

ARSENIC-CONTAMINATED SOILS

Toxicological Parameters

Discussion Materials

Prepared for the Science Advisory Board

May 2004

I. Background Information

A wide range of health effects have been associated with exposure to arsenic. These include skin problems (e.g., hyperpigmentation, skin keratosis), gastrointestinal problems (e.g., nausea, diarrhea), nerve damage, diabetes, cardiovascular effects (e.g., hypertension) and several forms of cancer (e.g., skin, bladder, lung). Ecology typically uses slope factors and reference doses published in the Environmental Protection Agency's (EPA) Integrated Risk Information System (IRIS) database to characterize the toxicity/carcinogenicity of hazardous substances when establishing cleanup standards under the Model Toxics Control Act (MTCA) Cleanup Regulation unless (1) a value is not available in the IRIS database for a particular substance or (2) Ecology determines that there is clear and convincing scientific evidence which demonstrates that the use of a published value is inappropriate.

EPA has published a reference dose for chronic oral exposure (0.0003 mg/kg/day), an oral cancer slope factor (1.5 (mg/kg/day)⁻¹) and an inhalation unit risk factor (0.0043 (ug/m³)⁻¹). IRIS does not contain a reference dose based on acute or sub-chronic exposure. These values were published in 1993 and updated in 1998. Since those updates, an extensive amount of new scientific information has become available on the toxicity and carcinogenic characteristics of arsenic. During the last five years, the Agency for Toxic Substances and Disease Registry, the National Research Council, the Environmental Protection Agency and the California Office of Environmental Health Hazard (OEHHA) have completed comprehensive reviews and evaluations of the available scientific information. The State of California, the Environmental Protection Agency and the Consumer Product Safety Commission have used the new information to establish toxicity measures that are different than the IRIS values, and have used those toxicity measures to support decisions on drinking water standards and use of chromated copper arsenate (CCA)-treated play equipment.

Ecology is currently evaluating how to use the new scientific information on arsenic toxicity and carcinogenicity as it designs and implements programs to address arsenic-contaminated soils. The MTCA Cleanup Regulation establishes several procedural and substantive requirements to guide such evaluations. WAC 173-340-702(15) specifies:

(15) New scientific information. The department shall consider new scientific information when establishing cleanup levels and remediation levels for individual sites. In making a determination on how to use this new information, the department shall, as appropriate, consult with the science advisory board, the department of health and the United States Environmental Protection Agency. Any proposal to use new scientific information shall meet the quality of information requirements in subsection (16) of this section.....

WAC 173-340-702(15) specifically directs Ecology to consider new scientific information when establishing cleanup levels and remediation levels for individual sites. While the present evaluation is not designed to establish cleanup levels or remediation levels for individual sites, Ecology believes that the quality of information requirements provides a sound framework for considering the information and issues associated with selecting an appropriate cancer slope factor (or range of values) for the present evaluation. Ecology's initial review of the quality of information requirements is discussed below.

II. Questions for the Science Advisory Board

Ecology is currently working with the Science Advisory Board to complete a review of Ecology's working definition for moderate levels of arsenic- and lead-contaminated soils. The working definition was developed using (1) the reference dose for chronic oral exposure published in the IRIS database, (2) the oral slope factor published in the IRIS database and (3) a toxicity measure based on acute/sub-chronic exposure developed by the Washington Department of Health. Ecology is currently evaluating how to use new scientific information when deciding how to address arsenic-contaminated soils that Ecology would like the Board to address:

- ***Does the SAB agree with Ecology's conclusion that there is clear and convincing scientific evidence to support the use of an oral slope factor for inorganic arsenic that is significantly different than the value published in the IRIS database? If yes, does the SAB agree with Ecology's conclusion that slope factors between 3.7 and 23 (mg/kg/day)⁻¹ represent a range of scientifically defensible values?***

Ecology believes there is clear and convincing scientific evidence supporting the development and use of an oral slope factor based on increased rates of bladder and lung cancer. The primary rationale for concluding there is clear and convincing evidence supporting the use of a cancer slope factor that is different than the value currently published in the IRIS database is based on three main considerations: (1) Study results from several countries provide evidence that ingestion of inorganic arsenic increases the risks of lung cancer, bladder cancer and possibly other internal cancers (e.g., kidney). The National Research Council (2001) concluded that "...internal cancers are more appropriate as an endpoint for risk assessment than non-melanomic skin cancer because internal cancers are more life-threatening..."; (2) Results from several of these studies provide dose response information that can be used to calculate cancer slope factors. The cancer slope factors calculated using this information range from 3.7 to 23 (mg/kg/day)⁻¹; the range of estimated slope factors are considerably higher than the IRIS value; and (3) Study results from Taiwan, Chile and Argentina indicate that excess deaths attributable to skin cancer represent <1 to 10 percent of the total excess cancer deaths due to lung, bladder, kidney and skin cancer observed in those studies. While there is considerable uncertainty associated with these and other slope factor estimates, it appears that sole reliance on the IRIS slope factor may underestimate the upper bound on overall cancer risks associated with arsenic exposure.

- ***Does the SAB agree with Ecology's conclusion that the chronic oral reference dose published in the IRIS database remains an appropriate value for use in evaluating chronic human exposure to soils containing elevated concentrations of inorganic arsenic?***

Ecology believes that the chronic oral reference dose published in the IRIS database remains an appropriate value for use in evaluating chronic human exposure to arsenic-contaminated soils. The primary rationale for this conclusion includes three main considerations: (1) the IRIS value was developed through a process that involved extensive review and analysis that considered available studies, uncertainties and potential confounding factors; (2) the primary study used to estimate a "no observed adverse effect level" (NOAEL) involved a large study population that included sensitive individuals; and (3) EPA applied an uncertainty factor of 3 to account for lack of data on reproductive

toxicity as a critical effect and some uncertainty on whether the NOAEL accounts for all sensitive individuals. Ecology is aware that several studies published subsequent to the completion of the EPA value provide sufficient dose-response information to calculate reference doses for other types of non-cancer health effects (other than skin lesions). The range of calculated values includes values that are an order of magnitude higher or lower than the IRIS value. However, the vast majority of calculated values fall within a factor of 3 (higher or lower) of the IRIS value which is similar to the range of uncertainty reflected in EPA's guidance on the use of the current IRIS value¹.

- ***Does the SAB agree with Ecology's conclusion that there is clear and convincing scientific evidence to support the use of an acute reference dose for arsenic that is different than the chronic reference dose published in the IRIS database? If yes, does the SAB agree that a value of 0.005 mg/kg/day is within the range of scientifically defensible values?***

Ecology believes it is appropriate to use an oral reference dose of 0.005 mg/kg/day to characterize the health risks associated with acute and sub-chronic exposure to arsenic-contaminated soils. This value was developed by the Washington Department of Health (White, 1999) to support cleanup decisions at the Everett Smelter site and is consistent with the range of values being used by other state and federal environmental agencies. It was developed using widely accepted scientific methods.

¹ EPA (1998) stated "...[t]here was not a clear consensus among Agency scientists on the oral RfD. Applying the Agency's RfD methodology, strong scientific arguments can be made for various values within a factor of 2 or 3 of the currently recommended RfD value, i.e., 0.1 to 0.8 ug/kg/day. It should be noted, however, that the RfD methodology, by definition, yields a number with inherent uncertainty spanning perhaps an order of magnitude. New data that possibly impact on the recommended RfD for arsenic will be evaluated by the Work Group as it becomes available. Risk managers should recognize the considerable flexibility afforded them in formulating regulatory decisions when uncertainty and lack of clear consensus are taken into account."

II. Quality of Information Analysis

Oral Slope Factor

The Environmental Protection Agency's (EPA) has published an oral slope factor in the Integrated Risk Information System (IRIS) database. The value in the IRIS database ($1.5 \text{ (mg/kg/day)}^{-1}$) is based on a study where increased rates of skin cancer were observed among residents in villages in southwestern Taiwan where drinking water wells had elevated levels of arsenic. When preparing the IRIS value, EPA reviewed the results of several studies reporting an association between elevated levels of arsenic in drinking water and increased rates of several internal cancers. However, EPA concluded that "...[d]ose response data have not been developed for internal cancers for the Taiwanese population. The data of Chen et al. are considered inadequate at present..." (EPA, 1998). Subsequent to publishing the updated IRIS value, an extensive amount of new scientific information has become available on relationships between exposure to inorganic arsenic in drinking water and increased rates of lung and bladder cancer. During the last five years, the National Research Council (NRC, 1999, 2001), the Environmental Protection Agency (2000a) and the California Office of Environmental Health Hazard (OEHHA, 2004) have completed comprehensive reviews and evaluations of the available scientific information.

Ecology believes there is clear and convincing scientific evidence supporting the development and use of an oral slope factor based on increased rates of bladder and lung cancer. Studies conducted in Taiwan, Chile, Argentina and Japan provide (1) sufficient evidence to conclude that ingestion of inorganic arsenic increases the risk of developing lung and bladder cancers and (2) dose-response data that is sufficient to calculate an oral slope factor. Ecology believes that the range of slope factors calculated from these studies ($3.7 - 23 \text{ (mg/kg/day)}^{-1}$) represents a range of scientifically plausible values for use in evaluating health risks associated with arsenic-contaminated soils.

- (i) ***Whether the information is based on a theory or technique that has widespread acceptance within the relevant scientific community.***

Summary: The methods used to develop oral slope factors are based on several theories and principles:

- 1) **Sufficient Evidence of Carcinogenicity:** It is scientifically valid to classify a substance as a human carcinogen based on results from well-conducted human studies showing increased cancer incidence/mortality.
- 2) **Use of Study Results to Predict Risks in Other Population Groups:** It is scientifically valid to use the results of increased cancer incidence/mortality from various study populations (i.e., residents of southwest Taiwan, Chile and Argentina) to predict cancer risks in the United States population;
- 3) **Lack of a Threshold for Cancer Effects:** Unless substance-specific evidence is available demonstrating a threshold for carcinogenic effects, it is scientifically valid to assume any level of arsenic exposure increases the probability of

developing cancer and that the probability of developing cancer increases with increasing exposure.

- 4) High-to-Low Dose Extrapolation: It is appropriate to extrapolate cancer risks observed at high levels of exposure in the study populations to predict cancer risks at lower exposures in the United States population.

There is widespread acceptance of these theories and principles within the scientific and regulatory community. Over the last 5 years, the Environmental Protection Agency, several scientific review committees and the State of California have developed or reviewed oral cancer slope factors based on increased incidence of bladder and lung cancer. While there are differences in the technical methods used to derive the various oral slope factors, all of these efforts reflect general acceptance of the four principles summarized above.

- National Research Council (1999) – Arsenic in Drinking Water
- EPA Drinking Water Program (2000a) – National Primary Drinking Water Regulations: Arsenic and Clarifications to Compliance and New Source Contaminants Monitoring: Notice of Data Availability;
- EPA Science Advisory Board (2000) – Arsenic Proposed Drinking Water Regulation: A Science Advisory Board Review of Certain Elements of the Proposal;
- National Research Council (2001) – Arsenic in Drinking Water: 2001 Update.
- EPA Office of Pesticide Programs (2003) – A Probabilistic Risk Assessment for Children Who Contact CCA-Treated Playsets and Decks – Draft Preliminary Report (November, 2003)
- California Environmental Protection Agency/Office of Environmental and Human Health Assessment (2004) – Arsenic in Drinking Water – California Public Health Goal.

(ii) *Whether the information was derived using standard testing methods or other widely accepted scientific methods.*

Summary: The range of cancer slope factors developed by different agencies, scientific panels and individuals are all based on the results from peer-reviewed studies that have been evaluated using widely accepted risk assessment methods. However, there are several sources of uncertainty (e.g., shape of dose-response curve). Much of the variability in cancer slope factors can be traced to the use of different methods for dealing with these sources of uncertainty. Examples of methodological differences include:

- Mathematical Models for Extrapolating from High-to-Low Exposure Levels: The shape of the dose-response curve for arsenic-induced cancer is one of the largest sources of uncertainty in arsenic risk assessment. There is currently no clear biological basis for selecting a statistical model to extrapolate results from high-to-low arsenic exposures. In the most recent scientific reviews (NRC 1999;

EPA, 2000d; and NRC, 2001), several scientific panels have concluded that the general Poisson approach is an appropriate method to use in estimating low-dose risks. However, the various analyses have been performed using different relative risk models (additive vs. multiplicative) and different comparison populations (internal vs. external comparison).

