-day			
27						15-19	years	0.82	microgram/kg-day			
28						20-44	years	0.93	microgram/kg-day			
29						45-64	years	1.1	microgram/kg-day			
30						65-74	years	1.095	microgram/kg-day			
31						75+	years	1.08	microgram/kg-day			
32												
33												
34						**Age**		**Length**	**Fraction of 75 year lifetime**			
35		Age weighted ADRI:				<0.5	months	0.5	0.01			
36						0.5-0.9	months	0.5	0.01			
37						1-3	years	3	0.04			
38						4-6	years	3	0.04			
39						7-10	years	4	0.05			
40						11-14	years	4	0.05			
41						15-19	years	5	0.07			
42						20-44	years	25	0.33			
43						45-64	years	20	0.27			
44						65-74	years	10	0.13			
45						75+	years	0	0.00			
46												
47												
48		Mean age-weighted ADRI =			1.129	microgram/kg-day						
49												
50												
51		Assume this ADRI is distributed lognormally in a population, all exposed at the proposed MCL										
52												
53			The mean of this lognormal distribution is Cell E48 =					1.129				
54			The GSD of this lognormal distribution is				1.75					
55												
56												
57		We will multiply the mean value in Cell E48 by a "variability factor" which has a mean of 1 and a GSD equal to Cell G54										
58			The median of this lognormal distribution is mean * exp(-LN^2(GSD)/2) =							0.86		
59												
60			This "variability factor" has a sampled value of:					6.21				
61												
62		We then sample for the value of ADRI for an individual, multiplying the sampled "variability factor" in Cell H60										
63			by the mean age-weighted ADRI value in Cell E48:									
64												
65				Sampled ADRI =		7.01	microgram/kg-day					
66												
67												
68		The median slope factor for this compound is:					3.00E-05	per microgram/kg-day			**Meta-Analysis**	
69		The GSD of this lognormal distribution is					2.2					
70												
71												
72											Pc	
73		The sampled slope factor			#1		3.36E-05	per microgram/kg-day			2.36E-04	Pc1
74					#2		2.23E-05				1.56E-04	Pc2
75					#3		9.35E-05				6.55E-04	Pc3
76					#4		1.09E-05				7.61E-05	Pc4
77					#5		6.07E-05				4.25E-04	Pc5
78					#6		1.50E-05				1.05E-04	Pc6
79					#7		7.65E-06				5.37E-05	Pc7
80					#8		2.75E-05				1.93E-04	Pc8
81					#9		3.26E-05				2.29E-04	Pc9
82					#10		1.28E-05				8.94E-05	Pc10
83					#11		1.04E-05				7.28E-05	Pc11
84					#12		4.90E-06				3.44E-05	Pc12
85					#13		1.94E-05				1.36E-04	Pc13
86					#14		3.58E-05				2.51E-04	Pc14
87					#15		4.01E-05				2.81E-04	Pc15
88					#16		3.16E-05				2.22E-04	Pc16
89					#17		3.20E-05				2.24E-04	Pc17
90					#18		2.26E-05				1.59E-04	Pc18
91					#19		3.70E-05				2.59E-04	Pc19
92					#20		2.66E-05				1.87E-04	Pc20

	A	B	C	D	E	F	G	H	I	J	K	L
1	**Intersubject Variability in ADRI and Risk**											
2												
3		Enter the proposed MCL:			20	microgram/L						
4												
5												
6						**Age**		**IR/BW**				
7		Mean value of IR/BW for age group:				<0.5	months	0.0524	L/kg-day			
8						0.5-0.9	months	0.0362	L/kg-day			
9		(Source: EPA Exposure Factor Handbook)				1-3	years	0.0468	L/kg-day			
10		pp.3-6				4-6	years	0.0379	L/kg-day			
11						7-10	years	0.0269	L/kg-day			
12						11-14	years	0.0202	L/kg-day			
13						15-19	years	0.0164	L/kg-day			
14						20-44	years	0.0186	L/kg-day			
15						45-64	years	0.0220	L/kg-day			
16						65-74	years	0.0219	L/kg-day			
17						75+	years	0.0216	L/kg-day			
18												
19												
20						**Age**		**ADRI**				
21		ADRI by age group:				<0.5	months	1.048	microgram/kg-day			
22						0.5-0.9	months	0.724	microgram/kg-day			
