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ARSENIC PROPOSED DRINKING WATER REGULATION: A SCIENCE ADVISORY BOARD REVIEW OF CERTAIN ELEMENTS OF THE PROPOSAL

A REPORT BY THE EPA SCIENCE ADVISORY BOARD

December 12, 2000

EPA-SAB-DWC-01-001

The Honorable Carol Browner
Administrator
United States Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Subject: Arsenic Proposed Drinking Water Regulation: A Science Advisory Board Review of Certain Elements of the Proposal

Dear Ms. Browner:

This review was conducted by a panel established by the Science Advisory Board (SAB) consisting of the twelve members of SAB's Drinking Water Committee (DWC) and five consultants who were asked to participate in order to provide expertise not held by the members of the DWC. One of these consultants also served on the National Research Council Subcommittee on Arsenic in Drinking Water. This review panel will be referred to hereafter in this report as the Panel. The report was developed in response to interactions with representatives from the Agency's Office of Water during the June 2000 and August 2000 DWC meetings.

The principal task before the Panel was to consider certain technical issues raised by EPA relative to its proposed reduction of the Maximum Contaminant Level (MCL) for arsenic in drinking water from 50 to 5 μg/L. The Panel commends the Agency for undertaking this proposal.

It has been clear for some time that reconsideration of the arsenic MCL is necessary. The Panel recognizes the need for a reduction in the MCL, however, individual participants in the review hold diverse opinions about the most appropriate level for the MCL and about how that level should be attained. Attachment A to this report entitled, *A Minority Report on Arsenic in Drinking Water: The Unique Susceptibility of Children to Arsenic*, was authored by a consultant to the Panel, to present his analysis of the differential sensitivity of children to arsenic and the rationale for his preference for Agency action in this regard. Though the majority of the Panel agrees with his general thesis, which asserts that children can be at greater risk from exposure to contaminants due to their high ingestion of drinking water per unit body weight, they do not agree with the conclusion in the analysis that indicates that this has been demonstrated for arsenic. Attachment B provides a statement by a member of the DWC, indicating support of the minority report. At the request of one member of the Executive

Committee, we also append comments critical of the Panel's report by another member of the National Research Council Subcommittee on Arsenic in Drinking Water, and a response to these comments from the Chairman, of the SAB Arsenic Review Panel (Attachment C).

In the majority report, the Panel commented on two aspects important to determining the proposed MCL: the scientific basis of the health assessment, and some technical issues associated with the economic and engineering analyses. Regarding the health assessment, it appears to the Panel that the Agency accepted, as a risk assessment *per se,* a National Research Council (NRC) analysis that was intended to determine whether the available human data (especially that from a study in Taiwan) were sufficiently detailed to support a formal risk assessment. The NRC indicated that its analysis was not meant to substitute for further investigation of the most appropriate method for assessing the risk posed by arsenic in drinking water. The NRC also noted a number of factors that likely differ between the Taiwanese study population and the U.S. population and which might influence the validity of arsenic cancer risk estimates in the United States. Even though the Agency did its own risk characterization (i.e., they combined the NRC risk factors with U.S. exposure information and arsenic occurrence distributions to obtain a range of risks for use in their benefits analysis), they chose not to quantitatively take any of these factors into account at this time.

The Panel agrees with conclusions reached by the NRC in its 1999 report on arsenic, especially their conclusion that "there is sufficient evidence from human epidemiological studies...that chronic ingestion of inorganic arsenic arsenic causes bladder and lung, as well as skin cancer." The NRC also stated that currently the Taiwanese data are the best available for quantifying risk; however, they also cautioned EPA about certain issues associated with directly applying that study to the U.S., and the Panel agrees and joins the NRC in emphasizing these cautions. In particular, clear deficiencies in selenium intake in the Taiwanese population, other nutritional factors, genetic differences, socioeconomic differences between the study area and the general population of Taiwan, and the need for well designed epidemiology studies which use good exposure measures for individuals in the study population were identified. We note, however, that this Panel does not believe that resolution of all these factors can nor must be accomplished before EPA promulgates a final arsenic rule in response to the current regulatory deadlines. However, resolution of the critical factors noted by this Panel, and the NRC, should not be put off indefinitely. Resolution in time for the next evaluation cycle for the arsenic regulation should be considered as a goal.

The Panel also went beyond the NRC report when new information provided reasons for doing so. In particular, since the NRC report was issued, further analyses of the Taiwanese data have been performed that show that conclusions from this data are very sensitive to the model used for their analysis. The analysis also shows a very significant impact depending upon whether one uses unexposed populations outside the study area for a comparison (control) group or uses relatively less exposed populations within Taiwan who are likely still exposed to some arsenic but may be similar in other ways to the study population. The ultimate risk number derived from the Taiwanese study has proven very sensitive to the decision about the appropriateness of the comparison population. This of

course, has important implications for the use of the data to estimate arsenic risk in the U.S. Also a study in Utah suggests that some U.S. populations may be less susceptible to the development of cancer, than those in Taiwan, although the Panel found that study difficult to use in a quantitative way because of the manner in which the data were presented. Also, a recently published study suggests that the incremental increases in lung and bladder cancers observed in the Taiwan study are of roughly the same magnitude, rather than the NRC's inference of a potentially two- to five-fold greater rate of lung cancer relative to bladder cancer.

As noted by the NRC, the mechanisms associated with arsenic-induced cancer most likely have a sublinear character, which implies that linear models, such as those used by the Agency, overestimate the risk. Similar advice was provided to EPA in an SAB/DWC report as early as 1989 (SAB, 1989) and in a peer review conducted for the Agency in 1997 (ERG, 1997). Nonetheless, the Panel agrees with the NRC that available data do not yet meet EPA's new criteria for departing from linear extrapolation of cancer risk

In summary, the Panel recommends that in future considerations of the risks posed by arsenic in drinking water, (that is, following the finalization of the current proposed rule), the Agency should generate a formal risk assessment that thoroughly explores, to the extent possible: a) the impact of probable differences between the Taiwanese study population and the U.S. population; b) the sensitivity of available data to a wider range of alternative risk extrapolation models; and c) findings from other epidemiological and toxicological studies that may be completed by that time.

The Panel discussed at some length the Agency's proposal to issue a Health Advisory to alert mothers who prepare formula using drinking water that such water might contain arsenic. This advisory is intended as an interim measure that would apply during the time between promulgation of a final rule and its implementation. The Agency provided no details to the Panel on the form or method of issuing the proposed Health Advisory. However, from the Agency's general discussion, it appears to the Panel majority that the envisioned advisory is different from past health advisories that have been issued by the Office of Ground Water and Drinking Water. Because the audience, in this case, differs from those for most such Drinking Water Health Advisories, the methods of communication of the advisory might need to be different. Therefore, the Panel provided advice on certain issues that it believes the Agency should consider should it decide to issue such a Health Advisory. The minority report mentioned earlier supports release of a Health Advisory by EPA without reservation.

The Panel has some concerns about the economic and engineering assessment. In part, this is because of the limited information provided to the Panel on the Agency approach to determining the benefits of a decreased MCL, and because of differences between the Agency projections and those of other organizations. In addition, there were several assumptions made in EPA's analysis about the disposal of arsenic residuals that the Panel thought may not be realistic. First, the Panel felt that assuming that high-salt residuals can be disposed of through publically owned treatment works (POTWs) is questionable based on the strict limits on total dissolved solids in wastewater. Second, the

Panel questioned the assumption that the residuals resulting from all treatments can be disposed of in municipal landfills as a non-hazardous waste.

Another problem is that while many of the treatment options identified as best available technology (BAT) are fairly standard in drinking water treatment, they have not been applied or optimized for arsenic removal at a large scale. The behavior of arsenic is fairly unusual, and it is not clear that these technologies can be simultaneously operated efficiently for arsenic removal and for their other intended purposes.

The Panel also suggested that there should be some further thought given to the concept of affordability as applied to this new MCL. They are concerned that costs to households served by the small systems (the systems predominantly impacted by the arsenic rule) could force tradeoffs that might not lead to the greatest overall public health improvement. Households with lower incomes will pay a proportionately larger part of their incomes as a result of system compliance with new arsenic control regulations than will those with higher income levels. This would be further exacerbated by additional rules, now under consideration, because each new rule will add its own incremental costs to the overall cost of drinking water for specific households.

The Panel moved beyond the scientific, economic, and engineering issues in the Charge to provide their insights on some policy matters, based upon their experience and informed observations. Specifically, the majority of the Panel members felt that there is adequate basis for the Agency to consider use of its discretionary authority under the Safe Drinking Water Act of 1996 to consider MCLs other than the proposed 5 µg/L. In light of the continuing uncertainties in the risk estimates, technology, and significant implementation costs, the Panel majority felt that the Agency could consider a "phased rule" that would be applied, first to a subset of potentially affected systems with the highest exposures. Such an approach would effectively an adaptive management strategy that couples immediate action with future flexibility to respond to results from both experience and research. The minority report mentioned earlier does not support this approach.

Thank you for the opportunity to review these elements of the arsenic proposal. We would be happy to continue to engage with EPA as it pursues this action. We look forward to your response to this report.

Sincerely,

/ s /
Dr. Morton Lippmann , Interim Chair
Science Advisory Board

/ s /
Dr. Richard Bull, Chair
Drinking Water Committee
Science Advisory Board

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Science Advisory Board
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Arsenic Review Panel

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1. EXECUTIVE SUMMARY

The Science Advisory Board (SAB) met from June 5 - 7, 2000 and again on August 8, 2000 to consider components of the Agency's proposal for a new Maximum Contaminant Level (MCL) for arsenic in drinking water. The review was conducted by a panel (referred to in this report as the Panel) composed of the twelve members of the SAB's Drinking Water Committee (DWC) to which was added five consultants who provided expertise to supplement that possessed by the DWC members.

The current MCL for arsenic is 50 µg/L, and the proposed rule would lower that to 5 µg/L. The proposal also requests comments on alternatives of 3, 10 and 20 µg/L. The lowering of a national standard by a factor of ten is a major change having significant cost impacts. In the case of arsenic, the costs involved are substantial, but somewhat problematic, because it demands a level of treatment not ordinarily utilized in the small community water systems that are the principal focus of the rule.

This report has two parts. The basic report provides the majority opinion supported by most of the Panel members and consultants. The second is a minority report prepared after the Panel attempted but was unable to agree on a single document that would provide a combined message giving both the majority and minority views. The minority report (Attachment A) entitled *A Minority Report on Arsenic in Drinking Water: The Unique susceptibility of Children to Arsenic*, was prepared by Dr. John Rosen, a pediatrician and consultant to the Panel for the arsenic review. That document provides his analysis of issues relevant to the differential sensitivity of children and the rationale for his preference for Agency action in this regard. Dr. Rosen reviews the impact of toxicants on children's central nervous system, cardiovascular development, reproductive and developmental organs, and carcinogenesis and concludes that children are at greater risk of harmful effects from arsenic than are adults and that additional safety factors are needed to protect children. The Panel majority does not disagree with many of the statements in that minority report, especially the reasonableness of the general thesis that children are at greater risk from toxicants because of their greater water ingestion per unit of body weight. However, on some specific issues and in his conclusion that susceptibility has been specifically demonstrated for arsenic, the majority and minority views departs.