- Estimating Exposure Levels in the Study Population: The primary studies used to develop cancer slope factors used broad exposure classifications based on the levels of arsenic in village drinking water wells. When calculating a cancer slope factor, the risk assessor must make assumptions regarding (1) the amount of water consumed in the study population and U.S. population; (2) the amount of arsenic exposure resulting from dietary exposure; and (3) the average body weights in both the study and U.S. population. The various analyses have been performed using different assumptions about drinking water intake, dietary exposure and body weights.

(iii) ***Whether a review of relevant scientific information, both in support of and not in support of the proposed modification, has been provided along with the rationale explaining the reasons for the proposed modification.***

Summary: Ecology has reviewed the reports from scientific review committees, the current scientific literature and recent regulatory analyses in order to identify key issues and the range of viewpoints on those issues. The primary rationale for concluding there is clear and convincing scientific evidence supporting the use of a cancer slope factor that is different than the value currently published in the IRIS database includes the following:

- Study results from several countries provide evidence that ingestion of inorganic arsenic increases the risks of lung cancer, bladder cancer and possibly other internal cancers (e.g., kidney). The NRC (2001) concluded that "...internal cancers are more appropriate as an endpoint for risk assessment than non-melanomic skin cancer because internal cancers are more life-threatening..." (p. 68).
- Results from several of these studies provide dose response information that can be used to calculate cancer slope factors. The cancer slope factors calculated using this information range from 3.7 to 23 (mg/kg/day)⁻¹; the range of estimated slope factors are considerably higher than the IRIS value; and
- Study results from Taiwan, Chile and Argentina indicate that excess deaths attributable to skin cancer represent <1 to 10 percent of the total excess cancer deaths due to lung, bladder, kidney and skin cancer observed in those studies. While there is considerable uncertainty associated with these and other slope factor estimates, it appears that sole reliance on the IRIS slope factor may underestimate the upper bound on overall cancer risks associated with arsenic exposure.

There are several arguments that have been used to support a position that the current slope factor is inappropriate for estimating cancer risks posed by arsenic-contaminated soils. Many of the same arguments could also be raised in the context of the slope factor based on internal cancers. These include:

- It is not appropriate to use a linear non-threshold model when evaluating cancer risks associated with arsenic exposure, and slope factors based on a linear model are likely to overestimate cancer risks in the United States.
- The assumptions used to estimate arsenic exposure levels in the Taiwanese studies are too low and produce cancer slope factors that overestimate cancer risks in the United States.
- There are several differences between the study populations (southwestern Taiwan) and United States population that raise questions about the validity of slope factors based on results from those studies.
- Epidemiology studies of United States residents exposed to elevated levels of inorganic arsenic in drinking water have not reported increases in the types of cancers commonly associated with arsenic exposure. The recent study of bladder cancer in the western United States (Steinmaus, et al., 2003) suggests a lower potency for bladder cancer than predicted by cancer models. However, the studies also suggest a higher risk among smokers.

Most of this information was considered by the National Research Council (NRC) during its review of the health risks associated with exposure to arsenic in drinking water. While acknowledging some of these arguments had merit, the concluded that the weight of scientific evidence supported the conclusion that exposure to arsenic increases the risk of several types of internal cancers and that internal cancers should be considered in the risk assessment process. The NRC considered these issues when selecting the methods for characterizing arsenic's carcinogenic potential.

- (iv) ***Whether the assumptions used in applying the information to the facility are valid and would ensure the proposed modification would err on behalf of protection of human health and the environment.***

Summary: There are many sources of uncertainty and variability that complicate efforts to establish cancer slope factors, and regulatory agencies often must make assumptions when using available information to establish health-based concentrations. Most of the arguments against the use of a slope factor based on internal cancers (or in support of a lower value) reflect legitimate differences of opinion on how to address such uncertainties. The key assumptions underlying the cancer slope factor are valid and appear to err on behalf of protection of human health, in particular:

- the more recent slope factor estimates consider multiple cancer types;
- the various slope factors were estimated using a non-threshold cancer model;
- the assumptions used to estimate exposure levels in study populations represent scientifically plausible estimates that are health-protective; and

- the study populations include groups that may be more susceptible to the health effects associated with arsenic exposure (e.g., poor nutritional status).
- (v) ***Whether the information adequately addresses populations that are more highly exposed than the population as a whole and are reasonably likely to be present at the site.***

Summary: Young children generally receive a higher average daily dose of arsenic per body weight than older age groups because of (1) behavior differences that result in higher incidental soil ingestion rates and (2) greater absorption of ingested arsenic. Young children may also be more sensitive than adults and older children (on a per unit-body weight basis) because they are unable to detoxify and eliminate hazardous substances as rapidly as adults. For example, methylation of inorganic arsenic affects its toxicity and carcinogenicity, and some studies indicate that children have lower rates of methylation of inorganic arsenic than adults. However, methylation is no longer thought to be only a detoxification process. Consequently, it is unclear whether differences in methylation rates would increase or decrease intrinsic sensitivity to inorganic arsenic. Ginsberg (2003) has reviewed information in the IRIS database and concluded that “short-term exposures in early life are likely to yield a greater tumor response than short-term exposures in adults, but similar response when compared to long-term exposure in adults.”² EPA (2003d) has published an external review draft document³ which presents an approach for assessing cancer susceptibility from early-life exposures. EPA (2003a) considered this issue when evaluating the health risks associated with exposure to CCA-treated wood and concluded that (1) “...the data needed to account for an accurate representation of early-life exposure to arsenic appears to be insufficient...” and (2) “... an adjustment factor does not appear to be appropriate in the cancer risk assessment associated with arsenic exposure...”. The latter conclusion appears to be based on two main points. First, EPA notes that the NRC (2001) concluded that inorganic arsenic and its metabolites have been shown to induce chromosomal alterations and large deletion mutations – but not point mutations. Second, EPA noted that the cancer slope factor is based on epidemiology studies where the study population includes the sensitive population groups exposed to inorganic arsenic during the most sensitive periods of time.

- (vi) ***Whether adequate quality assurance and quality control procedures have been used, any significant anomalies are adequately explained, the limitations of the information are identified and the known or potential rate of error is acceptable.***

Summary: Ecology has relied on studies and committee analyses that have been subjected to extensive public and peer review.

² Ginsberg (2003) concluded that risks resulting from early-life exposure can be 10-fold higher than risks from exposure of similar duration later in life.

³ *Supplemental Guidance for Assessing Cancer Susceptibility from Early Life Exposure to Carcinogens* (EPA, 2003)

Chronic Reference Dose

The Environmental Protection Agency (EPA) has published a reference dose for chronic oral exposure in the Integrated Risk Information System (IRIS) database. The value in the IRIS database (0.0003 mg/kg/day) is based on a study where increased rates of skin lesions and possible vascular complications were observed among residents in villages in southwestern Taiwan where drinking water wells had elevated levels of arsenic. Subsequent to publishing the updated IRIS value, an extensive amount of new scientific information has become available on relationships between exposure to inorganic arsenic in drinking water and other types of non-cancer health effects (e.g., hypertension, cerebrovascular disease, diabetes mellitus, heart disease and developmental neurotoxicity). During the last five years, the National Research Council (NRC), the Environmental Protection Agency and the California Office of Environmental Health Hazard (OEHHA) have completed comprehensive reviews and evaluations of the available scientific information.

Ecology believes that the chronic oral reference dose published in the IRIS database remains an appropriate value for use in evaluating chronic human exposure to arsenic-contaminated soils. The primary rationale for this conclusion includes three main considerations: (1) the IRIS value was developed through a process that involved extensive review and analysis that considered available studies, uncertainties and potential confounding factors; (2) the primary study used to estimate a NOAEL involved a large study population that included sensitive individuals; and (3) EPA applied an uncertainty factor of 3 to account for lack of data on reproductive toxicity as a critical effect and some uncertainty on whether the NOAEL accounts for all sensitive individuals. Ecology is aware that several studies published subsequent to the completion of the EPA value provide sufficient dose-response information to calculate reference doses for other types of non-cancer health effects (other than skin lesions). The range of calculated values includes values that are an order of magnitude higher or lower than the IRIS value. However, the vast majority of calculated values fall within a factor of 3 (higher or lower) than the IRIS value which is similar to the range of uncertainty reflected in EPA's guidance on the use of the current IRIS value⁴.

- (i) ***Whether the information is based on a theory or technique that has widespread acceptance within the relevant scientific community.***

Summary: The approach for establishing reference doses is widely used by state, federal and international environmental agencies to identify environmental levels that are unlikely to cause adverse effects in humans. The general theories and principles underlying this approach have broad scientific acceptance and are reflected in the risk assessment methods used by the Environmental Protection Agency, the World Health Organization and scientific panels charged with reviewing and providing recommendations on hazardous substances (including arsenic).

⁴ EPA (1998) stated "...[t]here was not a clear consensus among Agency scientists on the oral RfD. Applying the Agency's RfD methodology, strong scientific arguments can be made for various values within a factor of 2 or 3 of the currently recommended RfD value, i.e., 0.1 to 0.8 ug/kg/day. It should be noted, however, that the RfD methodology, by definition, yields a number with inherent uncertainty spanning perhaps an order of magnitude. New data that possibly impact on the recommended RfD for arsenic will be evaluated by the Work Group as it becomes available. Risk managers should recognize the considerable flexibility afforded them in formulating regulatory decisions when uncertainty and lack of clear consensus are taken into account."

(ii) *Whether the information was derived using standard testing methods or other widely accepted scientific methods.*

Summary: The approach for identifying reference doses or similar measures of non-cancer health effects (e.g., Minimal Risk Level, acceptable daily intakes) relies on widely accepted scientific methods. The methodology is widely used by state, federal and international health and environmental agencies to identify environmental levels that are unlikely to cause adverse effects in humans. In its simplest form, the approach for establishing a reference dose involves five basic steps:

- Identify critical health endpoints using the results from animal bioassays or human epidemiology studies.
- Identify a point of departure for critical health endpoints using the results from animal bioassays or human epidemiology studies. Traditionally, the point of departure is defined by either the “no observed adverse effect level” (NOAEL) or “lowest observable adverse effect” (LOAEL). In addition, EPA is using the Benchmark Dose or Effective Dose (ED) to define the point of departure. For example, the ED₀₁ would be an effective dose for 1% of the population. The LED₀₁ would be the 95% lower confidence limit for the ED₀₁.
- Identify appropriate uncertainty factors that take into account (1) variations in response among different species (UF_A) (2) variations in individual sensitivity (UF_H); (3) extrapolation from results involving less-than-chronic exposure (UF_S); (4) extrapolation from a LOAEL to a NOAEL (UF_L); (5) data gaps (UF_D). An uncertainty factor of 1, 3 or 10 is assigned, as appropriate, to each of these areas, with cumulative uncertainty factors ranging from 1 to 1000 or more.
- Identify an appropriate modifying factor that takes into account factors such as differences in the absorption of a chemical from food and water.
- Calculate a reference dose by dividing the NOAEL or equivalent measure by the various uncertainty and modifying factors using the following equation.

$$\text{Reference dose (mg/kg/day)} = \text{Point of Departure (e.g., NOAEL)} / (\text{UF} * \text{MF})$$

(iii) *Whether a review of relevant scientific information, both in support of and not in support of the proposed modification, has been provided along with the rationale explaining the reasons for the proposed modification.*

Summary: Ecology is not proposing to use a reference dose for chronic oral exposure that is different than the value published in the IRIS database. However, Ecology recognizes that available scientific studies provide sufficient dose-response data to calculate reference doses for chronic oral exposure for several types of non-cancer health effects (other than skin lesions) that are different than the value published in the IRIS database. Consequently, arguments can be made to continue to use the current IRIS value, calculate a lower value or calculate a higher value.