23						1-3	years	0.936	microgram/kg-day			
24						4-6	years	0.758	microgram/kg-day			
25						7-10	years	0.538	microgram/kg-day			
26						11-14	years	0.404	microgram/kg-day			
27						15-19	years	0.328	microgram/kg-day			
28						20-44	years	0.372	microgram/kg-day			
29						45-64	years	0.44	microgram/kg-day			
30						65-74	years	0.438	microgram/kg-day			
31						75+	years	0.432	microgram/kg-day			
32												
33												
34						**Age**		**Length**	**Fraction of 75 year lifetime**			
35		Age weighted ADRI:				<0.5	months	0.5	0.01			
36						0.5-0.9	months	0.5	0.01			
37						1-3	years	3	0.04			
38						4-6	years	3	0.04			
39						7-10	years	4	0.05			
40						11-14	years	4	0.05			
41						15-19	years	5	0.07			
42						20-44	years	25	0.33			
43						45-64	years	20	0.27			
44						65-74	years	10	0.13			
45						75+	years	0	0.00			
46												
47												
48		Mean age-weighted ADRI =			0.451	microgram/kg-day						
49												
50												
51		Assume this ADRI is distributed lognormally in a population, all exposed at the proposed MCL										
52												
53			The mean of this lognormal distribution is Cell E48 =					0.451				
54			The GSD of this lognormal distribution is				1.75					
55												
56												
57		We will multiply the mean value in Cell E48 by a "variability factor" which has a mean of 1 and a GSD equal to Cell G54										
58			The median of this lognormal distribution is mean * exp(-LN^2(GSD)/2) =							0.86		
59												
60			This "variability factor" has a sampled value of:					0.21				
61												
62		We then sample for the value of ADRI for an individual, multiplying the sampled "variability factor" in Cell H60										
63			by the mean age-weighted ADRI value in Cell E48:									
64												
65				Sampled ADRI =		2.80	microgram/kg-day					
66												
67												
68		The median slope factor for this compound is:					3.00E-05	per microgram/kg-day			**Meta-Analysis**	
69		The GSD of this lognormal distribution is					2.2					
70												
71												
72											Pc	
73		The sampled slope factor			#1		3.36E-05	per microgram/kg-day			9.44E-05	Pc1
74					#2		2.23E-05				6.24E-05	Pc2
75					#3		9.35E-05				2.62E-04	Pc3
76					#4		1.09E-05				3.05E-05	Pc4
77					#5		6.07E-05				1.70E-04	Pc5
78					#6		1.50E-05				4.20E-05	Pc6
79					#7		7.65E-06				2.15E-05	Pc7
80					#8		2.75E-05				7.72E-05	Pc8
81					#9		3.26E-05				9.15E-05	Pc9
82					#10		1.28E-05				3.58E-05	Pc10
83					#11		1.04E-05				2.91E-05	Pc11
84					#12		4.90E-06				1.38E-05	Pc12
85					#13		1.94E-05				5.44E-05	Pc13
86					#14		3.58E-05				1.01E-04	Pc14
87					#15		4.01E-05				1.12E-04	Pc15
88					#16		3.16E-05				8.87E-05	Pc16
89					#17		3.20E-05				8.96E-05	Pc17
90					#18		2.26E-05				6.34E-05	Pc18
91					#19		3.70E-05				1.04E-04	Pc19
92					#20		2.66E-05				7.47E-05	Pc20

	A	B	C	D	E	F	G	H	I	J	K	L
1	**Intersubject Variability in ADRI and Risk**											
2												
3		Enter the proposed MCL:			10	microgram/L						
4												
5												
6						**Age**		**IR/BW**				
7		Mean value of IR/BW for age group:				<0.5	months	0.0524	L/kg-day			
8						0.5-0.9	months	0.0362	L/kg-day			
9		(Source: EPA Exposure Factor Handbook)				1-3	years	0.0468	L/kg-day			
10		pp.3-6				4-6	years	0.0379	L/kg-day			
11						7-10	years	0.0269	L/kg-day			
12						11-14	years	0.0202	L/kg-day			
13						15-19	years	0.0164	L/kg-day			
14						20-44	years	0.0186	L/kg-day			
15						45-64	years	0.0220	L/kg-day			
16						65-74	years	0.0219	L/kg-day			
17						75+	years	0.0216	L/kg-day			
18												