Dr. Barbara Harper, a toxicologist with the Yakima Indian Nation and a member of the Drinking Water Committee, also provided a statement of support for the minority report's dissenting view (Attachment B). Dr. Harper concludes that children are a generally vulnerable or sensitive population and she prefers precaution when data are substantially suggestive of increased effects in children, as she believes to be the case for arsenic. She further states that Native American Tribes and migrant workers constitute unique populations who should not be last in line for arsenic reduction because of economic or technologic reasons.

The major source document on arsenic's health effects used by the Panel was the National Research Council's report on arsenic in drinking water (NRC, 1999). In recognition of the importance

of this report to the Panel's deliberations, Dr. Louise Ryan, a member of the NRC Subcommittee was asked and did serve as a consultant on the SAB Panel both to ensure an adequate understanding of the NRC effort as well as to provide expertise on modeling issues that are key aspects in understanding arsenic risk from drinking water in the United States. In addition, the Panel considered additional material that it identified in order to answer the charge questions about the forms of arsenic that are responsible for its adverse effects and the influence of dietary arsenic sources on the risks projected from the arsenic studies conducted in Taiwan. The Panel also responded to specific EPA questions about the necessity for issuing a Health Advisory to communicate to mothers who may be using tap water for the preparation of infant formula.

The Panel agreed with the major conclusions in the 1999 NRC document. These are noted throughout the SAB Panel's report. The Panel did go beyond the NRC conclusions in a few instances where new information provided additional insight since the NRC review was completed. These instances, too, are noted in the Panel document. The major conclusions shared by both the SAB Panel and the NRC Subcommittee include:

a) The Panel agrees that the existing national arsenic standard for drinking water (50 µg/L) is too high and should be decreased;

b) The Panel agrees that setting a specific standard involves factors beyond just science issues, therefore, it is not appropriate for the science advisors to determine such levels;

c) The Panel agrees that data from the ecological study conducted in Taiwan, though not ideal for risk assessment, are the best available at this time for determining arsenic's carcinogenic dose-response;

d) The Panel agrees that the Agency should conduct a formal risk assessment that considers additional epidemiology studies and population factors to the extent practicable, in order to improve the validity of the U.S. assessment of arsenic risk from drinking water;

e) The Panel agrees that there is not now sufficient evidence for the Agency to abandon the linear-at-low-dose model, although most data suggest that mechanisms that have been associated with arsenic are indeed sublinear.

It is important to note that as the Panel's Arsenic Report was being discussed by the SAB Executive Committee (EC), one EC member entered into the record comments made by Dr. Alan Smith, another member of the NRC Subcommittee on Arsenic, in response to EPA's proposed arsenic rule-making, in which he commented on the cover letter of the SAB Panel's draft report. These comments raised objections to three points in the Committee's draft which was being reviewed by the EC:

a) The DWC misinterpreted the NRC report

b) The DWC incorrectly asserted that if the risk were as high as 1 in 100, the effect should be more evident in the U.S. than it apparently is

c) The DWC inappropriately accepted the analysis of Morales, Ryan, et al., which presented results without the use of a comparison population known to be unexposed.

These comments are included in and have been responded to in a separate document which is included as Attachment C to this report.

In general, the Panel concludes that determining the forms of arsenic responsible for producing adverse effects has become more complex since the publication of the NRC report. It can no longer be concluded that inorganic forms are the only active forms responsible for the carcinogenic effects associated with arsenic. However, because arsenic in drinking water is largely of the inorganic form, that then is the appropriate form for EPA's regulatory focus. Recent findings have also complicated comparisons of the relative importance of food and water sources of arsenic. As long as the agency relies upon linear extrapolations of arsenic's cancer risk, these problems can be minimized by simply considering drinking water arsenic as an incremental risk superimposed on a more complex and less understood background of total arsenic in food. However, this approach does not resolve the fact that arsenic levels in food are several times that in drinking water. In fact, the Panel concluded that, reducing drinking water arsenic exposure to levels below that found in food may reach a point of greatly diminished return in terms of substantial reductions in risk from arsenic in the environment in general and in the impacted communities. Nevertheless, actions to reduce the MCL for arsenic will provide the largest benefit to communities with unusually high levels of arsenic in their drinking water.

The NRC report noted that mechanisms associated with arsenic-induced cancer likely have a sublinear character. Similar advice was provided to EPA in an SAB/DWC report as early as 1989 (SAB, 1989) and in a peer review conducted for the agency in 1997 (ERG, 1997). Nonetheless, the Panel agreed with the NRC conclusion that the available data do not yet meet EPA's new criteria for departing from linear extrapolation of cancer risk.

In commenting on the Agency's interpretation of the NRC's arsenic report, the Panel noted its belief that EPA took the modeling activity in the NRC report as being prescriptive despite the clearly stated NRC intention that their efforts were illustrative, not actual risk assessments (see page 295-296, NRC 1999). In addition, the Agency has not yet conducted an updated risk assessment for arsenic in the U.S.

The Panel also considered some issues on the nutritional status of the Taiwanese study population that were highlighted in the NRC report (page 295, NRC, 1999) and the issue of lung cancer risk. An analysis available since the NRC report (Morales, Ryan, et al., 2000) led the Panel to

conclude that the contribution of lung cancer to overall risk is about the same as that of arsenic's bladder cancer risks. The Panel focused on and reemphasized the NRC's cautions about the selenium status of the study population in Taiwan. Studies in the U.S. and in Holland have documented significant elevations of bladder and lung cancer in individuals with low selenium intake. The selenium status of the general U.S. population is much higher than that of the studied Taiwanese population. This is not to dismiss the possibility of certain populations in the U.S. having a similar deficiency nor the possibility that those living below the poverty line in the U.S. might have sensitivities linked to that situation.

The Panel noted that the NRC subcommittee reviewed the Taiwanese studies and its limitations at length, noting that, "No human studies of sufficient statistical power or scope have examined whether consumption of arsenic in drinking water at the current MCL results in an increased incidence of cancer or non-cancer effects."(NRC, 1999, p.7). The NRC also noted that epidemiological studies in Chile and Argentina have observed arsenic-related risks of lung and bladder cancer of the same magnitude as those reported in Taiwan, at comparable levels of exposure (several hundred micrograms/liter–p.2, 7 and 292). However, with respect to estimating risk, the NRC stated that "In the absence of a well-designed and well-conducted epidemiological study that includes individual exposure assessments, the subcommittee concluded that ecological studies from the arsenic endemic area of Taiwan provide the best available empirical human data for assessing the risks of arsenic-induced cancer." The Panel agreed.

The majority of the SAB Panel concluded that an analysis published since the NRC report (Morales, Ryan, et al., 2000) provides important additional insights on the use of the Taiwanese data for risk estimation in the U.S. As noted in the NRC report, "...the choice of the model used for statistical analysis can have a major impact on estimated cancer risks at low-dose exposures, ..." (NRC, 1999, p.8). Morales, Ryan, et al., support this conclusion and also demonstrate by applying several models to the Taiwanese data, that the conclusion one draws from the data is very sensitive to the type of comparison population with which the study population is compared. The Morales, Ryan, et al. paper does not select a particular model as most appropriate; however, the SAB Panel, after discussions in their meetings which involved Dr. Ryan, believe that the model which does not use an unexposed comparison population group should be relied upon by EPA for its risk calculations. This conclusion is controversial, as noted in the comments made by one member of the SAB Executive Committee, citing the comments of Dr. Alan Smith (referenced above) and that member and Dr. Smith both disagree with this Panel's conclusions about the Morales, Ryan, et al., study (see Attachment C).

The Panel recommends that in the future (i.e., following the finalization of the current proposed rule) the Agency make a stronger effort to assess the risks of arsenic exposure by conducting a formal risk assessment that, to the extent possible, quantitatively considers well-designed epidemiology studies that appropriately measure exposure and those additional issues mentioned by the NRC as being necessary to improve the validity of the assessment of risk in the U.S. (e.g., selenium intake, other nutritional factors, socioeconomic differences). Such a risk assessment should also consider, to the

extent possible, important characteristics of children that might increase their risk to arsenic, e.g., differences in diet, metabolism, body weight, specific age groups, consumption of water, toxic effects of arsenic in a rapidly growing organism, and exposure estimates per unit of body weight. The Agency should also address the full suite of both cancer and non-cancer effects associated with arsenic.

The Panel discussed the need for EPA's issuance of a Health Advisory to mothers who might use arsenic containing drinking water to mix formula for their young infants. This would apply during the interval between promulgation of the final rule and its full implementation. While most participants thought an advisory was potentially valuable, the lack of a clear description from EPA of what an advisory would contain or on how it would be implemented kept them from fully endorsing this concept. The majority view reflected a concern that an Advisory could be issued without providing information on appropriate actions, or without advising mothers about how to contact public health officials for assistance in their decisions on appropriate actions. The Panel noted that the decision about whether to release a Health Advisory or not is an EPA policy decision. However, research in the area of risk communication, as practiced in the pediatric and public health communities, might provide important guidance on how such an Advisory should be framed if the Agency decides to move in that direction. The goal should be to inform in such a manner as to achieve an appropriate response, without leading to overreaction. One member and one consultant to the Panel disagreed and endorsed the need for EPA to issue a health advisory for arsenic in drinking water, and indicated that past Agency practices would be suitable for an advisory in the case of arsenic contamination as well (see Attachments A and B).

The Agency also directed questions to the Panel on the cost of compliance with the proposed rule, with particular attention directed at disposal options for brines and other residuals from treatment and factors used in the selection of alternative treatment technologies. In addition to these specific charge questions, the Panel chose to comment on aspects of affordability and its interaction with risk tradeoffs.

The Panel agrees that EPA addressed the spectrum of residual disposal alternatives; however, they felt that certain alternatives may not be viable in some cases due to potential constraints placed on utilities. The Panel questions whether the disposal of high-total dissolved solid (TDS) brines to a publicly owned treatment work (POTW) is viable due to regulatory limits on TDS and dilution of organic wastes in many systems, particularly in the western U.S.

Generally, the Panel believes that the costs estimated by the Agency for the rule appear to be low. However, the panel notes that it had only limited information from the Agency on its complex approach to identifying the costs and benefits for this regulation. In regard to costs, the Panel questions whether the technologies identified as best available technologies (BAT) have been implemented or optimized for arsenic removal at treatment plant scale. If optimization of these technologies for arsenic removal reduces their effectiveness for other purposes for which they have been designed, the actual costs of compliance could be underestimated.

Despite the uncertainties attending the arsenic regulatory issue, there seems to be a growing consensus among those familiar with the issue in support of a meaningful reduction in the current MCL for arsenic. Certainly, this is a conclusion common to both the NRC report and this SAB Panel report. Even so, individual participants in this SAB Panel review vary considerably on where they believe the actual MCL should be set. Because of the technological uncertainties, and uncertainties in the assessment of arsenic risk in the U.S., the Panel moved beyond its traditional role as technical advisor and provided its insights on this policy matter based upon their experience and their informed observations. Specifically, the majority of the Panel members felt that there is reason to suggest that the Agency could consider using an adaptive management approach (e.g., a phased rule) which would couple immediate action with future flexibility. However, those endorsing the idea believed that initially setting the MCL at a level intermediate between the current MCL and the ultimate target MCL would result in treatment by a smaller, but representative, number of community water systems which also are the ones with the highest arsenic contaminant levels. Their experience would then provide needed data to actually plan for the much larger number of systems that would be required to treat if a lower MCL were later identified as the ultimate target. A minority of the Panel disagreed. Those opposed to such an approach were concerned that it would not protect children as expeditiously as possible.