- Calculating a Lower Value: The IRIS value was published in the mid-1990's, and there have been numerous studies completed since that time that provide

dose-response information that is suitable for calculating reference doses based on several health endpoints (many of which are considered to represent more severe health effects than skin lesions). The OEHHA (2004) has reviewed most of the recent studies on the health effects associated with exposure to elevated levels of inorganic arsenic in drinking water, and used the EPA Benchmark Dose software to calculate ED₀₁ and LED₀₁ values. OEHHA used the results of those analyses to develop a health protection concentration for arsenic in drinking water. However, the ED₀₁ and LED₀₁ values can also be used as points of departure to calculate a range of reference doses for chronic oral exposure. The calculated values (shown in Table 7 below) generally fall within a range that is roughly an order of magnitude higher or lower than the current IRIS value. OEHHA established a non-cancer health protection concentration of 0.9 ug/dL. That value is based on a study by Chiou et al. (1997) who reported an increased prevalence of cerebrovascular disease among residents in northeast Taiwan. This corresponds to a reference dose (or equivalent parameter) of 0.0001 mg/kg/day. This value is based on a more severe health effect (cerebrovascular disease) than the IRIS value (skin lesions) and is two-to-three times lower than the current EPA value.

- Calculating a Higher Value: It is also possible to argue for the use of a higher value, given newer studies and information that has become available since EPA published in the IRIS value. For example, the studies that formed the basis for the chronic reference dose (Tseng 1977; Tseng et al. 1968) contain limited information on arsenic exposure other than the average drinking water concentrations in each village. In calculating the NOAEL value, EPA made several assumptions on water intake and dietary intake of arsenic in order to express the NOAEL value in units of mg/kg/day⁵. NRC (2001) reviewed these assumptions (in the context of cancer risks) and recommended the use of different estimates for water intake and dietary contributions of arsenic. Use of the NRC values would result in a calculated NOAEL that is slightly higher than the EPA value (0.001 mg/kg/day vs. 0.0008 mg/kg/day). However, the difference between the two values is well within the range of plausible values identified by EPA in the IRIS summary. In addition, the primary studies used to establish the current reference dose used broad exposure classifications that tend to underestimate the exposure levels for people found to have arsenic-related skin lesions. Despite these and other issues, it is difficult to envision a convincing set of arguments that would serve to justify the use of a higher value given the results of EPA's original analysis in support of the IRIS value, the conclusions of the National Research Council and the range of results from the OEHHA dose-response assessments.

⁵ EPA used the exposure assumptions similar to those used in calculating the oral slope factor: (1) the average arsenic levels in drinking water were 0.009 mg/L which was the arithmetic mean of a range of values from 0.001 to 0.017; (2) the average person consumed 4.5 L of water/day and weighed 55 kgs.; (3) consumption of sweet potatoes and rice were assumed to contribute an additional 0.002 mg/day of arsenic.

- (iv) *Whether the assumptions used in applying the information to the facility are valid and would ensure the proposed modification would err on behalf of protection of human health and the environment.*

Summary: There are many sources of uncertainty and variability that complicate efforts to establish reference doses and regulatory agencies. However, Ecology believes that the methods and key assumptions underlying the reference dose for chronic oral exposure remain valid and appear to err on behalf of protection of human health.

- (v) *Whether the information adequately addresses populations that are more highly exposed than the population as a whole and are reasonably likely to be present at the site.*

Summary: Young children generally receive a higher average daily dose of arsenic per body weight than older age groups because of (1) behavior differences that result in higher incidental soil ingestion rates and (2) greater absorption of ingested arsenic. Young children may also be more sensitive than adults and older children (on a per unit-body weight basis) because they are unable to detoxify and eliminate hazardous substances as rapidly as adults. The National Research Council (2001) reviewed this issue and concluded that "...[i]t is unclear whether infants and young children might be more susceptible to arsenic induced health effects, particularly those for non-cancer end points where less-than-lifetime exposures are important and children's greater water consumption per unit of body weight might put them at relatively greater risk" (p. 160).

- (vi) *Whether adequate quality assurance and quality control procedures have been used, any significant anomalies are adequately explained, the limitations of the information are identified and the known or potential rate of error is acceptable.*

Summary: Ecology has relied on studies and committee analyses that have undergone extensive public and peer review.

Oral Reference Dose (Less-Than-Lifetime Exposure)

EPA's IRIS database has no published reference dose for less-than-lifetime exposure for inorganic arsenic. When preparing the working definition for moderate levels of arsenic-contaminated soils, Ecology used an oral reference dose of 0.005 mg/kg/day to characterize the health risks associated with acute and sub-chronic exposure to arsenic-contaminated soils. This value was developed by the Washington Department of Health to support cleanup decisions at the Everett Smelter site and is based on an evaluation of health studies and case reports prepared by the Washington Department of Health (DOH).

- (i) ***Whether the information is based on a theory or technique that has widespread acceptance within the relevant scientific community.***

Summary: The approach for establishing reference doses is widely used by state, federal and international environmental agencies to identify environmental levels that are unlikely to cause adverse effects in humans. The general theories and principles underlying this approach have broad scientific acceptance and are reflected in the risk assessment methods used by the Environmental Protection Agency, the World Health Organization and scientific panels charged with reviewing and providing recommendations on hazardous substances (including arsenic).

- (ii) ***Whether the information was derived using standard testing methods or other widely accepted scientific methods.***

Summary: The approach for identifying reference doses or similar measures of non-cancer health effects (e.g., acceptable daily intakes) relies on widely accepted scientific methods. As discussed in the previous section, the basic methodology is widely used by health and environmental agencies to identify environmental levels that are unlikely to cause adverse effects in humans.

- (iii) ***Whether a review of relevant scientific information, both in support of and not in support of the proposed modification, has been provided along with the rationale explaining the reasons for the proposed modification.***

Summary: The Washington Department of Health (DOH) reviewed the available data⁶ on the acute and sub-chronic toxicity of arsenic. DOH concluded that 0.05 mg/kg/day represents a best estimate of the LOAEL based on several studies that reported transient adverse health effects in people who ingested 0.035 to 0.071 milligrams of arsenic per kilogram of body weight as a single dose, or over the course

⁶ Studies reviewed by DOH included (1) a study by Mizuta et al. (1956) in which 400 people in Japan reported multiple adverse health effects from the ingestion of soy sauce contaminated with arsenic, (2) a report by Franzblau and Lilis (1989) of a husband and wife who experienced a variety of health effects following the periodic (1-2 times per week) ingestion of drinking water containing 9,000 to 10,900 ug/L of arsenic, (3) a report of adverse health effects experienced by a family after ingesting well water containing 108 ug/L of arsenic (Armstrong, et al. 1984) and (4) reports of adverse health effects following the use arsenical compounds as medicines (Solis-Cohen and Githens, 1928).

of one day⁷. DOH used an uncertainty factor of 10 to extrapolate from the LOAEL to a NOAEL. A 10-fold uncertainty factor was considered appropriate for extrapolating from the LOAEL to a NOAEL⁸ because (1) of the severity of symptoms noted in some patients near or moderately above a LOAEL of 0.05 mg/kg/day (e.g., peripheral neuropathy, gastrointestinal bleeding, liver damage, low blood counts, CNS dysfunction and abnormal electrocardiograms); (2) humans appear to be more sensitive to arsenic's toxic effects than animals; and (3) there is little information on the dose-response relationships for arsenic. Tsuji et al. (2004) have argued against the use of uncertainty factors larger than 10 because (1) a reference dose of 0.005 mg/kg/day is less than an order of magnitude above the chronic NOAEL and (2) the weight of evidence indicates that arsenic toxicity at lower exposure levels is a function of cumulative dose.

The Agency for Toxic Substances and Disease Registry (ATSDR) (2000a) and EPA (2002, 2003) have also conducted extensive reviews of the scientific literature and developed reference doses ranging from 0.0017 mg/kg/day to 0.015 mg/kg/day. Similar to the DOH review, EPA and ATSDR concluded that 0.005 represents a reasonable estimate of the LOAEL. However, the evaluations reached different conclusions regarding the appropriate uncertainty factors (3 vs. 10 vs. 30) to be used to establish a reference dose (or similar measure of toxicity). The rationale for using uncertainty factors of 30 and 3 are summarized below:

- Uncertainty Factor = 30: EPA (2003a) developed a reference dose of 0.0017 mg/kg/day using an uncertainty factor of 30 to extrapolate from the LOAEL to a NOAEL. This was based on recommendations from the FIFRA Scientific Advisory Panel charged with reviewing EPA's approach for evaluating health risks posed by the use of chromated copper arsenate (CCR)-treated wood. The arguments in support of this approach are summarized in the minutes from the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) Scientific Advisory Panel meeting held October 23-25, 2001. Those arguments include:
 - A LOAEL of 0.05 mg/kg/day is an appropriate LOAEL for evaluating the toxic effects associated with short (1-30 days) and intermediate (31-180 day) arsenic exposure. The FIFRA Panel concluded that, while confidence in dose estimates from Mizuta et al. (1956) and Franzblau and Lilis (1979) is low, the confidence in 0.05 as an appropriate LOAEL is quite high given that other clinical studies have reported symptoms associated with the ingestion of inorganic arsenic.
 - A 10-fold uncertainty factor is appropriate for extrapolating from the LOAEL to a NOAEL because (1) of the severity of symptoms noted in some patients near or moderately above a LOAEL of 0.05 mg/kg/day (e.g., peripheral

⁷ DOH also concluded that 1 mg/kg/day represents a best estimate of a LOAEL for lethal effects based on reported deaths following ingestion of 0.32 mg/kg-day of arsenic (single dose in one individual) and approximately 0.37 to 2.37 mg/kg-day (about one week of exposure for two individuals).

⁸ Alternately, the 10-fold uncertainty factor could be viewed as including two parts: (1) a 3-fold UF for extrapolating from the LOAEL to the NOAEL and (2) a 3-fold UF to account for uncertainties in the database.

neuropathy, gastrointestinal bleeding, liver damage, low blood counts, CNS dysfunction and abnormal electrocardiograms); (2) humans appear to be more sensitive to arsenic's toxic effects than animals; and (3) there is little information on the dose-response relationships for arsenic.

- The majority of the Panel recommended the use of an additional intraspecies uncertainty factor to provide for the protection of children. This was based on the fact that (1) there are groups of children that are at special risk of arsenic toxicity due to nutritional deficiencies and/or concurrent exposure to other components of chromated copper arsenate; (2) there is a high level of uncertainty on the toxicokinetics of arsenic and its metabolites in children; and (3) there is inadequate information on neurological effects of arsenic exposure at or near the LOAEL value.
- Uncertainty Factor = 3: EPA (2002) developed a reference dose of 0.015 mg/kg/day using an uncertainty factor of 3 to extrapolate from the LOAEL to a NOAEL. Tsuji et al. (2004, in press) have reviewed the available information on arsenic health effects and summarized the arguments in support of this approach:
 - The NOAEL appears to be close to the LOAEL, within an order of magnitude or less;
 - Prevalence of effects is based on study populations that are generally 0-9 years old who have had more cumulative exposure (i.e., higher prevalence of effects) and possibly lower calculated dose-per-body weight than a time-weighted average dose from ages 0-6 years.
 - Exposed populations included malnourished children and other sensitive individuals (Chen et al., 2001a; Mazumder et al., 1998; Zaldivar and Guiller, 1977) which may increase susceptibility to arsenic health effects.
 - Populations evaluated for subchronic effects often had in-utero exposure via drinking water. In a risk assessment application in soil, in-utero exposure would be low because of the lower soil ingestion rates of adults/pregnant women compared to children.
 - Doses for water exposure in some studies (e.g., Mazumder et al., 1998) do not include additional exposure from inorganic arsenic in foods or dietary use of water (see Schoof et al., 1998; U.S. EPA, 2000). Thus, actual exposure is greater in these cases.
 - Many of the studies include broad categories of exposure in which exposure misclassification (e.g., use of an average or median dose for a group with a range of exposure) has likely led to underestimation of exposure in study subjects exhibiting effects (Brown et al., 1997), and thereby potential downward bias in the LOAEL.