19												
20						**Age**		**ADRI**				
21		ADRI by age group:				<0.5	months	0.524	microgram/kg-day			
22						0.5-0.9	months	0.362	microgram/kg-day			
23						1-3	years	0.468	microgram/kg-day			
24						4-6	years	0.379	microgram/kg-day			
25						7-10	years	0.269	microgram/kg-day			
26						11-14	years	0.202	microgram/kg-day			
27						15-19	years	0.164	microgram/kg-day			
28						20-44	years	0.186	microgram/kg-day			
29						45-64	years	0.22	microgram/kg-day			
30						65-74	years	0.219	microgram/kg-day			
31						75+	years	0.216	microgram/kg-day			
32												
33												
34						**Age**		**Length**	**Fraction of 75 year lifetime**			
35		Age weighted ADRI:				<0.5	months	0.5	0.01			
36						0.5-0.9	months	0.5	0.01			
37						1-3	years	3	0.04			
38						4-6	years	3	0.04			
39						7-10	years	4	0.05			
40						11-14	years	4	0.05			
41						15-19	years	5	0.07			
42						20-44	years	25	0.33			
43						45-64	years	20	0.27			
44						65-74	years	10	0.13			
45						75+	years	0	0.00			
46												
47												
48		Mean age-weighted ADRI =			0.226	microgram/kg-day						
49												
50												
51		Assume this ADRI is distributed lognormally in a population, all exposed at the proposed MCL										
52												
53			The mean of this lognormal distribution is Cell E48 =					0.226				
54			The GSD of this lognormal distribution is				1.75					
55												
56												
57		We will multiply the mean value in Cell E48 by a "variability factor" which has a mean of 1 and a GSD equal to Cell G54										
58			The median of this lognormal distribution is mean * exp(-LN^2(GSD)/2) =							0.86		
59												
60			This "variability factor" has a sampled value of:					0.21				
61												
62		We then sample for the value of ADRI for an individual, multiplying the sampled "variability factor" in Cell H60										
63			by the mean age-weighted ADRI value in Cell E48:									
64												
65				Sampled ADRI =		1.40	microgram/kg-day					
66												
67												
68		The median slope factor for this compound is:					3.00E-05	per microgram/kg-day			**Meta-Analysis**	
69		The GSD of this lognormal distribution is					2.2					
70												
71												
72											Pc	
73		The sampled slope factor			#1		3.36E-05	per microgram/kg-day			4.72E-05	Pc1
74					#2		2.23E-05				3.12E-05	Pc2
75					#3		9.35E-05				1.31E-04	Pc3
76					#4		1.09E-05				1.52E-05	Pc4
77					#5		6.07E-05				8.50E-05	Pc5
78					#6		1.50E-05				2.10E-05	Pc6
79					#7		7.65E-06				1.07E-05	Pc7
80					#8		2.75E-05				3.86E-05	Pc8
81					#9		3.26E-05				4.58E-05	Pc9
82					#10		1.28E-05				1.79E-05	Pc10
83					#11		1.04E-05				1.46E-05	Pc11
84					#12		4.90E-06				6.88E-06	Pc12
85					#13		1.94E-05				2.72E-05	Pc13
86					#14		3.58E-05				5.03E-05	Pc14
87					#15		4.01E-05				5.62E-05	Pc15
88					#16		3.16E-05				4.43E-05	Pc16
89					#17		3.20E-05				4.48E-05	Pc17
90					#18		2.26E-05				3.17E-05	Pc18
91					#19		3.70E-05				5.19E-05	Pc19
92					#20		2.66E-05				3.73E-05	Pc20

	A	B	C	D	E	F	G	H	I	J	K	L
1	**Intersubject Variability in ADRI and Risk**											
2												
3		Enter the proposed MCL:			5	microgram/L						
4												
5												
6						**Age**		**IR/BW**				
7		Mean value of IR/BW for age group:				<0.5	months	0.0524	L/kg-day			
8						0.5-0.9	months	0.0362	L/kg-day			
9		(Source: EPA Exposure Factor Handbook)				1-3	years	0.0468	L/kg-day			
10		pp.3-6				4-6	years	0.0379	L/kg-day			
11						7-10	years	0.0269	L/kg-day			
12						11-14	years	0.0202	L/kg-day			
13						15-19	years	0.0164	L/kg-day			