The Panel also discussed the issue of affordability for this rule, both alone and in combination with other drinking water regulations that are being developed. The possibility of the co-occurrence of factors such as small communities, along with high arsenic levels, poverty, and special populations concerned the Panel. This was especially of concern to the two Panelists who authored Attachments A and B. As they noted there are more than 13 million Americans living below the poverty line. Further, they hold particular concerns for poor people in the Southwestern U.S., such as Native American tribes, who both suffer from poor nutrition and live in areas with high arsenic concentrations. As such, they believe that a co-occurrence of these factors might create population groups in the U.S. that are similar to those in the Taiwanese study population that was the source of the dose-response information used in the Agency's risk determination. The Panel believes that this situation could have implications both for the risk assessment in the U.S. (i.e., sensitive subpopulations) and for the risk management decision as well (i.e., in terms of overall use of resources to maximize public health gains).

2. INTRODUCTION AND CHARGE

2.1 Introduction

EPA's Office of Ground Water and Drinking Water (OGWDW) proposed a new Maximum Contaminant Level (MCL) for arsenic of 5 µg/L on June 22, 2000 (EPA, 2000). This is a substantial change from the current MCL of 50 µg/L. The existing MCL was based on concerns related to arsenic carcinogenicity with a primary focus on skin cancer. In considering the revision of the MCL, new data on several issues were considered. These included:

a) The quality of the available epidemiological data;

b) Consideration of internal cancers and other health effects attributed to arsenic in continuing analyses of the data from Taiwan and other populations having drinking water with elevated arsenic levels;

c) The applicability of the data from Taiwan to the U.S. population;

d) Whether the mechanisms involved require linear or non-linear risk extrapolation; and

e) Practical limitations on the measurements of low levels of arsenic in drinking water.

Since the arsenic MCL was last considered, there have been new analyses conducted on the available epidemiological data (some new studies have at least qualitatively supported the findings in Taiwan), and the focus of the analyses have turned from skin cancer to internal cancers, particularly cancers of the bladder and lung (NRC, 1999). There are now data that allow us to begin to consider whether risk extrapolation for low doses should be linear or non-linear. However, studies now suggest that the mechanisms involved in arsenic-induced cancer are more complex than previously recognized. This led the NRC to conclude that although there are data that support non-linear risk extrapolation, they are not sufficiently clear for identifying a point of departure based on alternative modes of action. Finally, there are now data that support much lower practical quantitation limits for arsenic in drinking water.

2.2 Charge

The Agency charge to the SAB Panel concerned both health effects and treatment technology issues. The specific questions from the Agency follow.

2.2.1 Arsenic Health Effects Charge to the SAB

Charge Question 1: **Concentration on inorganic arsenic as principal form causing health effects.** EPA has identified inorganic arsenic as the principal form causing health effects, and the literature indicates that most arsenic in drinking water is inorganic. EPA's Maximum Contaminant Level Goal (MCLG) and MCL do not distinguish between arsenate and arsenite. Does the SAB have perspectives on this issue that it believes EPA should consider in developing its risk assessment?

Charge Question 2: **Implications of natural arsenic exposure through food.** The 1999 NRC report estimated the daily inorganic food intake by assuming that 10% of the arsenic in seafood is inorganic, and all other foods are 100% inorganic arsenic. NRC noted that these assumptions set an upper bound on the contribution from food, which is about 10 µg a day for adults. Does SAB agree with the implied NRC perspective that relative source contribution of food should be taken into consideration in the setting of the drinking water standard and how might we consider this and communicate it to the public?

Charge Question 3: **Health Advisory on low arsenic water and infant formula.** The NRC report was inconclusive about the health risks to the pregnant woman, developing fetus, infants, lactating women, and children. Given the potential for cardiovascular disease (as evidenced by EPA's Utah studies and extensive other data) and uncertainty about risks to infants, EPA plans to issue a health advisory to recommend use of low-arsenic water in preparation of infant formula. Is this precautionary advice appropriate given the available information?

2.2.2 Arsenic Treatment Charge to the SAB

Charge Question 4: Decision tree for waste disposal options for arsenic treatment brines and spent media. EPA identified waste disposal options that will likely be used for arsenic treatment residuals. EPA assigned national selection probabilities to each of option in a decision tree. Some people are concerned that after the drinking water MCL is lowered, the Toxicity Characteristic for arsenic will be lowered and that many drinking water treatment residuals will be subject to the costly hazardous waste management regulations. EPA believes that its analysis shows that residuals should be nonhazardous, under the current TC of 5 mg/L and even if the TC were revised to 0.5 mg/L. EPA suggests that important questions relating to waste disposal do not relate to hazardous waste disposal. Rather, for brines, they relate to questions such as TDS (total dissolved solids) restrictions in waters receiving brine, and restrictions on sanitary sewer discharge due to TBLLs (technically based local limits).

For sludge disposal, they relate to restrictions that may be placed on land application, which may result in more systems using landfills.
Based upon a review of the attached materials, does the SAB believe that the EPA produced an accurate projection of the likely disposal options for arsenic residuals and the distribution of these options by treatment type? What are the SAB's views on the advantages and the limitations of the various waste disposal options? What effect, if any, would the SAB's analysis of these advantages and limitations have on the probabilities assigned? What are the SAB's views on which options will be more likely used by small systems (less than 10,000 people), and which will be more likely used by larger ones?

Charge Question 5: **Decision tree for ground water treatment technologies.**
EPA has identified treatment technologies that will likely be used to treat arsenic in groundwater systems. These include ion exchange, activated alumina, reverse osmosis, coagulation-assisted microfiltration, greensand filtration, and point-of-use and point-of-entry devices. The EPA has also identified non-treatment options such as regionalization and alternate source. EPA consulted with small utilities and AWWA in order to identify issues which would affect selection of treatment technologies for small systems, which included cost, complexity of operation, chemical handling issues, and frequency of maintenance on point-of-use devices. EPA has assigned selection probabilities to each of these options in a decision tree that form the basis for the Agency's overall cost projections. The portions of the preamble that explain this decision tree as well as certain other relevant documents are attached.

Does the SAB agree with the principal "branches" of EPA's decision tree described in the attached documents and the likelihood that these options will be used for systems of various sizes with various source water characteristics? What views does the SAB have on EPA's description of the advantages and limitations of these treatment technologies? Would the SAB's views on the these advantages and limitations affect the probabilities assigned?

3. HEALTH EFFECTS ISSUES

3.1 Comments on the Evaluation of Health Effects and Risk Issues

3.1.1 Charge Question 1. Inorganic arsenic as the principal form causing health effects.

EPA has identified inorganic arsenic as the principal form causing health effects, and the literature indicates that most arsenic in drinking water is inorganic. EPA's MCLG and MCL do not distinguish between arsenate and arsenite. Does the SAB have perspectives on this issue that it believes EPA should consider in developing its risk assessment?

Because of the emergence of new data in the literature, the identity of the form(s) of arsenic responsible for health effects is not clear. The long-held hypothesis that inorganic forms are solely responsible for the carcinogenic effects of arsenic has been challenged by new experimental evidence that is discussed in the following portion of the report. However, because arsenic in drinking water is largely of the inorganic form, the Panel believes that it is appropriate for the Agency to make this its regulatory focus.

Studies available since the 19999 NRC report indicate that organic arsenicals are of interest as carcinogens (Wei et al., 1999; Arnold et al., 1999). In addition, the +3 valence state of monomethyl arsenic was found to be much more cytotoxic than inorganic forms (Petrick et al. 2000). On the one hand, methylation aids in the elimination of arsenic from the body, but on the other, it appears that it may generate chemical species that are responsible for adverse effects in some target organs or cells (Aposhian et al., 1999).

A carcinogenic response was observed in the bladder of rats administered dimethylarsinic acid (DMA) for their lifetime (Wei et al., 1999). These studies did not detect an increased incidence of urinary bladder tumors at 12.5 mg/L administered in the water; however, an increase was observed at doses of 50 and 200 mg/L DMA. Further, studies by Arnold et al. (1999) indicated a lack of a carcinogenic response to DMA in mice at concentrations of up to 100 mg/kg in the diet indicating that mice are resistant to bladder carcinogenesis by arsenic. However, Arnold, et al. (1999) confirmed that at 40 and 100 mg/kg DMA in the diet proved carcinogenic to the uroepithelium of the rat, while 2 and 10 mg/kg did not. The carcinogenic action is greater in female than male rats and is dose related at 40 and 100 mg/kg in female rats. In female rats exposed to DMA at 40 and 100 mg/kg in the diet, cytotoxicity was observed in the urinary bladder epithelium. These are the only animal studies performed in the absence of a co-carcinogen that demonstrate an induction of bladder cancer by arsenic or one of its metabolites when administered chronically. The doses of arsenic required are very high levels compared to the amount of DMA expected to be formed following ingestion of inorganic arsenic in drinking water. As a result these data point to the potential that another form(s) of arsenic is responsible. However, it is improbable that this carcinogenic result would be explained by conversion of DMA to inorganic arsenic (Carter et al., 1999).

The Panel recommends that future refinements of the risk assessment for arsenic consider the concentrations of various arsenic metabolites in the urine, the serum, and uroepithelial cells of rats treated with these same doses of DMA to the extent possible. This exercise would establish the relationship between bladder carcinogenesis and urine concentration and speciation of arsenic. This could be used to predict the concentrations of these arsenic metabolites that would be produced following exposure to inorganic forms of arsenic. In turn, this would inform the Agency on the intake of inorganic arsenic needed to produce carcinogenic concentrations of specific arsenic metabolites in the human bladder under a variety of different exposures. These models should consider the bladder as a reservoir for arsenic with the concentration varying over the course of the day.

This does not suggest that inorganic arsenic cannot also play a role in other target organs. Ng et al. (1999) found increased incidences of tumors in the lung and gastrointestinal tract when sodium arsenate was administered at 0.5 mg As/L in drinking water to female C57Bl/6J mice (corresponding to 67 µg/kg body weight per day). Lung cancer is also implicated in the human population exposed to arsenic (NRC, 1999). The varying responses of different test animals can reflect differences in genetic susceptibility. However, it is also consistent with the possibility that the development of tumors in different tissues could result from different metabolites or metabolite combinations.

Adding to the complexity are recent findings that a +3 valence state of organic arsenic is much more toxic to cells in culture than the +5 organic forms that have been previously studied. Petrick et al. (2000) found that monomethylarsonous acid, a +3 valence form of organic arsenic, is much more cytotoxic to cells in culture than inorganic forms of arsenic, as well as the +5 forms of methylated arsenic. Styblo et al. (1999; 2000) have very similar findings in cultures of rat hepatocytes and human cells derived from the liver, skin, urinary bladder, and cervix with the +3 form of DMA as well as MMA. These forms of arsenic are likely to be a short-lived intermediates *in vivo*, and as a consequence would be found only at low concentrations compared to the +5 forms. At any rate, it is no longer clear that the inorganic forms are the most toxic either (as opposed to being carcinogenic). Consequently, in the future, it will be much more important to specify the dose, endpoint and target organ when speaking of arsenic's toxicity, because the form responsible may well vary. Therefore, it is probable that human responses are determined by a variety of conditions and may involve interactions between metabolites.