- (iv) *Whether the assumptions used in applying the information to the facility are valid and would ensure the proposed modification would err on behalf of protection of human health and the environment.*

Summary: There are many sources of uncertainty and variability that complicate efforts to establish reference doses, and regulatory agencies often must make assumptions when using available information to establish health-based concentrations. The key assumptions underlying the reference dose for less than lifetime exposure appear to be valid and err on behalf of protection of human health.

- (v) *Whether the information adequately addresses populations that are more highly exposed than the population as a whole and are reasonably likely to be present at the site.*

Summary: Young children generally receive a higher average daily dose of arsenic per body weight than older age groups because of (1) behavior differences that result in higher incidental soil ingestion rates and (2) greater absorption of ingested arsenic. As note above, available studies do not indicate that children are more sensitive on a per unit-body weight basis where exposure levels are low enough that cumulative exposure over time is more important for predicting health effects than daily doses.

- (vi) *Whether adequate quality assurance and quality control procedures have been used, any significant anomalies are adequately explained, the limitations of the information are identified and the known or potential rate of error is acceptable.*

Summary: Ecology has relied on studies, and committee analyses that have undergone extensive public and peer review.

IV Information and Issues Associated With Evaluating the Toxicity of Inorganic Arsenic

A wide range of health effects have been associated with exposure to arsenic (NRC, 1999; ATSDR, 2000a; NRC, 2001; Goyer and Clarkson, 2001; EPA, 2003a; OHHEA, 2004). These include skin problems (e.g., hyperpigmentation, hyperkeratoses), gastrointestinal problems (e.g., nausea, diarrhea, stomach pain), nerve damage, diabetes, cardiovascular effects (e.g., hypertension) and several forms of cancer (e.g., skin, bladder, lung). In general, cancer is considered the most sensitive health endpoint (NRC, 2001).

Ecology typically uses slope factors and reference doses published in the Integrated Risk Information System (IRIS) database to characterize a substances toxicity/carcinogenicity when establishing cleanup standards under the MTCA Cleanup Regulation unless (1) a value is not available in the IRIS database for a particular substance or (2) Ecology determines that there is clear and convincing scientific evidence that demonstrates that the use of a published value is inappropriate. As discussed below, the IRIS database includes an oral slope factor, an inhalation slope factor⁹ and a reference dose for chronic oral exposure for inorganic arsenic. However, EPA has not published a reference dose for evaluating less-than-lifetime exposures.

This section is organized into three parts:

- Part 1 summarizes the range of cancer slope factors (or equivalent measures of carcinogenicity¹⁰) that have been used to evaluate oral and dermal exposure to elevated levels of inorganic arsenic and various sources of uncertainty and variability associated with the development and use of those values.
- Part 2 summarizes the range of chronic reference doses (or equivalent measures of non-cancer health effects) that have been used to evaluate oral and dermal exposure to elevated levels of inorganic arsenic and various sources of uncertainty and variability associated with the development and use of those values.
- Part 3 summarizes the range of acute and sub-chronic reference doses (or equivalent toxicity measures) that have been used to evaluate oral and dermal exposure to elevated levels of inorganic arsenic and various sources of uncertainty and variability associated with the development and use of those values.

⁹ When evaluating the health risks associated with exposure to arsenic-contaminated soils, Ecology also considers the health risks associated with inhalation of resuspended soils. EPA has published an Inhalation Unit Risk factor for inorganic arsenic of 0.0043 per $\mu\text{g}/\text{cm}^3$ in the Integrated Risk Information System (IRIS) database. This value was based on studies reporting increased rates of lung cancer among smelter workers in Montana (Brown and Chu, 1983a,b; Lee-Feldstein, 1983; Higgins, et al. 1982) and Washington (Enterline and Marsh, 1982). The EPA value represents the geometric mean of values from the two locations (Anaconda smelter (MT) geometric mean = 2.56E-3; Asarco smelter (WA) geometric mean = 7.19E-3). An inhalation unit risk factor of 4.3E-3 corresponds to a cancer slope factor of 15.1 mg/kg/day.

¹⁰ Both the NRC (2001), EPA (2000a) and OEHHA (2004) have developed measures of toxicity or carcinogenicity that are not expressed in terms of mg/kg/day. The measures can be transformed to a reference dose (expressed in terms of mg/kg/day) or cancer slope factor (expressed in terms of $(\text{mg}/\text{kg}/\text{day})^{-1}$) using the risk equations specified in WAC 173-340-720.

1. Cancer Slope Factors Used to Evaluate Oral and Dermal Exposure

Arsenic is classified as a “carcinogen”¹¹ under the MTCA Cleanup Regulation, a “known human carcinogen” (Group A) by the Environmental Protection Agency, “carcinogenic to humans” (Group 1) by the International Agency for Research on Cancer (IARC, 1987) and a “known to be” human carcinogen by the National Toxicology Program (NTP, 2002). The initial identification of arsenic as a known human carcinogen was based on studies showing an increased incidence of lung cancer among workers exposed to elevated levels of arsenic (Brown and Chu, 1983a, b; Lee-Feldstein, 1983; Higgins et al. 1982; Enterline and Marsh, 1982). Exposure to elevated levels of arsenic in drinking water was subsequently found to be associated with increased rates of skin cancer among populations in Taiwan (Tseng et al. 1968; Tseng, 1977). Additional studies of these populations have reported increased rates of lung, bladder, kidney and liver cancer among population groups exposed to elevated levels of arsenic in drinking water (Chen et al. 1985; Chen et al. 1988; Wu et al. 1989; Chen et al. 1992; Ferreccio et al. 2000; Smith et al. 1998; Tsuda et al. 1995; Hopenhayn-Rich et al. 1998).

Slope factors are used to characterize the relationship between exposure to a substance and the increased likelihood of developing cancer. The slope factor is used to estimate the probability (upper bound) that an individual will develop cancer as a result of exposure to a potential carcinogen. Slope factors are developed from the dose-response curves observed in human or animal studies. A wide range of slope factors (or equivalent measures) have been developed to evaluate the health risks posed by exposure to elevated levels of inorganic arsenic. These values are summarized in Table 1 and briefly discussed below.

¹¹ Under MTCA, “Carcinogen” means any substance or agent that produces or tends to produce cancer in humans. For implementation of this chapter, the term “carcinogen” will apply to substances on the United States Environmental Protection Agency lists of A (known human) and B (probable human), and any substance which causes a significant increased incidence of benign or malignant tumors in a single, well-conducted animal bioassay, consistent with the weight of evidence approach specified in the United States Environmental Protection Agency’s Guidelines for Carcinogen Risk Assessment as set forth in 51 FR 33992 et seq. as presently published or as subsequently amended or republished. (WAC 173-340-200)

Table 1: Summary of Range of Carcinogenic Slope Factors ((mg/kg/day) ⁻¹)				
Source	Value	Cancer Type	Studies	Extrapolation Method
Integrated Risk Information System (IRIS) (EPA, 1998)	1.5	Skin	Tseng et al. 1968; Tseng, 1977	Time- and dose-related formulation of the multistage model (Multiplicative Poisson)
National Research Council (1999)	1.1	Bladder	Chen et al. 1985, 1988, 1992; Wu et al. 1989	Multiplicative Poisson model (internal comparison group & linear extrapolation)
EPA Office of Drinking Water (EPA, 2001a)	0.4 - 3.7	Bladder and Lung	Chen et al. 1985, 1988, 1992; Wu et al. 1989 (analyses by Morales et al. 2000)	Multiplicative Poisson model (internal comparison group & linear extrapolation)
National Research Council (2001)	4.7 – 23	Bladder and Lung	Chen et al. 1985, 1992; Wu et al. 1989	Additive Poisson model (external comparison (SW Taiwan region) & linear extrap.)
Consumer Product Safety Commission (CPSC, 2003)	0.4 – 23	Bladder and Lung	Chen et al. 1985, 1988, 1992; Wu et al. 1989 (analyses by Morales et al. 2000)	Combination of EPA (2001a) and NRC (2001)
EPA Office of Pesticide Programs (OPP) (EPA, 2003a)	3.7	Bladder and Lung	Chen et al. 1985, 1988, 1992; Wu et al. 1989 (analyses by Morales et al. 2000)	Based on EPA (2001a)
California Office of Environmental Health Hazard Assessment (2004)	8 – 16	Bladder and Lung	Chen et al. (1985, 1988); Hopenhyn-Rich et al. (1996, 1998); Ferruccio et al. (2000); Smith et al. (1998); Tsuda et al. (1995)	

- **Integrated Risk Information System (IRIS):** EPA has published a cancer slope factor of 1.5¹² (mg/kg/day)⁻¹ in the IRIS database. This value is currently used by state and federal Superfund programs to evaluate health risks. The slope factor is based on the skin cancer prevalence and well-water data published by Tseng and coworkers (Tseng et al. 1968; Tseng, 1977). EPA used the multistage model to predict dose-specific and age-specific skin cancer prevalence rates associated with exposure to inorganic arsenic and extrapolated the risk estimates to the United States population based on assumptions about U.S. and Taiwan body weights and drinking water consumption. At that time, EPA concluded that the dose-response data for internal cancers developed by Chen et al. (1992) were not adequate to establish cancer unit risks/slope factors.

¹² The maximum likelihood estimates ranged from 1 to 2 (mg/kg/day)-1

- National Research Council (1999): The first NRC report on arsenic in drinking water provides an extensive discussion of the relevant studies and important statistical modeling issues associated with evaluating the risks of developing cancer as a result of oral exposure to inorganic arsenic. The report cautions that risk assessors should consider the choice of model, the choice of comparison population, the shape of the extrapolation curve and factors that could affect the arsenic-cancer relationships (e.g., diet, genetics). The NRC recommended using data on internal cancers (e.g., bladder, lung) to conduct risk assessments¹³ and included a range of unit risk factors based on bladder cancer data to illustrate the importance of model choices.
- EPA Office of Drinking Water: EPA used a range of slope factors ($0.4 - 3.7 \text{ (mg/kg/day)}^{-1}$) when evaluating the health risks associated with exposure to inorganic arsenic in drinking water (EPA, 2000a, 2001a). This range was based on EPA's analysis of the lung and bladder cancer data from southwestern Taiwan (Chen et al. 1988; Wu et al. 1989) and took into account recommendations from the NRC (1999), reviews and recommendations from EPA's Science Advisory Board (EPA, 2000d) and statistical analyses by Morales et al. (2000).
- National Research Council (2001): EPA requested that the National Research Council review scientific studies that had been published since its 1999 report and provide a critique of the approach used by the Office of Drinking Water to evaluate cancer risks. NRC (2001) based its review of the data from southwestern Taiwan (Chen et al. 1985; Chen et al. 1988; Wu et al. 1989; Chen et al. 1992) and the analysis by Morales et al. (2000). NRC considered several possible extrapolation models. The committee eventually selected an approach to characterize cancer risks that, while conceptually similar to earlier approaches (e.g., use of data from studies in southwest Taiwan, use of Poisson model), reflected several methodological differences that produce risk values that are higher than the risk values calculated by the earlier NRC committee. These differences include: (1) use of an additive Poisson model (as opposed to the multiplicative model used by NRC (1999)); (2) use of an external comparison group (as opposed to an internal comparison group); (3) use of an approach developed in the analysis of lung cancer from radon exposure to extrapolate from the Taiwan population to the U.S. population (NRC 1988); and (4) use of different assumptions on drinking water rates and dietary exposure. The NRC used the results of their evaluations to estimate the increased cancer risks associated with different levels of arsenic in drinking water. Although the NRC did not publish a slope factor, it is possible to derive a range of slope factors ($4.7 - 23 \text{ (mg/kg/day)}^{-1}$) based on the committee's risk calculations shown in Table 6-1 of their report.¹⁴

¹³ The NRC Subcommittee on Arsenic in Drinking Water (NRC, 1999) concluded "...that there is sufficient evidence from human epidemiological studies in Taiwan, Chile, and Argentina that chronic ingestion of inorganic arsenic causes bladder and lung cancer, as well as skin cancer...."