14						20-44	years	0.0186	L/kg-day			
15						45-64	years	0.0220	L/kg-day			
16						65-74	years	0.0219	L/kg-day			
17						75+	years	0.0216	L/kg-day			
18												
19												
20						**Age**		**ADRI**				
21		ADRI by age group:				<0.5	months	0.262	microgram/kg-day			
22						0.5-0.9	months	0.181	microgram/kg-day			
23						1-3	years	0.234	microgram/kg-day			
24						4-6	years	0.1895	microgram/kg-day			
25						7-10	years	0.1345	microgram/kg-day			
26						11-14	years	0.101	microgram/kg-day			
27						15-19	years	0.082	microgram/kg-day			
28						20-44	years	0.093	microgram/kg-day			
29						45-64	years	0.11	microgram/kg-day			
30						65-74	years	0.1095	microgram/kg-day			
31						75+	years	0.108	microgram/kg-day			
32												
33												
34						**Age**		**Length**	**Fraction of 75 year lifetime**			
35		Age weighted ADRI:				<0.5	months	0.5	0.01			
36						0.5-0.9	months	0.5	0.01			
37						1-3	years	3	0.04			
38						4-6	years	3	0.04			
39						7-10	years	4	0.05			
40						11-14	years	4	0.05			
41						15-19	years	5	0.07			
42						20-44	years	25	0.33			
43						45-64	years	20	0.27			
44						65-74	years	10	0.13			
45						75+	years	0	0.00			
46												
47												
48		Mean age-weighted ADRI =			0.113	microgram/kg-day						
49												
50												
51		Assume this ADRI is distributed lognormally in a population, all exposed at the proposed MCL										
52												
53			The mean of this lognormal distribution is Cell E48 =					0.113				
54			The GSD of this lognormal distribution is				1.75					
55												
56												
57		We will multiply the mean value in Cell E48 by a "variability factor" which has a mean of 1 and a GSD equal to Cell G54										
58			The median of this lognormal distribution is mean * exp(-LN^2(GSD)/2) =							0.86		
59												
60			This "variability factor" has a sampled value of:					0.21				
61												
62		We then sample for the value of ADRI for an individual, multiplying the sampled "variability factor" in Cell H60										
63			by the mean age-weighted ADRI value in Cell E48:									
64												
65				Sampled ADRI =		0.70	microgram/kg-day					
66												
67												
68		The median slope factor for this compound is:					3.00E-05	per microgram/kg-day			**Meta-Analysis**	
69		The GSD of this lognormal distribution is					2.2					
70												
71												
72											Pc	
73		The sampled slope factor			#1		3.36E-05	per microgram/kg-day			2.36E-05	Pc1
74					#2		2.23E-05				1.56E-05	Pc2
75					#3		9.35E-05				6.55E-05	Pc3
76					#4		1.09E-05				7.61E-06	Pc4
77					#5		6.07E-05				4.25E-05	Pc5
78					#6		1.50E-05				1.05E-05	Pc6
79					#7		7.65E-06				5.37E-06	Pc7
80					#8		2.75E-05				1.93E-05	Pc8
81					#9		3.26E-05				2.29E-05	Pc9
82					#10		1.28E-05				8.94E-06	Pc10
83					#11		1.04E-05				7.28E-06	Pc11
84					#12		4.90E-06				3.44E-06	Pc12
85					#13		1.94E-05				1.36E-05	Pc13
86					#14		3.58E-05				2.51E-05	Pc14
87					#15		4.01E-05				2.81E-05	Pc15
88					#16		3.16E-05				2.22E-05	Pc16
89					#17		3.20E-05				2.24E-05	Pc17
90					#18		2.26E-05				1.59E-05	Pc18
91					#19		3.70E-05				2.59E-05	Pc19
92					#20		2.66E-05				1.87E-05	Pc20

	A	B	C	D	E	F	G	H	I	J	K	L
1	**Intersubject Variability in ADRI and Risk**											
2												
3		Enter the proposed MCL:			3	microgram/L						
4												
5												
6						**Age**		**IR/BW**				
7		Mean value of IR/BW for age group:				<0.5	months	0.0524	L/kg-day			
8						0.5-0.9	months	0.0362	L/kg-day			
9		(Source: EPA Exposure Factor Handbook)				1-3	years	0.0468	L/kg-day			