Although there are exceptions, the principal forms of arsenic in drinking water are inorganic forms, and the Agency is setting a standard for arsenic as it appears in drinking water. Because the available data do not meet the Agency's criteria for abandoning the linear default assumption in estimating risk, it is best to deal with the incremental risk of arsenic in drinking water. For this reason alone, the Agency needs to focus on the inorganic forms of arsenic rather than attempting to deal with all potential forms of arsenic. It is not possible to consider contributions of different forms of arsenic to the overall response based on the data that are available today.

3.1.2 Charge Question 2: Implications of natural arsenic exposure through food.

The 1999 NRC report estimated the daily inorganic food intake by assuming that 10% of the arsenic in seafood is inorganic, and all other foods are 100% inorganic arsenic. NRC noted that these assumptions set an upper bound on the contribution from food, which is about 10 µg a day for adults. Does SAB agree with the implied NRC perspective that relative source contribution of food should be taken into consideration in the setting of the drinking water standard and how might we consider this and communicate it to the public?

Ideally, consideration of relative source contribution would place drinking water exposures into a practical context in which specific forms of a chemical would be weighted by the potency of the form of chemical that is present in producing the effect of interest. The above conclusions on the increasing uncertainty about which forms of arsenic are toxic, and the specific toxicity attributed to specific forms, makes it difficult to do such an evaluation of the comparative risks of arsenic in drinking water versus that in food with any great confidence. Thus, neither the NRC nor EPA were able to consider the kinetics of the formation of different arsenic species, and the Panel can only note that the lack of such data increases the uncertainty about the relative contribution of drinking water to cancer induced by arsenic relative to that in food.

In this section, the Panel provides an analysis to illustrate the relative contributions of arsenic in drinking water and food and their relative contributions to the health benefits achieved at a variety of alternative MCLs. This analysis concludes that for the populations consuming drinking water at average levels (1 liter/day), the assumption that is used as standard practice by EPA's Office of Water in its benefits assessment, the benefits rapidly reach a point of greatly diminished returns in terms of predicted reduction in risk. The Panel did note, however, that as long as the agency relies upon linear extrapolation of arsenic's cancer risk, these problem of food versus drinking water source contribution are minimized because the focus is upon incremental risk associated with drinking water alone. Even so, it appears that the intake of arsenic from food is several times that which is ingested in drinking water. The Panel analysis does reinforce the NRC conclusion about the sensitivity of the cancer risk assessment to the extrapolation model used to characterize low dose effects. It should be clear that the analysis that follows is not a risk analysis. Rather, it is an analysis of the benefits from risk reductions that are likely from arsenic decreases in drinking water in comparison to the levels associated with arsenic in food. As such the analysis focuses on the average case instead of the high-end case that would be typical of a risk assessment.

3.1.2.1 Arsenic Exposures Through Food

The NRC report summarized available information on arsenic in food supplies. These estimates were based on combining information on average diets by sex and age groups with data available on the total arsenic content of the foods included in the diet. The average diets are based on FDA Total Diet Study for Market Baskets Collected for various time periods. For the 1991- 1997 period, total arsenic intake ranged from 2.15 µg/day for 6-11 month infants to 99.1 µg/day for 60-65 year males (NRC, 1999, Table 3-6).

Total arsenic consumed in foods is not directly comparable to total arsenic in drinking water in terms of toxicity. Seafood contributes about 90% of the total arsenic intake from food. Much of the arsenic in seafood is in two organic forms – arsenobetaine (AsB) and arsenocholine (AsC). These two forms are considered nontoxic, although, their carcinogenic potential has not been fully evaluated. In contrast, drinking water primarily contains inorganic arsenate and arsenite, both of which are considered toxic.

Comparisons between arsenic in food and arsenic in drinking water were made by assuming that 10% of the total arsenic in seafood is inorganic and that 100% of the total arsenic in food of terrestrial origin is inorganic. For adults, the average inorganic arsenic intake from foods, based on the above percentages, is 10 µg/day (NRC, 1999, p. 47). Average inorganic arsenic intake from food ranged from 1.34 µg/day for 6-11 month old infants to 12.54 µg/day for 60-65 year old males (NRC, 1999, Table 3-6).

EPA cited work MacIntosh, et al. (1997) to indicate the individual variability in inorganic arsenic intake from food. MacIntosh studied 785 adults and found a mean inorganic arsenic intake of 10.22 µg/day, with a standard deviation of 6.54 µg/day and a range of 0.36-123.84 µg/day, using semi-quantitative food surveys. This variability is apparently due to variations in diet rather than variations in the inorganic arsenic content of individual foods.

The NRC (1999) and the EPA (2000) documents do not contain information on the regional variability of arsenic content in foods within the United States. Generally speaking, the food supply within the United States is considered to be rather homogeneous (Schoof et al., 1999). Nevertheless, some individuals could have substantial differences in their arsenic intake via food.

3.1.2.2 Arsenic Concentrations in Drinking Water

Using compliance monitoring data from 25 states, the EPA estimated the numbers of ground water and surface water Community Water Systems (CWS) with treated water falling in various ranges of arsenic concentrations (EPA, 2000, Table V- 3 and V-4). Using this information, the Panel prepared concentration exceedency curves for CWSs using ground and surface waters (Figure 1). The EPA tables provided information whereby percentages of CWSs having concentrations exceeding 2.0, 3.0, 5.0, 10.0, 15.0, 20.0, 30.0 and 50.0 µg/L could be determined. These concentrations represent the points plotted in Figure 1. EPA states that the distribution of arsenic concentrations in CWSs is independent of the size of the CWS (EPA, 2000). Consequently the plots of concentration exceedency curves for CWSs also represent concentration exceedency curves for the entire population served by ground water and surface water CWSs. It is evident from the curves that groundwater has much higher arsenic concentrations than surface water. It is also evident from the curves that, while most CWSs have concentrations below the proposed MCL, treated water from some CWSs has arsenic concentrations considerably in excess of the proposed MCL.

The above data can be used to estimate the population-weighted average concentrations of arsenic in drinking waters from ground and surface water CWSs. For this estimate, the percentage of the CWSs in each interval (e.g. >10.0 to 15.0 µg/L) was multiplied by the midpoint concentration for that interval (e.g. 12.5 µg/L) to obtain a weighted concentration for that interval. Summing the weighted concentrations for all intervals gives the average concentration. For ground water supplies the average concentration of arsenic is 2.85 µg/L, while for surface water supplies the average is 1.46 µg/L. Since surface water serves 66% of the total population on CWSs and ground water serves 34%, the overall weighted average concentration of arsenic in drinking water is 1.93 µg/L.

3.1.2.3 Comparison of Arsenic Intake from Food and Drinking Water

Figure 1 also represents the relative intake of arsenic from food and water. The Panel's analysis followed the standard EPA-Office of Water practice for benefits analyses in that it used the average of drinking water consumption levels for CWSs of 1.0 L/day (EPA, 2000). This contrasts with the standard practice used in risk assessment in which a drinking water consumption rate of 2 liters/day for an adult, which actually approximates the 90th percentile intake (EPA, 2000). Because the arsenic intake in food is the average dietary intake, the Panel decided to calculate drinking water intake based on average drinking water consumption. As previously stated, use of average consumption values in these calculations is consistent with approaches used in benefits assessments.

With an average drinking water consumption of 1.0 L/day, the Y-axis in Figure 1 represents both the concentration in µg/L and the dose in µg/day. The food intake is represented by the gray area on the graph under the dashed line at 10 µg/day. Comparisons of the area under the drinking water exceedency curve with the area under the food "curve" reflect the relative contributions of each pathway to the total intake of inorganic arsenic in the diet.

The relative contributions of drinking water and food to total arsenic intake at the current MCL of 50 µg/L are shown in Table 1. Data are included for ground water and surface water supplies, as well as for the weighted total for the entire population of CWSs (both ground and surface). On average, drinking water contributes 16.3% of the inorganic arsenic intake and food contributes 83.7 %. Thus, water treatment to reduce drinking water concentrations has limited potential to reduce total arsenic intake on average, in the general population. However, for the part of the population consuming drinking water with high arsenic concentrations, water treatment can result in substantial reductions in combined food and water intake. For individuals consuming water at 50 µg/day, arsenic intake in water is five-fold higher than average food intake and would be substantially reduced.

3.1.2.4 Effects of MCL Choice on Drinking Water and Total Intake of Inorganic Arsenic

The Panel used the EPA data from which Figure 1 was produced to calculate the reductions in drinking water concentrations and total arsenic intake that would accompany various choices for the MCL. Those data, along with ancillary data, are shown in Table 2 and

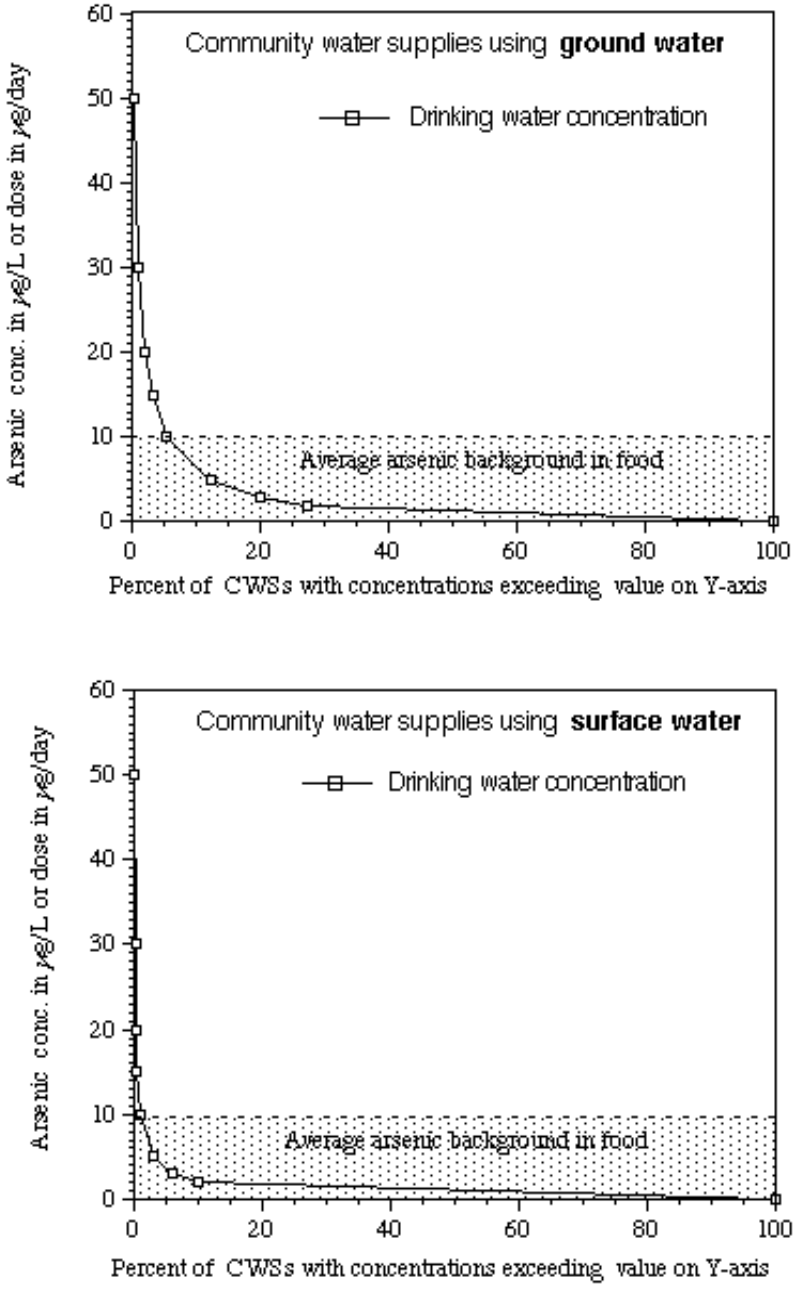

Figure 1. Arsenic concentration exceedency curves for community water supplies using ground and surface waters in relation to average arsenic intake in food. Community water supply data from tables V-3 and V-4 in the EPA proposed arsenic rule. (see text for explanation)

Table 1. Average contributions of drinking water and food to total arsenic doses for ground water CWSs, surface water CWSs, and weighted average for all CWSs for an MCL of 50 ug/L.