¹⁴ Table 6.1 of the NRC Report provides theoretical maximum likelihood estimates for excess lifetime cancer risk of lung and bladder cancer for the U.S. population exposed at various concentrations of arsenic in drinking water. The incidence estimates (expressed as cancer incidence per 10,000 people) can be used to calculate cancer slope factors using the standard risk assessment equation (cancer risk = slope factor x drinking water concentration x drinking water consumption rate/body weight). The range of calculated values are based on the average of male and female incidence estimates and different combinations of assumptions on (1) drinking water consumption (1 L/day or 2 L/day), (2) body weight (70 kg) and (3) background cancer rate (United States or Taiwan).

- Consumer Product Safety Commission (CPSC): The CPSC Directorate of Health Sciences used a range of cancer slope factors ($0.41 - 23 \text{ (mg/kg/day)}^{-1}$) when evaluating the health risks associated with exposure to chromated copper arsenate (CCA)-treated wood (CPSC, 2003). This reflects the full range of values extending from the low-end of the range calculated by the EPA Drinking Water Program (0.41) to the high end of the range of values (23) calculated from information in the NRC (2001) report.
- EPA Office of Pesticide Programs (OPP): The OPP used the upper-bound estimate prepared by the EPA drinking water program ($3.67 \text{ (mg/kg/day)}^{-1}$) when evaluating the health risks associated with exposure to CCA– treated wood (EPA, 2003a)¹⁵.
- California Office of Environmental Health Hazard Assessment (OEHHA): The California OEHHA has developed a public health goal for arsenic in drinking water based on carcinogenic and non-carcinogenic health effects. The public health goal (0.004 ug/L) for arsenic in drinking water is based on the increased lung and bladder cancer mortality rates observed in epidemiology studies of populations in Taiwan, Chile and Argentina. OEHHA used the results from those studies to calculate a cancer unit risk of $2.7 \times 10^{-4} \text{ (ug/L)}^{-1}$ which is based on lung and bladder tumors (combined) for both sexes. OEHHA used a low-dose linear extrapolation approach similar to that used by the National Research Council (NRC, 2001). The OEHHA cancer unit risk value can be used to calculate a cancer slope factor by solving the standard risk assessment equation ($\text{Risk} = \text{slope factor} \times \text{drinking water concentration} \times \text{drinking water consumption rate/body weight}$)¹⁶. Cancer slope factors based on the OEHHA cancer unit risk range from $8 - 16 \text{ (mg/kg/day)}^{-1}$.

All of the slope factors summarized in Table 1 have a plausible scientific basis. However, there are several sources of uncertainty¹⁷ and variability¹⁸ that complicate the interpretation and use of these values. While some of the variability in values in Table 1 reflects the fact that the values were developed at different times (with newer information being available for more recent values), much of the variability is due to the different approaches used to address these sources of uncertainty and variability. Specifically, the range of values reflects differences in the following:

- Choice of cancer endpoints used to develop slope factors;
- Choice of mathematical model used to estimate cancer risks;

¹⁵ EPA asked the FIFRA Science Advisory Panel to “...comment on whether in this probabilistic approach of using the upper-bound arsenic cancer slope factor combined with a high-end LADDs would result in an overestimation of risk for the more highly exposed percentiles of the population?...”. The panel’s response to this issue included the following: “...it is not appropriate to characterize the quoted arsenic cancer slope factor as an “upper bound”. The arsenic cancer slope factor cited in the document is derived from a central estimate ED01 from an analysis by Morales et al. (2000). Further work has since been done and published by Chen et al. (2003a,b) and the National Research Council (2001). Thus, more recent work presented updated estimates of arsenic cancer risks from both Taiwanese and Chilean studies that appear to predict higher risks than the slope factor characterized as an “upper bound” in the question to the Panel...” (EPA, 2004, p. 65).

¹⁶ Risk is set equal to 10^{-6} , the drinking water concentration is set equal to the unit cancer risk value

¹⁷ For purposes of this review, “uncertainty” refers to the lack of knowledge about the true value of a quantity and/or lack of knowledge about which of several models best describe a process.

¹⁸ For purposes of this review, “variability” refers to the heterogeneity of values (e.g., exposure, metabolism, etc.) over time, locations or individuals.

- Choice of methods and assumptions used to estimate exposure in study populations;
- Choice of factors to account for uncertainty and variability in human susceptibility.

Some of these methods and assumptions are briefly discussed below.

- **Choice of Cancer Endpoint Used to Develop Slope Factors:** Chronic exposure to inorganic arsenic in drinking water has been found to be associated with increased risk of developing lung, bladder, skin and kidney cancer. Some of the variation in published slope factors is due to the fact that the available values are based on different cancer endpoints or combinations of cancer endpoints: (1) the slope factor published in the IRIS database is based on skin cancer prevalence data; (2) the NRC (1999) value is based on bladder cancer mortality; and (3) the EPA (2001), NRC (2001) and OEHHA (2004) values are based on bladder and lung cancer mortality data. Given current information, approaches based on a combination of lung and bladder cancer are considered superior to approaches based on a single cancer endpoint. However, use of this approach reflects an underlying assumption that lung and bladder cancer are the most important contributors to overall cancer risk. The OEHHA (2004) evaluated this assumption by incorporating the added risk of dying from skin and kidney cancer by using the ratio of the total excess cancer deaths relative to excess lung cancer deaths from all studies. Based on that analysis, OEHHA concluded that cancer potency estimates based on all four cancer endpoints was approximately 20 percent higher than potency estimates based solely on lung and bladder cancer.
- **Choice of Mathematical Model Used to Estimate Cancer Risks:** The shape of the dose-response curve for arsenic-induced cancer is one of the largest sources of uncertainty in arsenic risk assessment. There is currently no clear biological basis for selecting a model to extrapolate results from high-to-low arsenic exposures. Most recent scientific reviews (NRC 1999; EPA, 2000d; and NRC, 2001) have concluded that the general Poisson approach is an appropriate method for evaluating cancer risks posed by oral exposure to inorganic arsenic.
 - **Dose-Response Relationships:** All of the values in Table 1 are based on the assumption that there is a linear relationship between cancer risks and arsenic exposure at low doses. However, there is a great deal of uncertainty regarding the shape of the dose-response curve for arsenic at low exposure levels. This uncertainty leaves room for multiple opinions on this issue. For example, as part of their review of Ecology's plans for cleanup of the Everett Smelter Site, Asarco argued that the assumption of linearity of arsenic risk at low dose is false¹⁹. However, EPA (2000a) reviewed this issue and concluded there is no basis for determining the shape of a sub-linear dose response curve for inorganic arsenic. The EPA Science Advisory Board (EPA, 2000d) and the National Research Council (NRC, 2001) both agreed with EPA's conclusions²⁰. For example, the

¹⁹ Asarco's rationale for their opinion included: (1) there is no known biological mechanism by which arsenic could have this effect (i.e., it does not cause somatic changes in DNA, and the potential biological mechanisms by which it might affect cancer risk are all associated with a sub-linear dose response or a practical threshold below which arsenic has no adverse effect; (2) arsenic is a demonstrated essential element in animals and a likely essential nutrient for humans; and (3) humans methylate inorganic arsenic to organic forms that are quickly eliminated through the urine (see Aldrich, 1999).

²⁰ The Science Advisory Board (EPA, 2000) concluded that the "available data do not yet meet EPA's new criteria for departing from linear extrapolation of cancer risk".

NRC (2001) concluded that "...[t]he current mode of action data are insufficient to guide the selection of a specific dose-response model. The additive Poisson model with linear term in dose is a biologically plausible model that provides a satisfactory fit to the epidemiological data and represents a reasonable model choice for use in the arsenic risk assessment..." (p. 209).

- **Relative Risk Model:** While the various scientific reviews appeared to agree that the Poisson approach is an appropriate method for evaluating cancer risks, these groups reached different conclusions on the choice of relative risk model. Specifically, the NRC (1999) and the EPA Science Advisory Board concluded it was appropriate to use a multiplicative model of relative risk (i.e., assumes that cumulative exposure to arsenic increases the risk of lung and bladder cancer by a factor that multiplies the background mortality rate). The committee selected this approach based on their conclusion that it is consistent with the expected trend for lung and bladder cancer with age. However, the NRC (2001) reviewed those evaluations and noted several limitations²¹ and recommended the use of an additive risk model (assumes that the same cumulative exposure causes the same absolute increase in risk at all ages). The committee's choice was based on considerations of biological plausibility and consistency with other recommended approaches for quantitative dose response assessment (Smith et al. 1992). As shown in Table 2, the ED₀₁'s calculated using an additive risk model tend to be lower (and slope factors tend to be higher) than values based on a multiplicative risk model.

Table 2: Comparison of ED₀₁ and Estimated Slope Factors Using Multiplicative and Additive Risk Models (Based on data from Table 5.3 of NRC (2001) (slope factor calculations are based on 2 L/day and 70 kg body weight).			
Cancer Endpoint	Model Assumptions	ED₀₁ (LED₀₁)	Slope Factor
Lung (Male)	Multiplicative (linear dose)	84 (72)	4.2 (4.9)
	Additive (linear dose)	38 (37)	9.2 (9.5)
Bladder (Male)	Multiplicative (linear dose)	317 (286)	1.1 (1.2)
	Additive (linear dose)	102 (94)	3.4 (3.7)
Lung (Female)	Multiplicative (linear dose)	94 (84)	3.7 (4.2)
	Additive (linear dose)	33 (31)	10.6 (11.3)
Bladder (Female)	Multiplicative (linear dose)	443 (406)	0.8 (0.9)
	Additive (linear dose)	138 (125)	2.5 (2.8)

²¹ (1) It was not straightforward to incorporate the baseline cancer risk based on the US population – better approach is to base the ED calculation on the BEIR IV formula used in analysis of lung cancer mortality associated with radon; (2) If the baseline risks in the US are higher than Taiwan, then the use of the BEIR IV approach will result in lower ED₀₁'s than alternative approaches (earlier approaches).

- **Internal vs. External Comparison Populations:** The slope factors based on bladder and lung cancer were developed using two types of comparison populations. The values developed by NRC (1999) and EPA (2000²²) used the variation in cancer rates between villages to determine the dose-response relationship (internal comparison group). However, the NRC (2001²³) values were developed by comparing cancer rates in the study population (SW Taiwan) with the cancer rates in a separate comparison population (the entire Taiwanese population) (external comparison group). As shown in Table 3, the estimated ED₀₁'s tend to be lower (and slope factors tend to be higher) for models that incorporate an external comparison population (i.e., the entire Taiwanese population). However, the choice of comparison population does not appear to have as large an effect on ED₀₁ and LED₀₁ values as other methodological choices.

Table 3: Comparison of ED₀₁'s and Slope Factors Calculated With Internal and External Comparison Populations (Based on Table 10-12 of NRC 1999)			
Cancer Endpoint	Methods & Assumptions	ED₀₁ (LED₀₁)	Slope Factor
Bladder (Male)	Multiplicative (linear dose) – Internal Comparison	404 (323)	0.9 (1.1)
Bladder (Male)	Multiplicative (linear dose) – External Comparison	443 (407)	0.8 (0.9)

- **Choice of Methods and Assumptions Used to Estimate Exposure in Study Populations:** The primary studies used to develop cancer slope factors used broad exposure classifications based on the levels of arsenic in village drinking water wells. When calculating a cancer slope factor, the risk assessor must make assumptions regarding (1) the amount of water consumed in the study population and U.S. population, (2) the amount of arsenic exposure resulting from dietary exposure; and (3) the average body weights in the both the study and U.S. population. The various analyses have been performed using different assumptions about drinking water intake, dietary exposure and body weights. In general, assumptions that

²² EPA (2000a) selected a model that did not use an external comparison group. This choice was based on consideration of several factors: (1) EPA found that most of the models that incorporate an external comparison population result in a dose response that is supra-linear at low doses, and EPA concluded there is no evidence to support such a relationship; (2) recommendations from the EPA Science Advisory Board that supported EPA choice; (3) models with external comparison groups were found to be more stable in the evaluation performed by Morales et al. (2000); and (4) SAB consensus that that the comparison populations (the overall Taiwan population) were not appropriate control groups for the study area.