10		pp.3-6				4-6	years	0.0379	L/kg-day			
11						7-10	years	0.0269	L/kg-day			
12						11-14	years	0.0202	L/kg-day			
13						15-19	years	0.0164	L/kg-day			
14						20-44	years	0.0186	L/kg-day			
15						45-64	years	0.0220	L/kg-day			
16						65-74	years	0.0219	L/kg-day			
17						75+	years	0.0216	L/kg-day			
18												
19												
20						**Age**		**ADRI**				
21		ADRI by age group:				<0.5	months	0.1572	microgram/kg-day			
22						0.5-0.9	months	0.1086	microgram/kg-day			
23						1-3	years	0.1404	microgram/kg-day			
24						4-6	years	0.1137	microgram/kg-day			
25						7-10	years	0.0807	microgram/kg-day			
26						11-14	years	0.0606	microgram/kg-day			
27						15-19	years	0.0492	microgram/kg-day			
28						20-44	years	0.0558	microgram/kg-day			
29						45-64	years	0.066	microgram/kg-day			
30						65-74	years	0.0657	microgram/kg-day			
31						75+	years	0.0648	microgram/kg-day			
32												
33												
34						**Age**		**Length**	**Fraction of 75 year lifetime**			
35		Age weighted ADRI:				<0.5	months	0.5	0.01			
36						0.5-0.9	months	0.5	0.01			
37						1-3	years	3	0.04			
38						4-6	years	3	0.04			
39						7-10	years	4	0.05			
40						11-14	years	4	0.05			
41						15-19	years	5	0.07			
42						20-44	years	25	0.33			
43						45-64	years	20	0.27			
44						65-74	years	10	0.13			
45						75+	years	0	0.00			
46												
47												
48		Mean age-weighted ADRI =			0.068	microgram/kg-day						
49												
50												
51		Assume this ADRI is distributed lognormally in a population, all exposed at the proposed MCL										
52												
53			The mean of this lognormal distribution is Cell E48 =					0.068				
54			The GSD of this lognormal distribution is				1.75					
55												
56												
57		We will multiply the mean value in Cell E48 by a "variability factor" which has a mean of 1 and a GSD equal to Cell G54										
58			The median of this lognormal distribution is mean * exp(-LN^2(GSD)/2) =							0.86		
59												
60			This "variability factor" has a sampled value of:					6.21				
61												
62		We then sample for the value of ADRI for an individual, multiplying the sampled "variability factor" in Cell H60										
63			by the mean age-weighted ADRI value in Cell E48:									
64												
65				Sampled ADRI =		0.42	microgram/kg-day					
66												
67												
68		The median slope factor for this compound is:					3.00E-05	per microgram/kg-day			**Meta-Analysis**	
69		The GSD of this lognormal distribution is					2.2					
70												
71												
72											Pc	
73		The sampled slope factor			#1		3.36E-05	per microgram/kg-day			1.42E-05	Pc1
74					#2		2.23E-05				9.36E-06	Pc2
75					#3		9.35E-05				3.93E-05	Pc3
76					#4		1.09E-05				4.57E-06	Pc4
77					#5		6.07E-05				2.55E-05	Pc5
78					#6		1.50E-05				6.30E-06	Pc6
79					#7		7.65E-06				3.22E-06	Pc7
80					#8		2.75E-05				1.16E-05	Pc8
81					#9		3.26E-05				1.37E-05	Pc9
82					#10		1.28E-05				5.36E-06	Pc10
83					#11		1.04E-05				4.37E-06	Pc11
84					#12		4.90E-06				2.06E-06	Pc12
85					#13		1.94E-05				8.16E-06	Pc13
86					#14		3.58E-05				1.51E-05	Pc14
87					#15		4.01E-05				1.69E-05	Pc15
88					#16		3.16E-05				1.33E-05	Pc16
89					#17		3.20E-05				1.34E-05	Pc17
90					#18		2.26E-05				9.52E-06	Pc18
91					#19		3.70E-05				1.56E-05	Pc19
92					#20		2.66E-05				1.12E-05	Pc20

	A	B	C	D	E	F	G	H	I	J	K	L
1	**Intersubject Variability in ADRI and Risk**											
2												
3		Enter the proposed MCL:			1	microgram/L						
4												
5												
6						**Age**		**IR/BW**				