Water Source	Pathway	Average Arsenic dose (mg/day)	Percent by Pathway
Ground Water (GW)	Water	2.85	22.2
	Food	10.0	77.8
	Total	12.85	100
Surface Water (SW)	Water	1.46	12.7
	Food	10.0	87.3
	Total	11.46	100
Weighted Average	Water	1.93	16.3
(0.34 GW and 0.66 SW)	Food	10.0	83.7
	Total	11.93	100.0

Figures 2 & 3. The effects of treatment to reduce drinking water concentrations can be viewed as truncating the portion of the area under the drinking water exceedency curve (Figure 1) at the level of the MCL. The reduction in the area under the curve reflects the effect of treatment on average drinking water concentrations. For these calculations, we assumed that the arsenic concentrations for all supplies having higher concentrations than the proposed MCL would be reduced to 80% of the MCL value. This is the same assumption as that made by the Agency (EPA, 2000). The effects of MCL choice on average drinking water concentrations are shown in Figure 2. Imposing an MCL of 5.0 µg/L would reduce the average drinking water concentrations from its current value of 1.93 µg/L to 1.40 µg/L.

The reductions in peak concentrations and the percentage reductions in peak concentrations associated with each proposed MCL are also shown in Table 2. It should be noted that reductions of these sizes would only occur for individuals consuming water at or near the current 50 µg/L MCL value.

The percent reductions in drinking water doses and total doses (DW plus food) for various MCL choices are shown in Figure 3A and Table 2. At an MCL of 20 µg/L, drinking water and total doses are reduced by 8.3% and 1.3% respectively, while at an MCL of 3 µg/L , they are reduced by 36.5% and 5.9%. Because drinking water currently comprises only 16.3% of the total inorganic arsenic intake (average consumption levels) and most of the population already consumes drinking water with arsenic concentrations less than 3.0 µg/L, the potential for reducing total arsenic intake is only 5.9% at the lowest MCL we are to consider.

The number of treatment plants required to achieve the reductions in arsenic intake associated with MCL choices is shown in Figure 3B. The slopes of these curves represent the efficiency (reduction/CWSs requiring treatment) of reducing arsenic exposure associated with various MCLs. The efficiency in reducing exposure for going from an MCL of 50 µg/L to 20 µg/L is 3.5 times greater than the efficiency in going from 5 µg/L to 3 µg/L.

3.1.2.5. Influence of MCL Choice on Estimated Health Benefits

As noted by the NRC, estimates of cancer risk from arsenic in drinking water are sensitive to a number of factors, including at least the selection of the model used to represent the dose response curve, the implications of exposure measurement and grouping that exist in the ecological studies of arsenic's effects in Taiwan. Therefore, the Panel's consideration of the contribution to risk from arsenic in drinking water relative to arsenic in food reflects some of the same problems. Even though both the NRC and this Panel consider the most-likely arsenic dose-response curve to be sublinear, there are not yet sufficient quantitative data available to link key events in arsenic's cancer induction to the dose-response curve and thus permit a departure from linear cancer risk estimation approaches. Because of this, the linear extrapolation default was used in EPA's earlier risk assessment (EPA, 1988) to estimate cancer risks. The linear default was also used by EPA as the basis for estimating bladder cancer risk reduction benefits in support of the current arsenic proposal. This is supported by conclusions from the NRC Subcommittee that conducted the arsenic review (NRC, 1999), as well as this SAB Panel.

If the dose response curve is linear, the health benefits are directly proportional to average doses and changes in health benefits associated with changes in the MCL would be directly proportional to the changes in drinking water and total doses presented in Table 2 and Figure 3. For example, at an MCL of 3.0 µg/L, the adverse health effects associated with drinking water arsenic would be reduced by 36.5% while adverse health effects associated with total arsenic intake (food plus water) would be reduced by 5.9%. Other MCL choices are accompanied by smaller reductions in adverse effects.

As discussed earlier, we do not really know what the equivalency of the various forms of arsenic are in their intrinsic contribution to the development of cancer. Given that the Agency is relying on linear extrapolation, the Panel recommends that the Agency simply look at the incremental risk associated with drinking water, as that is the controllable risk. Nevertheless, progressing to ever lower arsenic levels, below those levels found in the U.S. diet, provides an ever diminishing return in mean arsenic exposure per dollar invested in water treatment.

The Panel agrees with the NRC Arsenic Subcommittee in concluding that a linear dose response curve is a practical interim measure even though existing information on arsenic's mode of action suggests that the dose response would exhibit sublinear characteristics. If the dose-response curve is sublinear, reductions of arsenic levels in the high ranges of exposure would have larger health benefits than those estimated using linear risk estimation techniques,

Table 2. Effects of arsenic MCL selection on average concentrations in drinking water, on percent reductions in average arsenic doses in drinking water and in food plus drinking water, on the reductions and percent reductions in peak concentrations, and on the number of CWSs requiring treatment to reach the MCL.

Parameter	Current MCL (µg/L)	Proposed MCLs			
	50 µg/L	20 µg/L	10 µg/L	5 µg/L	3 µg/L
Average Ground Water Concentration (µg/L)	2.85	2.52	2.15	1.71	1.39
Average Surface Water Concentration (µg/L)	1.46	1.38	1.34	1.24	1.14
Weighted Average DW Concentration (µg/L)	1.93	1.77	1.62	1.40	1.23
Percent Reduction in DW Concentration/Dose	0	8.3	16.3	27.7	36.5
Percent Reduction in DW Plus Food Total Dose	0	1.3	2.6	4.5	5.9
Reduction in DW Peak Concentration (µg/L)	0	30	40	45	48
Percent reduction in DW peak concentration	0	60	80	90	94
Number of CWSs Requiring Treatment	0	929	2,455	5,621	9,330

and reductions in exposure in the low range of exposures would have smaller health benefits, than their corresponding reductions in average concentrations. Under a linear dose-response curve, an MCL of 3 µg/L reduced adverse health effects by a factor of almost 4.5 times that achieved by an MCL of 20 µg/L (reduction in average concentrations by 5.9% and 1.3% respectively). Under a sublinear dose-response curve, the ratio of the health benefits at an MCL of 3.0 µg/L to that for an MCL of 20 µg/L would be less than 4.5 fold, possibly much less. Under a sublinear dose-response curve, the curves in Figure 3B would shift such that the slope (efficiency) between MCLs of 50 µg/L and 20 µg/L would be relatively steeper and the slope between 5 µg/L and 3 µg/L would be relatively flatter.

Under a sublinear dose-response curve there will be a region where exposures to arsenic from food and drinking water begin to interact significantly. The benefits of water treatment depend on where the reductions in total dose (food plus water) occur along the dose-response curve. This calculation would require a well-defined sublinear dose-response curve. The generation of such a curve requires a more quantitative understanding of how the mechanisms by

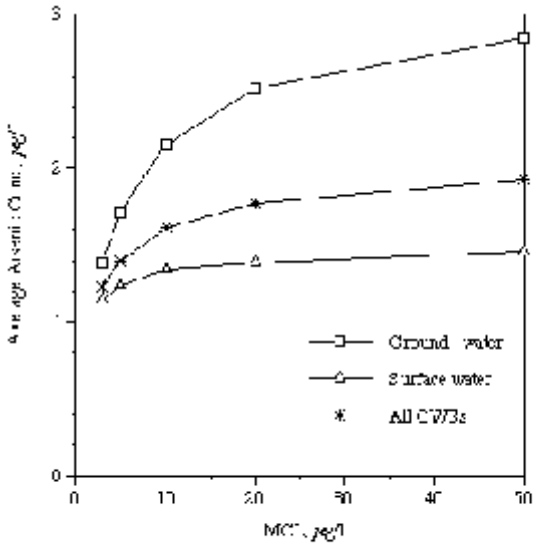

Figure 3. Effects of MCL level on average arsenic concentrations in ground water CWSs, surface water CWSs and weighted average drinking water from all CWSs.

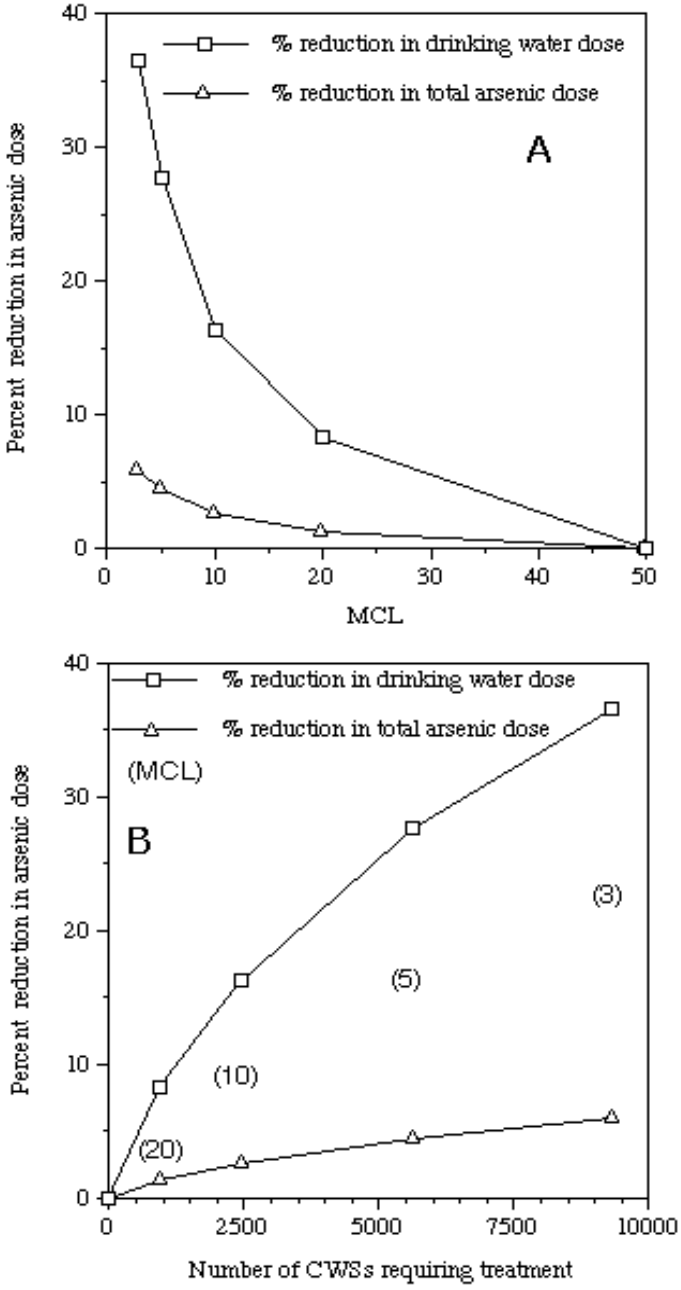

Figure 3. Relationship between percent reduction in drinking water and in total arsenic dose and choice of MCL (A) and number of CWSs requiring treatment (B).

which arsenic contribute to its adverse health effects. Further, generation of any specific sublinear dose-response curve from current epidemiological studies would likely be very difficult to justify due to the general lack of measurable health effects in the low dose range.