²³ NRC (2001) carefully considered this issue and concluded that it was appropriate to use a model that includes an external comparison group. This was based on several lines of reasoning including: (1) a recent paper by Tsai et al. does not support claim that SW Taiwanese population differs from overall Taiwan population in important ways that affect cancer rates; (2) available dose-response data cannot distinguish between linear and supra-linear models; (3) mechanistic arguments for a sub-linear dose response curve do not necessarily apply at the population level; (4) evidence that a supra-linear dose response is plausible (it could result from a subpopulation that is susceptible to low doses of arsenic and/or dose misclassification due to high concentrations in food or movement of people between villages; and (5) results based on the use of an external comparison group are less likely to be affected by measurement error because the model fit is anchored by a large comparison group.

lead to higher arsenic exposure estimates (mg/kg/day) in the study population result in lower cancer slope factor estimates.

- **Water Consumption Rates:** In order to estimate the cancer risks associated with a particular level of arsenic in drinking water, the risk assessor must make assumptions about water consumption in both the U.S. population and the study population. For example, most of the assessments reflect the assumption that the Taiwanese consume more water per body weight than the U.S. population. However, some of the variations in slope factor estimates reflect different assumptions on the relative water intake rates. In general, assumptions that increase the estimated water intake for the Taiwanese population result in a lower slope factor. The assumptions used in the various assessments are summarized in Table 4.

Source	Taiwanese Population	U.S. Population
Integrated Risk Information System (IRIS) (EPA, 1998)	Taiwanese male weighs 55 kg and drinks 3.5 L of water/day. Taiwanese female weighs 50 kg and drinks 2 L of water/day	“Reference” U.S. resident weighs 70 kg and consumes 2 liters of water per day
EPA Office of Drinking Water (EPA, 2001)	Taiwanese male weighs 55 kg and drinks 3.5 L of water/day. Taiwanese female weighs 50 kg and drinks 2 L of water/day	Monte Carlo Analysis of CSFII water intakes
National Research Council (2001)	Exposures equal to 3 times U.S. default rate	Mean daily average from CSFII of 1 L/day for males and females

- **Contribution of Arsenic in Diet to Overall Exposure and Health Risks:** The various assessments have made exposure adjustments based on the assumption that the staple foods in the southwestern Taiwanese region (rice and sweet potatoes) absorb a great deal of water when cooked and, consequently, increased the amount of arsenic exposure in the study area. Some of the variations in slope factor estimates reflect different assumptions on the amount of dietary arsenic exposure. In general, assumptions that increase the estimated dietary arsenic intake for the Taiwanese population result in lower slope factors. The assumptions used in the various assessments are summarized in Table 5.

Source	Methods and Assumptions
Integrated Risk Information System (IRIS) (EPA, 1998)	
EPA Office of Drinking Water (EPA, 2001)	Adjusted lower bound estimates by assuming that people in the study area consumed an additional L of water per day (absorption of water in rice and sweet potatoes). Also multiplied lower bound estimate by fraction of arsenic consumed per kilogram contributed by drinking water
National Research Council (2001)	Added 30 ug/day to estimated arsenic drinking water intakes to account for arsenic in food.

- Choice of Factors to Account for Uncertainty and Variability in Human Susceptibility: There is considerable variability in people's response to similar levels of arsenic exposure. Such variability may arise due to variations in arsenic metabolism, interactions with other chemicals, nutritional differences or other factors.
 - Variation in Metabolism: The NRC (2001) concluded that the extent to which metabolic variability affects a person's susceptibility to cancer or systemic toxicity with arsenic exposure is an important uncertainty. The committee summarized several studies indicating variability in enzyme activity and methylated forms of arsenic. They also noted that methylation of arsenic (previously considered as a detoxification pathway) now appears to also play a role in converting inorganic arsenic into more toxic forms as part of the metabolic process leading to excretion from the body.
 - Nutritional Status: Poor nutrition may increase a person's susceptibility to arsenic and other hazardous substances. This may occur as result of (1) low intake of fruits and vegetables with bioactive constituents that protect against cancer; (2) protein deficiencies that may affect the ability to methylate arsenic; or (3) other factors. ATSDR (1999) summarized studies indicating that arsenic absorption and child susceptibility to arsenic are increased by several types of nutritional deficiencies (e.g., calcium, vitamin D, iron, zinc and others). Asarco and others have argued that the Taiwan data are not applicable to the U.S. population because of significant differences in nutritional status between the two populations. However, the NRC (2001) reviewed this issue and concluded that it was unlikely that confounding by diet is responsible for the association between arsenic exposure and cancer.²⁴

²⁴ The National Research Council reached several conclusions on the question of whether dietary differences between Southwest Taiwan and U.S. populations were a significant confounding factor: (1) the magnitude of observed effects is so high that it cannot be accounted for by known or hypothesized dietary factors; (2) diet has rarely been found to be a significant source of confounding in other situations where dietary factors have been explicitly studied; and (3) in the absence of clear evidence of a biological mechanism for arsenic-induced cancer, the possibility of a relatively minor degree of unmeasured confounding remains, even if diet is an unlikely candidate.

- Interactions With Other Chemicals: Cadmium and lead exposure have been found to inhibit arsenic methylation and, consequently, also affect arsenic toxicity. Zinc and copper appear to have antagonistic effects. Studies also suggest that manganese may increase arsenic absorption and retention.
- Early-Life Exposures: Ginsberg (2003) states that for a “vast majority of chemicals that have cancer potency estimates on IRIS, the underlying database is deficient with respect to early-life exposures.” He concluded that based on the results of his study “short-term exposures in early life are likely to yield a greater tumor response than short-term exposures in adults, but similar response when compared to long-term exposure in adults.” He estimated that risks resulting from early-life exposure could be 10-fold higher than risks from exposure of similar duration later in life. EPA (2003d) has published an external review draft document²⁵ which presents an approach for assessing cancer susceptibility from early-life exposures. EPA (2003a) considered this issue when evaluating the health risks associated with exposure to CCA-treated wood. EPA concluded that (1) “...the data needed to account for an accurate representation of early-life exposure to arsenic appears to be insufficient...” and (2) “... an adjustment factor does not appear to be appropriate in the cancer risk assessment associated with arsenic exposure...” The latter conclusion appears to be based on two main points. First, EPA notes that the NRC (2001) concluded that inorganic arsenic and its metabolites have been shown to induce chromosomal alterations and large deletion mutations – but not point mutations. Second, EPA noted that the cancer slope factor is based on epidemiology studies where the study population includes the sensitive population groups exposed to inorganic arsenic during the most sensitive periods of time. However, EPA noted there are new studies that indicate that exposure to arsenic from drinking water during pregnancy may be associated with decreased birth weights (Hopenhayn, 2003) and increased cancer incidence in children later in life (Waalkes, 2003).
- Form of Arsenic Causing Health Effects: The NRC (2001) summarized several studies that indicate that inorganic forms of arsenic are not solely responsible for the toxic effects of arsenic. They recommended that future risk assessments should provide quantitative information on how the intake of inorganic arsenic is related to concentration of arsenic metabolites in the urine and to bladder cancer. The EPA Science Advisory Board considered this issue and concluded that since the principal forms of arsenic in drinking water are inorganic – it was appropriate to make inorganic arsenic the regulatory focus. A similar situation exists with respect to arsenic-contaminated soils.

²⁵ *Supplemental Guidance for Assessing Cancer Susceptibility from Early Life Exposure to Carcinogens* (USEPA, 2003)

2 Reference Doses Used to Evaluate Chronic Oral and Dermal Exposure

Reference doses²⁶ are used to evaluate the potential for non-cancer health effects following exposure to hazardous substances. Several chronic reference doses or equivalent toxicity measures have been developed to evaluate the health risks posed by exposure to elevated levels of arsenic. Those values are summarized in Table 6 and briefly discussed below.

Source	RfD	Primary Studies	Critical Effects	NOAEL/LOAEL	Uncertainty Factors
Environmental Protection Agency (EPA, 1998)	3 E-04	Tseng, 1977; Tseng et al. 1968	Skin lesions	0.0008 (NOAEL)	3X (human variability)
Agency for Toxic Substances & Disease Registry (ATSDR, 2000)	3 E-04	Tseng, 1977; Tseng et al. 1968.	Skin lesions	0.0008 (NOAEL)	3X (human variability)
Consumer Product Safety Commission (CPSC, 2003)	8 E-05	Tseng, 1977; Tseng et al. 1968	Skin lesions	0.0008 (NOAEL)	10X (human variability)
California Office of Environmental Health Hazard Assessment (2004)	1.4 E-04	Chiou et al. 1997	Cerebrovascular disease	3 (mg/L)yr (LED01 = LOAEL)	10X (human variability)

- Environmental Protection Agency:** EPA has published a chronic oral reference dose for inorganic arsenic of 0.0003²⁷ mg/kg/day in the Integrated Risk Information System (IRIS) database. This value was based on studies by Tseng et al. (1968) and Tseng (1977) which reported increased incidence of skin lesions (e.g., hyperpigmentation and keratosis) and possible vascular complications among populations exposed to elevated levels of arsenic in drinking water. The results of these studies were used to calculate a NOAEL of 0.0008 mg/kg/day. When calculating the reference dose, EPA used an uncertainty factor of 3 "...to account for both the lack of data to preclude reproductive toxicity as a critical effect and to

²⁶ Reference doses are duration-specific estimates (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive groups) that is likely to be without an appreciable risk of deleterious effects – even in sensitive individuals. Reference doses are derived from the “No-observed-adverse-effect level” (NOAEL) or “Lowest-observed-adverse-effect level” (LOAEL) observed in human or animal studies by consistent application of uncertainty factors.

²⁷ EPA included a note in the IRIS entry which states: “NOTE: There was not a clear consensus among Agency scientists on the oral RfD. Applying the Agency’s RfD methodology, strong scientific arguments can be made for various values within a factor of 2 or 3 of the currently recommended RfD value, i.e., 0.1 to 0.8 ug/kg/day. It should be noted, however, that the RfD methodology, by definition, yields a number with inherent uncertainty spanning perhaps an order of magnitude. New data that possibly impact on the recommended RfD for arsenic will be evaluated by the Work Group as it becomes available. Risk managers should recognize the considerable flexibility afforded them in formulating regulatory decisions when uncertainty and lack of clear consensus are taken into account.”

account for some uncertainty in whether the NOAEL of the critical study accounts for all sensitive individuals²⁸.