7		Mean value of IR/BW for age group:				<0.5	months	0.0524	L/kg-day			
8						0.5-0.9	months	0.0362	L/kg-day			
9		(Source: EPA Exposure Factor Handbook)				1-3	years	0.0468	L/kg-day			
10		pp.3-6				4-6	years	0.0379	L/kg-day			
11						7-10	years	0.0269	L/kg-day			
12						11-14	years	0.0202	L/kg-day			
13						15-19	years	0.0164	L/kg-day			
14						20-44	years	0.0186	L/kg-day			
15						45-64	years	0.0220	L/kg-day			
16						65-74	years	0.0219	L/kg-day			
17						75+	years	0.0216	L/kg-day			
18												
19												
20						**Age**		**ADRI**				
21		ADRI by age group:				<0.5	months	0.0524	microgram/kg-day			
22						0.5-0.9	months	0.0362	microgram/kg-day			
23						1-3	years	0.0468	microgram/kg-day			
24						4-6	years	0.0379	microgram/kg-day			
25						7-10	years	0.0269	microgram/kg-day			
26						11-14	years	0.0202	microgram/kg-day			
27						15-19	years	0.0164	microgram/kg-day			
28						20-44	years	0.0186	microgram/kg-day			
29						45-64	years	0.022	microgram/kg-day			
30						65-74	years	0.0219	microgram/kg-day			
31						75+	years	0.0216	microgram/kg-day			
32												
33												
34						**Age**		**Length**	**Fraction of 75 year lifetime**			
35		Age weighted ADRI:				<0.5	months	0.5	0.01			
36						0.5-0.9	months	0.5	0.01			
37						1-3	years	3	0.04			
38						4-6	years	3	0.04			
39						7-10	years	4	0.05			
40						11-14	years	4	0.05			
41						15-19	years	5	0.07			
42						20-44	years	25	0.33			
43						45-64	years	20	0.27			
44						65-74	years	10	0.13			
45						75+	years	0	0.00			
46												
47												
48		Mean age-weighted ADRI =			0.023	microgram/kg-day						
49												
50												
51		Assume this ADRI is distributed lognormally in a population, all exposed at the proposed MCL										
52												
53			The mean of this lognormal distribution is Cell E48 =					0.023				
54			The GSD of this lognormal distribution is				1.75					
55												
56												
57		We will multiply the mean value in Cell E48 by a "variability factor" which has a mean of 1 and a GSD equal to Cell G54										
58			The median of this lognormal distribution is mean * exp(-LN^2(GSD)/2) =							0.86		
59												
60			This "variability factor" has a sampled value of:					6.21				
61												
62		We then sample for the value of ADRI for an individual, multiplying the sampled "variability factor" in Cell H60										
63			by the mean age-weighted ADRI value in Cell E48:									
64												
65				Sampled ADRI =		0.14	microgram/kg-day					
66												
67												
68		The median slope factor for this compound is:					3.00E-05	per microgram/kg-day			**Meta-Analysis**	
69		The GSD of this lognormal distribution is					2.2					
70												
71												
72											Pc	
73		The sampled slope factor			#1		3.36E-05	per microgram/kg-day			4.72E-06	Pc1
74					#2		2.23E-05				3.12E-06	Pc2
75					#3		9.35E-05				1.31E-05	Pc3
76					#4		1.09E-05				1.52E-06	Pc4
77					#5		6.07E-05				8.50E-06	Pc5
78					#6		1.50E-05				2.10E-06	Pc6
79					#7		7.65E-06				1.07E-06	Pc7
80					#8		2.75E-05				3.86E-06	Pc8
81					#9		3.26E-05				4.58E-06	Pc9
82					#10		1.28E-05				1.79E-06	Pc10
83					#11		1.04E-05				1.46E-06	Pc11
84					#12		4.90E-06				6.88E-07	Pc12
85					#13		1.94E-05				2.72E-06	Pc13
86					#14		3.58E-05				5.03E-06	Pc14
87					#15		4.01E-05				5.62E-06	Pc15
88					#16		3.16E-05				4.43E-06	Pc16
89					#17		3.20E-05				4.48E-06	Pc17
90					#18		2.26E-05				3.17E-06	Pc18
91					#19		3.70E-05				5.19E-06	Pc19
92					#20		2.66E-05				3.73E-06	Pc20

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