If data were available to demonstrate that the dose-response curve includes a threshold value then the arsenic doses from food and water would interact in the consideration of risk levels. If the total dose exceedency curve spans the threshold value, only that portion of the exceedency curve above the threshold is accompanied by adverse health effects. The procedures for estimating the health benefits of various MCL choices would be similar to those listed above for a sublinear dose-response curve. Information on the shape of the dose-response curve in the portion of the curve above the threshold value would be needed as well as the threshold. However, data do not currently exist to allow such an evaluation.

3.1.2.6 Discussion and Conclusions

In attempting to reduce the frequency of bladder cancers by reducing drinking water exposure to arsenic, the Agency is faced with minimal marginal risk reduction opportunities. For example, there are approximately 53,000 new cases of bladder cancer in the U.S. each year with over 12,000 bladder cancer fatalities (American Cancer Society, 2000). The number of bladder cancers attributable to arsenic can be estimated under the default assumption of a linear response of bladder cancers to total inorganic arsenic dose. At an MCL of 3.0 µg/L, EPA estimated an annual reduction in bladder cancers of 22-42 cases and a reduction in fatal bladder cancers of 5.7 to 10.9 per year (EPA, 2000). At an MCL of 3.0 µg/L, the total dose of arsenic is reduced by 5.9%. If a 5.9% reduction in arsenic dose results in a 22-42 case reduction in bladder cancer occurrence, then a 100% reduction would result in a 373 to 745 case reduction under a linear dose response relationship. Under this reasoning arsenic would be responsible for 0.7% to 1.4% of all bladder cancers in the United States. At an MCL of 3.0 µg/L, the accompanying 5.9 % reduction in total arsenic dose would reduce bladder cancers in the United States by 0.04% to 0.08%. At the proposed MCL of 5.0 µg/L, EPA states that there would be 16 to 36 fewer occurrences of bladder cancer. These represent reductions 0.03% to 0.07% in the annual occurrence of bladder cancers in the United States. Thus, it must be recognized that the impact of reduction of arsenic in drinking water at these levels is likely to have a very small impact on the overall incidence of bladder cancers in the country. Smoking and occupational exposures are thought to be the major causes of bladder cancer (American Cancer Society, 2000).

The above analyses indicate that average arsenic ingestion via food is considerably larger than average arsenic ingestion via drinking water even at the current MCL of 50 µg/L. For the limited populations where drinking water concentrations are at or near the current MCL, considerable reductions in total arsenic exposure can be achieved by reducing the MCL. By assuming a linear dose-response curve, the EPA was able to calculate the marginal benefits of drinking water treatment, even though food represents the major pathway of arsenic intake. If the mode of action supported a nonlinear response to total inorganic arsenic intake, food and water pathways would both have to be considered in calculating treatment benefits. Such calculations would require a well-defined nonlinear

dose-response curve and more information on the distribution of food intakes, neither of which are currently available. Consequently, the Panel concurs that EPA had no choice other than to proceed with marginal risk reduction calculations based solely on considerations of drinking water cancer risk reduction as calculated using a linear response model and ignoring food intake. However, it is also clear from the above analyses that there is a limit to the benefits that can be realized by reducing arsenic in drinking water. It should be kept in mind that regardless of the MCL chosen between 5 and 20 µg/L only the extreme levels will be reduced in drinking water. Conversely, the extremes in arsenic content of foods will remain unaltered by this regulatory action.

That said, it should be noted that studies show the potential for arsenic to cause non-cancer effects. Most of these studies do not yet provide sufficient data for quantitative risk assessment at this time, therefore, they can in general only be addressed by EPA qualitatively. The implication of the possibility of such additional risks is that a given level of arsenic exposure reduction that would come from lowering the MCL would also provide some additional level of benefit to the populations involved. The Panel and the NRC both agree that additional studies are needed to refine our understanding of not just arsenic's cancer effect, but its potential to cause other health effects.

3.1.3 Charge Question 3: Health Advisory on Low Arsenic Water and Infant Formula.

> The NRC report was inconclusive about the health risks to the pregnant woman, developing fetus, infants, lactating women, and children. Given the potential for cardiovascular disease (as evidenced by EPA's Utah studies and extensive other data) and uncertainty about risks to infants, EPA plans to issue a health advisory to recommend use of low-arsenic water in preparation of infant formula. Is this precautionary advice appropriate given the available information?

EPA plans to issue a health advisory to recommend the use of low-arsenic water in the preparation of infant formula. This advisory would be active during the period covering the interval between promulgation of the final rule and its full implementation, a period from 3 to 5 years. The Panel held extensive deliberations on the implications of such a health advisory. During the discussion, the Agency provided more detail about the type of health advisory envisioned and how it would be disseminated. The advisory would note that the exposure standard has been lowered but that implementation will be delayed for a period of years and in the interim parents concerned about arsenic risk to infants should consider using low arsenic water to prepare infant formula. Although most of the Panel agreed generally with the assertion that special circumstances pertain to infants that make it reasonable to consider them unique in regard to their response to contaminants in drinking water, and that this could require additional attention by the Agency during the implementation of a new arsenic drinking water regulation, the Panel was not able to reach consensus on an endorsement of EPA's intent to issue a Health Advisory whose purpose, content, and approach was not clear to the Panel. As a result, most of the members favored a response to the charge question that provided a series of cautions to the Agency as it moved forward to decide upon and develop their advisory.

The "Minority Report on Arsenic in Drinking Water" discussed earlier in this report, and contained in Attachment A, disagrees with certain elements of the Panel's reasoning for not giving a full endorsement to a Health Advisory for this purpose. The minority report written by a consultant to the Panel for the arsenic review provides his analysis of issues relative to the differential sensitivity of children to arsenic that departs from the majority opinion contained in this report in strength of its conclusion if not the general reasonableness of the need for increased concern for children, which is also held by the Panel. As noted earlier, one member of the Drinking Water Committee supported the minority opinion in regard to actions thought to be necessary to address concerns about the differential sensitivity of children to arsenic (this is discussed more fully later in this section).

The action contemplated by the Agency is different from the health advisories issued in the past and with which many of the DWC members are familiar. First, prior Health Advisories issued by the Office of Ground Water and Drinking Water were meant to provide advice to states and utilities to address infrequent occurrences of contamination, usually as the result of a spill. They are not enforceable standards nor are they used to directly inform the public about particular health hazards to potentially sensitive groups in the population. Second, as the Panel came to recognize during the discussion of the issue at the meeting, the Health Advisory would be an interim measure, and not a lower exposure recommendation for infants. The intent of this advisory is to alert parents that they may want to take early action to protect their children against this potential risk in the period before the standard is fully implemented. The Panel's greatest concern was that the Agency did not address how the target audience was to be reached and how they were to obtain information about alternatives to community drinking water for infant use that would allow them to effectively address any concerns parents might have.

EPA's motivation for issuing an advisory is concern about health risks to the developing child and uncertainty about cardiovascular risks to infants (that could be expressed later in life) as well as the higher per unit exposure to infants. It recognizes that children differ in many ways from adults. Differences in size, maturity of biochemical and physiological functions in major body systems, and variation in body composition (water, fat, protein and mineral content) all can modulate the severity of toxicity to any toxicant in a rapidly developing fetus-infant-child. Because newborns are the group most different anatomically and physiologically from adults, they could exhibit the most pronounced quantitative differences in sensitivity and susceptibility to environmental toxicants. The majority of the committee did not feel that data available to them on arsenic had demonstrated an increased sensitivity to arsenic in children. (This is discussed more fully below.) However, the Panel did note that infants consuming formula made from drinking water could reasonably be expected to receive a higher dose per unit body weight than adults based on information available on drinking water consumption in the U.S. (EPA, 1999).

The Panel noted that while the decision to release a Health Advisory or not is an EPA policy decision, research results in the area of risk communication as practiced in the pediatric and public health communities, can provide important guidance on how such an advisory should be framed if the Agency decides to move in that direction. The goal would be to inform in such a manner as to achieve

an appropriate response without leading to overreaction. The Panel also discussed whether the recommendation should solely focus on infants or if pregnant women should also be included in the warning and whether the advisory should contain specific recommendations for actions by the target audience (e.g., identify informed sources for obtaining follow up information, provide guidance on how to obtain sources of low arsenic drinking water, etc.).

As noted earlier, the Panel effort to reach consensus on fully endorsing the health advisory was impeded by the lack of specific information on the envisioned Health Advisory. As a result, the Panel chose to identify those concerns that were voiced at the review meeting and to suggest that in deciding on whether to go forward with an advisory which is a policy decision, that the Agency consider these concerns and develop and implement the advisory in a way that would not be counterproductive.

a) The Panel was of one mind that it was not the proper entity to design the envisioned Health Advisory and that its comments should not be viewed as comprehensive. However, the Panel recognized that the Health Advisory could have unintended consequences if it is not carefully designed and implemented. The contemplated advisory is not analogous in intent and likely content to other health advisories issued by the Office of Ground Water and Drinking Water in the past. The Panel suggested that it might better be identified as something other than a health advisory to avoid confusion.

b) Any health advisory of the type contemplated should focus on health professionals (pediatricians and public health officials) and not only be issued broadly to the public at large. These are the people in the community that can be depended upon to find alternatives within that community.

c) Alternatives must be identified that are reasonable for the community that is being notified. Bottled water will not have to be in compliance with the new arsenic standard until the regulation is effective, and consequently may contain levels similar to or greater than those in the public system. Hopefully, the bottled water industry will cooperate with the intent of this advisory as well as public water systems. However, the Panel noted that EPA has no direct jurisdiction over bottled water.

d) The advisory should include information on what is known about arsenic levels in baby foods and prepared formula.

e) The Panel felt that if an advisory is to be developed it should inform without alarming. Information should be provided that ensures that as a result of an advisory behavioral changes do not lead to inadequate fluid consumption by children, inadequate nutrition, or other unanticipated risks.

f) This is largely a policy issue. The available science does not speak clearly on the question of whether the sensitivity to arsenic is greater at an early age than as an adult.