- Agency for Toxic Substances and Disease Registry (ATSDR): ATSDR used information, methods and assumptions similar to those used by EPA (1998) to calculate a Minimal Risk Level (MRL) for chronic oral exposure to arsenic of 0.0003 mg/kg/day (ATSDR, 2000a, b).
- Consumer Product Safety Commission (CPSC): For purposes of evaluating the health risks associated with CCA-treated wood, CPSC used a chronic oral acceptable daily intake (ADI) of 0.00008 mg/kg/day. The ADI (which is conceptually similar to EPA's reference dose values²⁹) was estimated by applying an uncertainty factor of 10 (to account for differences in sensitivity among humans) to a NOAEL of 0.0008 mg/kg/day (based on the Tseng, 1977 and Tseng et al. 1968 studies).
- California Office of Environmental Health Hazard Assessment (OEHHA): The OEHHA (2004) has developed a public health goal for arsenic in drinking water based on non-cancer health effects. The non-cancer health protective value (0.9 ug/L) was based on a study by Chiou et al. (1997) who reported an increased prevalence of cerebrovascular disease among residents in northeast Taiwan³⁰. OEHHA used the EPA Benchmark Dose software to calculate ED₀₁ and LED₀₁ values based on the observed relationships between arsenic exposure (using two dose metrics (ug/L and (mg/L/yr) and the prevalence of cerebrovascular disease and cerebral infarction. The approach used to calculate health protective concentrations varied depending on the dose metric used to calculate the LED₀₁ values. For LED₀₁ values based on the ug/L dose metric, the health protection concentration was calculated by multiplying the LED₀₁ by the relative source contribution (0.2) and dividing by the uncertainty factor. For LED₀₁ values based on the (mg/L/yr dose metric, the health protection concentration was calculated by multiplying the LED₀₁ by the relative source contribution and dividing by the uncertainty factor and 70 years. The dose-response assessments underlying the health protection concentrations developed by OEHHA can also be used to calculate reference doses corresponding to the various health effects considered by OEHHA. Specifically, a reference-dose value can be calculated by multiplying the health

²⁸ The NOAEL based on the Tseng et al. and Tseng studies is somewhat limited by the fact that the majority of the study population was less than 20 years of age and skin lesions increase as a function of age.

²⁹ CPSC noted that "both the acceptable daily intake (ADI) and reference dose (RfD) are estimates of the amount of a chemical a person can be exposed to on a daily basis over an extended period of time (up to a lifetime) with a negligible risk of suffering deleterious effects (Hatlid, 2003, p. 16)

³⁰ OEHHA (2004) provided the following summary: "...Chiou et al. (1997) evaluated the dose response relationship between prevalence of cerebrovascular disease and ingested arsenic among residents of the Lanyang Basin in northeast Taiwan. A total of 8102 adults from 3901 households were recruited for the study. Arsenic in well water of each household was determined using hydride generation and atomic absorption spectrometry. Logistic regression analysis was used to estimate multivariate-adjusted odds ratios and 95 percent confidence intervals for various risk factors of cerebrovascular disease. A significant dose response relationship was observed between As concentration in well water and prevalence of cerebrovascular disease after adjustment for age, sex, hypertension, diabetes mellitus, cigarette smoking and alcohol consumption. The dose response was even more prominent for cerebral infarction, with multivariate-adjusted odds ratios (95 percent C.I.) of 1.0, 3.4 (1.6-7.3), 4.5 (2.0-9.9) and 6.9 (3.0-16), respectively, for those who consumed well water with As concentration of 0, 0.1-50.0, 50.1 - 299.9, and > 300 ug/L. For cumulative arsenic exposures of < 0.1, 0.1-4.9 and > 5.0 (mg/L)yr, the odds ratios were 1.00, 2.26, and 2.69 for cerebrovascular disease, and 1.00, 2.66, and 3.39 for cerebral infarction, respectively. All of the values above for As exposed groups were significantly greater than unexposed at p < 0.05 or less..." (pp. 68-69)

protection concentration by 2 L/day and dividing by the relative source contribution (0.2) and 70 kg. The reference-dose value corresponding to the noncancer health protection value (0.9 ug/L) is 0.00012 mg/kg/day.

The chronic reference-dose values summarized above are based on current scientific information. However, there are a number of issues associated with calculating such values for arsenic that are not fully resolved from a scientific standpoint. These issues include:

- **Identification of Critical Endpoints:** When considering the range of non-cancer health effects associated with inorganic arsenic exposure, skin lesions generally are considered to be the most sensitive endpoint. The EPA reference dose is based on skin lesions (hyperpigmentation, keratoses). However, there is some uncertainty on whether skin lesions represent the critical effect. For example, when establishing the RfD value, EPA noted there was limited data on reproductive effects and applied a 3X modifying factor to account for this data gap. The National Research Council (1999, 2001) summarized a number of recent scientific studies where an association between elevated levels of inorganic arsenic in drinking water and increased rates of hypertension and diabetes had been reported (Rahman et al. 1998, 1999; Chen et al. 1995, 1996). More recently, the California OEHHA (2004) has completed an extensive review of the scientific literature to support California's efforts to establish health protection concentrations for arsenic in drinking water. As noted above, the OEHHA prepared dose response assessments based on several different health endpoints using EPA's benchmark dose software and used those values to identify a range of health protection concentrations based on non-cancer effects. Table 7 summarizes the range of health protection concentrations calculated by OEHHA and the reference dose values that correspond to those concentrations. OEHHA (2004) based the non-cancer health protection goal (0.9 ug/L) on its analysis of the results from Chiou et al. (1997). The reference dose (1.4 E-04 mg/kg/day) corresponding to this health protection concentration is approximately half of the EPA value.

**Table 7: Comparison of Reference Doses Calculated Using Dose Response Assessments
Prepared by the Office of Environmental Health Hazard Assessment (OEHHA, 2004)**

Study	Species	Toxicity Endpoint	Dose Response Criterion	Dose	Units	UF	Health Protective Conc. (mg/L)	Calculated RfD (mg/kg/d)
Siripitayakunkit et al. 1999	Human	Developmental neurotoxicity, IQ deficit	LOAEL (est) & LED025	30	ug/L	30	0.0002	3.3E-05
Chiou et al. 1997	Human	Cerebral infarct	LED01	3.5	(mg/L)yr	30	0.00033	5.6E-05
Chen et al. 1996	Human	Ischemic heart disease mortality	LED01	5.5	(mg/L)yr	30	0.00052	8.7E-05
Mazumder et al. 1998	Human	Skin keratosis	LED05	0.00094	mg/kg-d	10	0.0066	9.4E-05
Chiou et al. 1997	Human	Cerebrovascular disease	LED01	3	(mg/L)yr	10	0.00086	1.4E-04
Mazumder et al. 1998	Human	Skin keratosis	LED01	50	ug/L	10	0.001	1.7E-04
Chiou et al. 1997	Human	Cerebral infarct	LED01	166	ug/L	30	0.0011	1.8E-04
Rahman et al. 1999	Human	Hypertension	LED10	5.8	(mg/L)yr	10	0.0016	2.8E-04
Chen et al. 1995	Human	Hypertension	LED10	7.2	(mg/L)yr	10	0.002	3.4E-04
Tseng 1977; Tseng et al. 1968	Human	Skin hyperpigmentation, keratosis	RfD	0.0003	mg/kg-d	3	0.0021	3.0E-04
Lai et al. 1994	Human	Diabetes mellitus	LED05	8.8	(mg/L)yr	10	0.0025	4.2E-04
Chiou et al. 1997	Human	Cerebrovascular disease	LED01	189	ug/L	10	0.0038	6.3E-04
Rahman et al. 1998	Human	Diabetes mellitus	LED05	210	ug/L	10	0.0042	7.0E-04
Wang et al. 2002	Human	Carotid atherosclerosis	LOAEL	20	(mg/L)yr	10	0.006	9.5E-04
Tseng et al. 1996	Human	Peripheral vascular disease	LOAEL (est)	20	(mg/L)yr	10	0.006	9.5E-04
Hanlon & Ferm, 1986	Hamster	Fetal malformation	LOAEL (PBPK adjusted)	2.8	mg/kg-d	1000	0.017	2.8E-03
Heywood & Sortwell, 1979	Monkey	Sudden death, possible CNS effects	LOAEL	2.8	mg/kg-d	1000	0.02	2.8E-03
Byron et al. 1967	Dog	Multiple effects (death, weight loss, etc)	NOAEL	1.25	mg/kg-d	100	0.088	1.3E-02
Byron et al. 1967	Rat	Weight loss, decreased survival, bile duct enlargement	NOAEL	3.12	mg/kg-d	100	0.22	3.1E-02

- **Identification of a Point of Departure** (e.g., NOAEL, LOAEL, ED, LED): Results from animal bioassays or human epidemiology studies/case reports are used to identify a point of departure. Traditionally, the point of departure is defined by either the “no observed adverse effect level” (NOAEL) or “lowest observable adverse effect” (LOAEL). In addition, EPA has developed the Benchmark Dose software package that can be used to calculate Benchmark Doses (BMD) or Effective Doses (ED) values that can be used to define the point of departure.
- **Model Selection and Parameter Choices:** Selection of the point of departure is influenced by choices made by the risk assessor with respect to methods, models and parameters. Table 8 illustrates the range of values that might be derived using the results from Chiou et al. (1997) and approaches that reflect different choices regarding (1) methods for identifying point of departure (BMD approach vs. single dose); (2) dose metric used in the analysis; and (3) effective dose used to estimate point of departure (e.g., LED₀₁, LED₀₅).

Table 8: Comparison of Benchmark Dose Values Based on Dose Response Information for Cerebrovascular Disease (Chiou et al. (1997))						
Regression Method	Point of Departure	BMDL	Dose Metric	UF	HPG	RFD
Quantal Linear	LED01	189	ug/L	10	0.0038	6.3E-04
Quantal Quadratic	LED01	292	ug/L	10	0.0019	9.7E-04
Quantal Linear	LED05	966	ug/L	10	0.0064	3.2E-03
Quantal Quadratic	LED05	659	ug/L	10	0.0044	2.2E-03
Quantal Linear	LED01	2.9	(mg/L)yr	10	0.00028	1.4E-04
Quantal Quadratic	LED01	5.3	(mg/L)yr	10	0.00050	2.5E-04

- **Exposure Estimates:** The primary studies available for calculating reference doses are human studies which generally use broad exposure classifications. When calculating a reference dose, the risk assessor must make assumptions regarding (1) the amount of water consumed in the study population and U.S. population, (2) the amount of arsenic exposure resulting from dietary exposure; and (3) the average body weights in the both the study population and U.S. population. The assumptions used to estimate exposure can have a large impact on the calculation results. In general, assumptions that lead to higher arsenic exposure estimates (mg/kg/day) in the study population result in higher reference dose estimates. For example, the studies that formed the basis for the chronic reference dose (Tseng 1977; Tseng et al. 1968) contain limited information on arsenic exposure other than the average drinking water concentrations in each village. In calculating the NOAEL value, EPA made several assumptions on water intake and dietary intake of arsenic in order to express the NOAEL value in units of mg/kg/day³¹.

³¹ EPA used the exposure assumptions similar to those used in calculating the oral slope factor: (1) the average arsenic levels in drinking water were 0.009 mg/L which was the arithmetic mean of a range of values from 0.001 to

NRC (2001) reviewed these assumptions (in the context of cancer risks) and recommended the use of different estimates for water intake and dietary contributions of arsenic. Use of the NRC values would result in a calculated NOAEL that is slightly higher than the EPA value (0.001 mg/kg/day vs. 0.0008 mg/kg/day). However, the difference between the two values is well within the range of plausible values identified by EPA in the IRIS summary.

- Uncertainty and Modifying Factors to Address Uncertainties and Variability: Identify appropriate uncertainty factors that take into account (1) variations in response among different species (UF_A); (2) variations in individual sensitivity (UF_H); (3) extrapolation from results involving less-than-chronic exposure (UF_S); (4) extrapolation from a LOAEL to a NOAEL (UF_L); and (5) data gaps (UF_D). An uncertainty factor of 1, 3 or 10 is assigned, as appropriate, to each of these areas, with cumulative uncertainty factors ranging from 1 to 1000 or more. EPA used an uncertainty factor of 3 to account for the limited data on reproductive effects and uncertainty on whether the Taiwan studies fully accounted for variations in susceptibility within human population groups. As discussed above, such variability may arise due to genetic variations in arsenic metabolism, interactions with other chemicals, nutritional differences or other factors.

0.017; (2) the average person consumed 4.5 L of water/day and weighed 55 kgs.; (3) consumption of sweet potatoes and rice were assumed to contribute an additional 0.002 mg/day of arsenic.