During its discussion of the value of issuing an advisory, the Panel received the recent Hopenhayn-Rich et al. (2000) study and there was disagreement within the Panel on its interpretation. The dissenting view of one consultant, supported by one member, is provided in Attachment A to this report. The Panel's majority view is that this study suggests that the links between arsenic in drinking water and any observed increases in still birth or neonatal mortality are associated with exposures to a very high concentration of arsenic (860 µg/L). While the Panel believes that it is generally reasonable to consider that children are generally at greater risk for a toxic response to any agent in water because of their greater drinking water consumption (on a unit body weight basis), they do not believe that this study demonstrates such a heightened sensitivity or susceptibility to arsenic.

For example, in the study, the concentrations that were possibly associated with adverse reproductive outcomes are also associated with toxicity in adults. There are significant uncertainties in the risks for developmental toxicity, cancer, and vascular disease at exposures in the 5 to 50 µg/L range. (The current MCL alternatives fall within this range and these would be the levels that a Health Advisory would address.) The Panel noted that in the Hopenhayn-Rich, et al. study the increases in still birth or neonatal mortality between Antofagasta and Valparaiso disappeared once the arsenic concentration in the Antofagasta drinking water fell to 110 µg/L or less (Figure 4). At that point, the stillbirth or infant mortality experienced in Antofagasta (that previously had high arsenic concentrations in water) was similar to that of the control town, Valparaiso, with arsenic concentrations less than 5 µg/L. Sometimes the effects in the exposed town were less than and sometimes greater than the effects in the control population (these were small differences and not in a consistent pattern and appeared to be due to randomness in the data, which were averaged in the original study over 4-year periods because of the considerable variation from year to year). Furthermore, it is not clear how the proposed putative effects of arsenic can account for the substantially elevated prenatal mortality seen prior to the increase in drinking water arsenic content that began in 1954 in the study population. Moreover, there was a downward trend in both the exposed and control populations over the period of observation that was apparently not related to arsenic in drinking water. In short, the Hopenhayn-Rich study appears to be an hypothesis generating study that, in light of the limitations just described, merits and requires further study before drawing final conclusions.

3.2 Comments on EPA's Interpretation of the NRC Report:

3.2.1 General Comments

This section of the report discusses some uncertainties associated with the Taiwanese study data used to characterize risks to U.S. populations from arsenic in drinking water. The NRC discussed the challenges that are presented to EPA in preparation of a risk assessment for arsenic in drinking water stating that, "In the absence of a well-designed and conducted epidemiological study that includes individual exposure assessments, the subcommittee concluded that ecological studies from the arsenic endemic area of Taiwan provide the best available empirical human data for assessing the risks of arsenic-induced cancer." (p. 7, NRC, 1999). In noting, however, that ecological data might be the only choice in the absence of such data the NRC stated that, "Such analyses must be conducted with caution, keeping in mind the potential for measurement error and confounding to bias the results. It is

important to remember that any risk assessment based on ecological data must be cautiously interpreted because of the inherent uncertainty in the exposure-assessment methods used for such studies." (Page 294, NRC 1999). They also noted that model choice has an impact on estimates of low-dose risks when the analysis is based on epidemiological data. (p. 294). Finally, the NRC noted that other factors might affect the risk assessment in Taiwan or extrapolations to the U.S. such as poor nutrition and low selenium concentrations in Taiwan, genetic and cultural characteristics, and arsenic intake from food." (p. 295)

The Panel notes its belief that the Agency may have taken the modeling activity in the NRC report as prescriptive despite NRC comments about possible limitations in the existing knowledge base and their intention that their efforts be seen as illustrative and not as actual risk assessments (see pages 264 and 295-296, NRC, 1999). The Agency did do a risk characterization using factors from the NRC report and occurrence information from their own efforts as the basis for their assessment of the benefits associated with risk reduction. They did not conduct the formal risk assessment integrating additional factors called for by NRC.

The Committee also learned of a broader set of analyses that have been published since the release of the NRC report (Morales, Ryan, et al., 2000) which may have important implications for risk levels associated with arsenic exposure. Ordinarily, epidemiology studies compare the disease incidence in an exposed population with a group that is unexposed (i.e., a comparison population). However, if there are substantive differences in the characteristics of the comparison population, the differences noted may not be valid. (This issue was also a concern to the NRC Subcommittee, see pages 285-288, NRC 1999.) It is possible to model dose-response without a comparison population by simply looking at the response rates within the exposed population as a function of the gradation of exposure.

Morales, Ryan et al., derived arsenic risk estimates using the comparison populations or simply basing the estimate simply on the dependence of cancer incidence within the population on exposure to arsenic. They concluded that the risk estimates were extremely sensitive to the use of comparison populations that were outside the study area (i.e., comparison with the whole of Taiwan, or the remaining portions of southwestern Taiwan that surround the study area). The panel focused on evidence provided in the NRC (1999) report that indicate that the population in the study area differed substantially from these comparison populations socioeconomically and in diet. At least one of these differences has been found to significantly associated with rates of bladder and lung cancer in other populations (these issues are discussed in detail in sections 3.2.1.1 and 3.2.1.2). Consequently, most members of the Panel came to the conclusion that the comparison populations were not appropriate control groups for the study area.

Morales, Ryan, et al. (2000) focused extensively on the impact of including a comparison population in the analysis of the Taiwanese data. As discussed in the NRC report, the available internal cancer data are based on 42 villages from the arsenic endemic region, hence all have

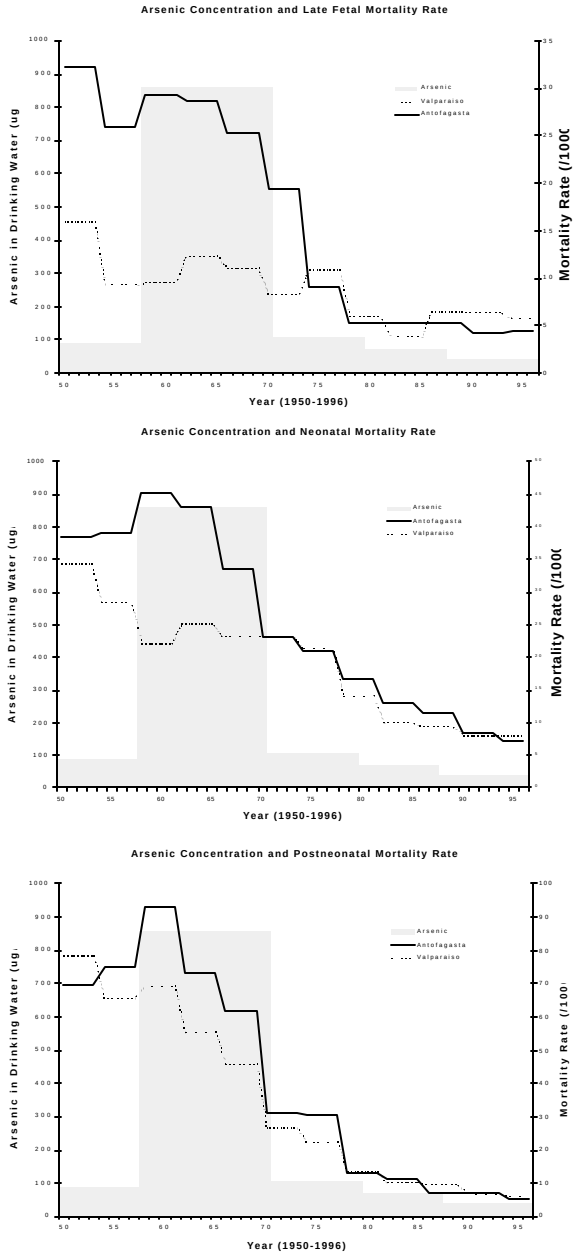

Figure 4. Arsenic Concentration and Reproductive Outcomes.*

*Note: Effects data are drawn from Table 3 in Hopenhayn-Rich, et al. (2000). The results were reported as the average of 4 year periods. Arsenic concentration data for the town of Antofagasta are from their Table 2 and were reported as the average of existing measurements for groupings of specified years (1950-1957, 1958-1970, 1980-1987, and 1988-1996). The year groupings for concentration data did not coincide with the year groupings for outcomes data. To depict the results, the average value are shown for each of the years in that group with shading in the figure. The increase in arsenic in 1958 was caused by using a new drinking water source for Antofagasta. In 1970, an arsenic-removal plant was installed and the arsenic concentration in the drinking water fell. The control town, Valparaiso, has no historical evidence of high arsenic concentration (noted in the text as below 5 ug/L in recent surveys and below the detection limit (20 ug/L) in more recent monitoring (1990-1994).

non-zero exposures to arsenic. Benchmark doses (BMDs) can be computed from a dose response model fitted to the village data and extrapolated to zero, or from models that use population-based data to specify expected cancer rates at the zero level of exposure. In going beyond the analysis in the NRC report, the expanded analyses of Morales, Ryan, et al. suggests that estimated BMDs are highly sensitive to inclusion of a comparison population. In addition to data on the whole of Taiwan, as was done in the NRC report, Morales, Ryan, et al. also considered a smaller comparison population based only on the southwestern region of Taiwan.

The expanded analyses of Morales, Ryan, et al., which included log and square root transformations of exposure, suggested that BMDs derived from models that include a comparison population could be an order of magnitude lower than those based on models that do not include a comparison population. For example, they found a 1% BMD of 23 µg/L for male bladder cancer f rom the best fitting model which includes the whole of Taiwan as a comparison population. The analogous result based on using only the southwestern region was 54 µg/L. In contrast to the variability of BMD estimates based on models that included a comparison population, Morales, Ryan, et al. (2000) found a high degree of stability for models fitted without use of a comparison population: 1% BMD estimates were consistently found to be around 400 µg/L.

Morales, Ryan, et al. (2000) also extended the NRC analysis to consider additional classes of dose response models and by including lung in addition to bladder cancer. An important finding was that arsenic associated risks from lung cancer are of a similar magnitude to those for bladder cancer. For example, the 1% BMD for lung cancer based on the best fitting model (no comparison population) was 343 µg/L for males and 256 µg/L for females.

The Panel had extensive discussions about the validity of estimates based on models that do not include a comparison population. Most members believe that possible reasons for not using models that include Taiwan-wide data as a comparison population include differences in lifestyles between the poor and rural population in the Taiwan arsenic endemic region and the general Taiwanese population and the influence of arsenic in food on risk in the population living in the arsenic endemic region. This could mean, for example, that someone classified as being exposed to 40 µg/L in water might actually have received a total exposure of 80 µg/L. BMDs calculated from models that include a comparison population will be particularly sensitive to bias in this setting, since the general population will not have the same background levels of arsenic or the same nutritional status as the study population. In contrast, analyses that use only data from the arsenic endemic region should provide fairly accurate estimates of the risk associated with incremental increases in the amount of arsenic in drinking water.

The Panel noted that issues related to choice and inclusion of a comparison population are also problematic for the Utah study (Lewis, et al., 1999). The study population in Utah was based on records from the Church of Jesus Christ of Latter-Day Saints. Just as in Taiwan, there are good reasons to believe that the analysis could be confounded by lifestyle differences between the study population and the general population in Utah. Indeed, the variability seen in the standardized mortality ratio (SMRs) reported in the study emphasizes this concern. The Panel recommends that additional

analyses be performed using data only from the study population and focusing on dose response within that population. The Panel is also concerned about the way in which exposure levels were categorized in the Utah study: by classifying subjects in terms of ppb-years of exposure, the study induces an association between exposure and age. The Panel recommends that the analysis be done with exposure represented by concentration in drinking water, not ppb-years of exposure. Then adjustments for cumulative exposure can be made separately.