3 Reference Doses Used to Evaluate Acute and Sub-Chronic Oral and Dermal Exposure

The estimated LD50 from arsenic ingestion is approximately 1-4 mg/kg in humans (ATSDR, 2000). Oral exposure to high non-lethal doses of arsenic causes irritation of the GI tract which leads to nausea and vomiting. Other signs may include neuritis and vascular effects. The initial symptoms associated with sub-chronic exposure to arsenic include vague weakness and nausea. As exposure continues, effects may include diarrhea, vomiting, anemia, injury to blood vessels, damage to kidney and liver and impaired nerve function that leads to a “pins and needles” sensation in the hands and feet.

Several “less-than-lifetime” reference doses or equivalent toxicity measures have been developed to evaluate the health risks posed by exposure to elevated levels of arsenic. Those values are summarized in Table 9 and briefly discussed below.

Source	RfD	Use	Primary Studies	Critical Effects	NOAEL/LOAEL	Uncertainty Factors
Washington Department of Health (DOH, 1999)	0.005 (0.0036 – 0.0071)	Acute & Sub-chronic	Mizuta et al. (1956); Franzblau & Lilis (1979)	GI symptoms, facial edema, neuropathy, skin lesions	0.036 – 0.071 (LOAEL)	10X (LOAEL to NOAEL)
Agency for Toxic Substances & Disease Registry (ATSDR, 2000)	0.005	Acute	Mizuta et al. (1956)	GI symptoms, facial edema, neuropathy, skin lesions	0.05 (LOAEL)	10X (LOAEL to NOAEL)
Environmental Protection Agency (EPA, 2002)	0.015	Acute & Sub-chronic	Mazumder et al. (1998)	Skin keratosis	0.015	1
EPA Office of Pesticide Programs (OPP) (EPA, 2003)	0.0017	Acute & Sub-chronic	Mizuta et al. (1956) Franzblau & Lilis (1979)	GI symptoms, facial edema, neuropathy, skin lesions	0.05 (LOAEL)	3X (intraspecies) 10X (LOAEL to NOAEL)

- Department of Health (White, 1999): The Washington Department of Health (DOH) reviewed the available data on the acute and sub-chronic toxicity of arsenic. DOH concluded that 0.05 mg/kg/day represents a best estimate of the LOAEL based on several studies that reported transient adverse health effects in people who ingested 0.035 to 0.071 milligrams of arsenic per kilogram of body weight as a single dose, or over the course of one day³². DOH used an uncertainty factor of 10 to extrapolate from the LOAEL to a NOAEL. Studies reviewed by DOH included; (1) a study by Mizuta et al. (1956) in which 400 people in Japan reported multiple adverse health effects from the ingestion of soy sauce contaminated with arsenic; (2) a report by Franzblau and Lilis (1989) of a husband and wife who experienced a variety of health effects following the periodic (1-2 times per week) ingestion of drinking water containing 9,000 to 10,900 ug/L of arsenic; (3) a report of adverse health effects

³² DOH also concluded that 1 mg/kg/day represents a best estimate of a LOAEL for lethal effects based on reported deaths following ingestion of 0.32 mg/kg-day of arsenic (single dose in one individual) and approximately 0.37 to 2.37 mg/kg-day (about one week of exposure for two individuals).

experienced by a family after ingesting well water containing 108 ug/L of arsenic (Armstrong et al. 1984); and (4) reports of adverse health effects following the use of arsenical compounds as medicines (Solis-Cohen and Githens, 1928).

- Agency for Toxic Substances and Disease Registry (ATSDR): ATSDR (2000) also reviewed the available data on acute and sub-chronic toxicity of arsenic and identified a LOAEL of 0.05 mg/kg/day based on the Mizuta et al. study. In that study, the exposure level causing effects was estimated to be about 3 mg/day which corresponds to a dose of 0.05 mg/kg/day. Based on this study, ATSDR derived an acute oral MRL of 0.005 mg/kg/day by using an uncertainty factor of 10 to extrapolate from the LOAEL to a NOAEL. ATSDR identifies the acute MRL for arsenic as a provisional value because the gastrointestinal effects and neurological effects observed at the LOAEL were considered serious. ATSDR recommends use of the MRL as a screening value.
- Environmental Protection Agency (2002): EPA Region VIII reviewed the available data on acute and sub-chronic toxicity of arsenic and identified a NOAEL of 0.015 mg/kg/day based on the results from a large cross-sectional study of arsenic-induced skin lesions in children (Mazumder et al. 1998). EPA concluded that an uncertainty factor of 1 was appropriate because the large number of children observed in the study included individuals likely to be sensitive to arsenic exposure. [Note: EPA (2003) reviewed this study and concluded that the effects observed by Mazumder et al. were likely due to chronic arsenic exposure and, consequently, that it was inappropriate to use this study as a basis for evaluating acute or sub-chronic exposure to arsenic.³³]
- EPA Office of Pesticide Programs (OPP): EPA reviewed the available studies on acute and sub-chronic exposure to arsenic and used the information in the case reports of Franzblau and Lilis and Mizuta et al. to select a LOAEL of 0.05 mg/kg/day. The LOAEL was based on reports of facial edema, gastrointestinal symptoms, neuropathy and skin lesions observed in these studies. A “margin of exposure” (MOE) of 30 was applied to the LOAEL to establish a reference dose of 0.0017. The use of an MOE of 30 was recommended by an EPA Science Advisory Panel based on their opinion that (1) the severity of symptoms near or moderately above the LOAEL (0.05 mg/kg/day) warranted a full uncertainty factor of 10 and (2) protection of children warranted an additional uncertainty factor of 3.

The “less-than-lifetime” reference doses summarized above are based on current scientific information. However, there are a number of issues associated with calculating such values for

³³ California Office of Environmental Health Hazard Assessment (OEHHA): has developed a public health goal for arsenic in drinking water based on carcinogenic and non-carcinogenic health effects. In developing those values, the OEHHA used the EPA Benchmark Dose software to calculate ED₀₁ and LED₀₁ values based on the observed relationships between arsenic exposure (using two dose metrics (ug/L and (mg/L/yr) and the prevalence of skin keratosis reported by Mazumder et al. (1998). The LED₀₁ values calculated by OEHHA can be used to calculate reference dose. Specifically, a reference-dose value (expressed as mg/kg/day) can be calculated by multiplying the LED₀₁ value (50 ug/L) by 2 L/day and then dividing by the uncertainty factor identified by OEHHA (10X) and 70 kg. The reference-dose value corresponding to the LED₀₁ calculated from the Mazumder et al. (1998) is 0.00014 mg/kg/day. OEHHA calculated this value for purposes of evaluating chronic arsenic exposure.

arsenic that are not fully resolved from a scientific standpoint. These issues are similar to those discussed in earlier sections and include: (1) uncertainty in arsenic exposure levels in studies; (2) uncertainty factors used to account for intra-individual variations in sensitivity; (3) uncertainty factors used to extrapolate from LOAELs to NOAELs; and (4) identification of critical effects. The different conclusions reached by the four evaluations (EPA, 2003; White, 1999; ATSDR, 2000; EPA, 2002) reflect different approaches for addressing these sources of uncertainty.

- EPA (2003) developed a reference dose of 0.0017 mg/kg/day using an uncertainty factor of 30 to extrapolate from the LOAEL to a NOAEL. This was based on recommendations from the FIFRA Scientific Advisory Panel charged with reviewing EPA's approach for evaluating the health risks posed by the use of chromated copper arsenate (CCA) treated wood. The arguments in support of this approach are summarized in the minutes from the FIFRA Scientific Advisory Panel meeting held on October 23-25, 2001. Those arguments include:
 - A LOAEL of 0.05 mg/kg/day is an appropriate LOAEL for evaluating the toxic effects associated with short (1-30 days) and intermediate (31-180 day) arsenic exposure. The FIFRA Panel concluded that, while confidence in dose estimates from Mizuta et al. (1956) and Franzblau and Lilis (1979) is low, the confidence in 0.05 as an appropriate LOAEL is "quite high" given that other clinical studies have reported symptoms associated with the ingestion of inorganic arsenic.
 - A 10-fold uncertainty factor is appropriate for extrapolating from the LOAEL to a NOAEL because (1) of the severity of symptoms noted in some patients near or moderately above a LOAEL of 0.05 mg/kg/day (e.g., peripheral neuropathy, gastrointestinal bleeding, liver damage, low blood counts, CNS dysfunction and abnormal electrocardiograms); (2) humans appear to be more sensitive to arsenic's toxic effects than animals; and (3) there is little information on the dose-response relationships for arsenic.
 - The majority of the Panel recommended the use of an additional intraspecies uncertainty factor of 3 to provide for the protection of children. This was based on three main factors: (1) there are groups of children that are at special risk of arsenic toxicity due to nutritional deficiencies and/or concurrent exposure to other components of chromated copper arsenate (CCA); (2) there is a high level of uncertainty on the toxicokinetics of arsenic and its metabolites in children; and (3) there is inadequate information on neurological effects of arsenic exposure at or near the LOAEL value.
- Both White (1999) and ATSDR (2000) developed a reference dose (or equivalent measure) of 0.005 mg/kg/day using an uncertainty factor of 10 to extrapolate from the LOAEL to a NOAEL. The arguments in support of this approach include:
 - A LOAEL of 0.05 mg/kg/day is an appropriate LOAEL for evaluating the toxic effects associated with short-term arsenic exposure. The LOAEL is based on the results from several studies and clinical reports.

- A 10-fold uncertainty factor is appropriate for extrapolating from the LOAEL to a NOAEL³⁴ because (1) of the severity of symptoms noted in some patients near or moderately above a LOAEL of 0.05 mg/kg/day (e.g., peripheral neuropathy, gastrointestinal bleeding, liver damage, low blood counts, CNS dysfunction and abnormal electrocardiograms); (2) humans appear to be more sensitive to arsenic's toxic effects than animals; and (3) there is little information on the dose-response relationships for arsenic.
- Neither White (1999) nor ATSDR (2000a) included an additional uncertainty factor (similar to EPA 2003a). Tsuji et al. (2004) have argued against the use of uncertainty factors larger than 10 because (1) a reference dose of 0.005 mg/kg/day is less than an order of magnitude above the chronic NOAEL and (2) the weight of evidence indicates that arsenic toxicity at lower exposure levels is a function of cumulative dose.
- EPA (2002) developed a reference dose of 0.015 mg/kg/day using an uncertainty factor of 3 to extrapolate from the LOAEL to a NOAEL. Tsuji et al. (2004, in press) have reviewed the available information on arsenic health effects and summarized the arguments in support of this approach:
 - The NOAEL appears to be close to the LOAEL, within an order of magnitude or less.
 - Prevalence of effects is based on study populations that are generally 0-9 years old who have had more cumulative exposure (i.e., higher prevalence of effects) and possibly lower calculated dose-per-body weight than a time-weighted average dose from ages 0-6 years.
 - Exposed populations included malnourished children and other sensitive individuals (Chen et al., 2001a; Mazumder et al., 1998; Zaldivar and Guiller, 1977) which may increase susceptibility to arsenic health effects.
 - Populations evaluated for sub-chronic effects often had in-utero exposure via drinking water. In a risk assessment application in soil, in-utero exposure would be low because of the lower soil ingestion rates of adults/pregnant women compared to children.
 - Doses for water exposure in some studies (e.g., Mazumder et al., 1998) do not include additional exposure from inorganic arsenic in foods or dietary use of water (see Schoof et al., 1998; U.S. EPA, 2000). Thus actual exposure is greater in these cases.
 - Many of the studies include broad categories of exposure in which exposure misclassification (e.g., use of an average or median dose for a group with a range of exposure) has likely led to underestimation of exposure in study subjects exhibiting effects (Brown et al., 1997), and thereby potential downward bias in the LOAEL.

³⁴ Alternately, the 10-fold uncertainty factor could be viewed as including two parts: (1) a 3-fold UF for extrapolating from the LOAEL to the NOAEL and (2) a 3-fold UF to account for uncertainties in the database.

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