Although the data provided in published results of the Lewis, et al. (1999) study imply that there was no excess bladder or lung cancer in this population, the data are not in a form that allows dose-response to be assessed dependably. In the public comment period during its June 5-7, 2000 meeting, the Panel learned that some of these data were being reanalyzed and that some changes in the results could occur. In terms of the cancer risk, this analysis is important for establishing the range of uncertainties that come from attempting to adapt data from Taiwan to estimating dose-response characteristics for the U.S. The completion of these analyses are important to the longer term consideration of arsenic risk in drinking water. However, the Panel does not think that the Agency should delay currently planned actions to decrease the MCL while the reanalysis is completed.

In summary, the Committee concludes that the Morales, Ryan, et al. (2000) paper is a useful expansion of the analysis provided in the NRC report. Risk estimates based on the use of population-based comparison groups appear to be unstable and lead to risk estimates that are unrealistically high. There is good reason to rely on the estimates that use only the data from the study area (i.e., no comparison population). These estimates consistently and stably predict a risk of a magnitude of one in one-thousand for both bladder and lung cancer at the current MCL of 50 µg/L using a linear model.

In the comments introduced into the record by one EC member as the Panel's Arsenic Report was being reviewed by the SAB Executive Committee (comments originating from Dr. Alan Smith, also of the NRC Arsenic Subcommittee, objected to the Panel's conclusions about the Morales, Ryan et al. model without a comparison population. He disagrees that EPA should rely upon this model for its evaluation of arsenic carcinogenicity. These comments are included in Attachment C.

The remainder of this subsection focuses more specifically on some of the factors that might account for differences in apparent susceptibility of the Taiwanese population to cancer and other adverse health effects relative to the U.S. population.

3.2.1.1 Shortcomings of the Taiwanese data.

As pointed out by NRC (1999), the Taiwan data has serious limitations for use in a quantitative assessment of risk in the U.S. (e.g., see comments on pages, 2 regarding improving the validity of risk assessment, p. 8 on other factors, p. 294 on cautions about exposure measurement and grouping). Below, the Panel reinforces these cautions from the NRC and briefly describes uncertainties that make it impossible to determine the extent to which well known risk factors for lung and bladder cancer might have contributed to the observations in Taiwan and therefore, have implications for arriving at an MCLG. This is not simply a question of inadequate knowledge of the smoking habits, endemic disease

and nutritional factors within the population, but of whether these factors might significantly modulate the arsenic effect. Considerable evidence has accumulated in recent years that arsenic has more marked properties as a cofactor (e.g. co-carcinogen, promoter, and perhaps progressor) than as the sole initiator of cancer. The area in Taiwan in which the arsenic exposed population lives is rural, quite poor, and has varying degrees of evidence of nutritional deficiencies that may be reasonable contributors to the observed effect either directly or indirectly enhancing the effects of arsenic. The sensitivity of the risk estimates to the use of comparison groups of the whole of Taiwan, or even the Southwestern area of Taiwan that includes the study population, highlights this issue. Comparing these results to the assessment of risk over gradients of arsenic suggests the possibility that these other factors also contribute to cancer risk in the area. This is because the dose-response curve can be viewed as having a non-zero intercept on the Y-axis when only the study population is considered. Despite its limitations, the results of the Utah study also suggest there are potential differences between the affected population in Taiwan and the U.S.

Considering the above factors leads to a conclusion that transferring the dose response curves describing the cancer risk in this section of Taiwan to the U.S. is likely to bias U.S. risk estimates towards overestimates. The magnitude of this bias could be large, but the Panel does not have the resources to resolve these issues more definitively.

3.2.1.2 Effects of nutrition and preexisting disease in populations that have been studied

A number of mitigating circumstances were identified in the NRC (1999) report that suggest that risk levels calculated from the Taiwanese data should not be rigidly extrapolated to the general U.S. population. Poor nutritional status is known to be characteristic of this population and others (Chile, India) that have been studied. A recent cohort study in Utah (Lewis et al., 1999), found no evidence of either bladder or lung cancer where mean drinking water concentrations of arsenic approached 200 µg/L. While these concentrations are up to an order of magnitude lower than found in sites where positive associations with cancer have been obtained, these results give rise to significant questions about whether the Taiwan data apply quantitatively to those U.S. populations that have a more adequate nutritional status.

Experimental work in animals establishes that deficiencies in selenium substantially increase the toxicity of arsenic (Pan et al., 1996). The NRC (1989) report summarizes the results from a survey of urinary selenium concentrations in Taiwan and other parts of the world. Essentially, the study population in Taiwan was estimated to have selenium intakes that were only 25% of the recommended dietary intake (NRC, 1989). Their intakes are less than 50% of the safe range identified by the World Health Organization (WHO, 1996). For this reason NRC recommended that the selenium status of the Taiwan population be taken into account in transferring the data to populations that are selenium sufficient. Neither NRC or EPA made an attempt to make these adjustments. The Panel identified a number of studies that have documented substantial effects of smaller selenium decrements on cancer of the bladder (Helzlsouer et al., 1989) and lung (Salonen et al. 1985; van den Brandt et al., 1993). The Panel strongly recommends that the Office of Water take this factor into account in its risk assessment

supporting an MCL. The Panel expects that additional data exists that could be used for estimating the extent to which nutritional deficiencies of the magnitude identified in Taiwan have on arsenic toxicity in general and on carcinogenicity specifically.

Another nutritional issue that has been identified in the Taiwanese population from which the data were obtained, was the potential for less than optimal intakes of methyl donors in the diet, such as methionine or choline. There are data to suggest that hypomethylation (as well as hypermethylation) of DNA does occur with exposure to various forms of arsenic (Zhao et al., 1997 as quoted by NRC, 1999). Choline deficiency has long been used experimentally as a tumor-promoting regime in animals (Lombardi et al., 1994; Saito et al., 1994), therefore it is probable that substantive deficiencies in the diet could increase sensitivity to arsenic induced cancer in humans. However, the NRC Panel did not indicate whether such deficiencies were documented in the Taiwanese population studied. There were indirect indications of what made up a substantial portion of the diet (rice and sweet potatoes), but the estimates were not quantitative, nor were other constituents of the diet discussed in quantitative terms.

Other characteristics of the Taiwanese diet may also have contributed to the increased susceptibility to cancer. Zinc insufficiency was postulated to occur in the blackfoot region of Taiwan, but subsequent estimates do not substantiate this. Zinc can protect against acute arsenic toxicity, although its influence on the chronic effects of arsenic are not known (NRC, 1999, p. 241). For the study population the diet consisted of 9% protein, while fat contributed 5% of the caloric intake. Poor diets may have also involved limiting levels of folate, methionine, cysteine, and B12.

In some Asian countries endemic infectious hepatitis has been known to be important in sensitizing populations to the hepatocarcinogenic effects of aflatoxin (Caselman, 1996). It would be useful to consider the incidence of infectious hepatitis in the study area of Taiwan to determine if that might contribute to the increased risk for liver cancer found in some studies. The NRC did not consider this recognized risk factor in its deliberations. The DWC suggests that EPA attempt to find out whether the area studied in Taiwan also has high rates of hepatitis which is known to act as a co-carcinogenic factor in liver cancer.

In summary, the characteristics of the Taiwanese population studied for arsenic carcinogenesis are not typical of the characteristics of the general U.S. populations, but there may be segments of the U.S. population which have one or more of the same potential co-risk factors as the Taiwanese population. For example, poor U.S. subpopulations, particularly in the rural Southwest, may have some of the nutritional deficiencies of concern (except selenium) in the Taiwan arsenic endemic region in terms of nutrition, etc., and they may be exposed to high levels of arsenic in their drinking water as well. The prevalence of the risk factors mentioned above need to be evaluated in both the Taiwanese and U.S. populations. These differences raise significant uncertainties about the accuracy of risk estimates that are based on the Taiwanese data. Unfortunately, the DWC cannot be more quantitative in its own assessment for lack of resources and time. For this reason, we join with the NRC (1999) recommendation that the Agency make a stronger effort to quantify risks in a way that attempts to take these factors into account. However, this should not significantly delay promulgation of a rule that

makes a significant reduction in the MCL for arsenic as there may be populations with similar nutritional deficiencies within the U.S.

3.2.1.3 Modes of action attributed to arsenic are sublinear.

Cancer has been produced in experimental animals with arsenic, but a measurable response has been most readily observed when combined with other treatments, such as the use of a tumor initiator (see Shirachi et al., 1983; Laib and Moritz, 1989). Yamamoto et al. (1995) using several different initiators, found DMA to be an effective promoter in the lung, bladder, kidney, liver and thyroid gland of the rat. The site concurrence for these tumors with the human data should be of interest. Wei et al. (1999) and Arnold et al. (1999) demonstrated that high doses of dimethylarsinic acid can produce bladder carcinogenesis in the rat and Ng et al. (1999) found that tumors of the lung, gastrointestinal tract, and liver were produced with 0.5 mg As/kg water as sodium arsenate.

Studies of arsenic's effects at the cellular and molecular level support a sublinear dose-response model (NRC, 1999). Its apparently non-linear effects in producing structural and numerical chromosomal abnormalities through apparently indirect mechanisms are one example. Similar arguments would be developed for the "comutagenic" activity of arsenic. Other plausible modes of action include modification of DNA methylation (presumably caused, in part, by arsenic's competition for methyl donors) are associated with altered gene expression. It would be anticipated that these effects behave in a sublinear way at low doses (i.e. possess effective thresholds).

There are abundant data that associates various forms of arsenic with a variety of mechanisms or modes of action. If they could be shown to uniquely or collectively account for human tumors, the dose-response curve could be viewed as being sublinear at low doses. NRC (1999) pointed out, however, that none of these alternative modes of action have been clearly demonstrated as essential in the development of arsenic-induced tumors. In most cases, even dose-response information showing parallels between those that produce tumors and those that activate these other mechanisms have not been explored. Therefore, the NRC concluded that the prudent course would be to use linear extrapolation. However, the data derived from studies attempting to identify mechanisms that are outlined in much more detail in the NRC report, suggest that applying linear models for low dose extrapolation may be conservative. In future risk assessments for arsenic in drinking water, the Panel suggests that the Agency explore additional models, [one such model would be the Moolgavkar, Venzon, Knudson (MVK) model].

3.2.1.4 Use of experimental data that were available and the need for further research

Because the Agency is presumed to be acting under a new set of cancer risk assessment guidelines, the Panel was somewhat surprised that the Agency did not at least provide some summary of the data that are available and how they inform the current risk assessment decision made by the Agency. There have been substantial breakthroughs in the development of animal models of arsenic carcinogenesis in the past several years. In part these data point up the weakness of some of the

arguments that have been made to attribute cancer risk to inorganic arsenic alone. The relative ease of producing bladder cancers in rats with dimethylarsenous acid may require some shift in the paradigm.

The Panel recognizes that in the case of arsenic where the margins between actual exposures and effects are small compared to most other contaminants, the final decisions will involve many non-scientific issues. However, these data are essential for identifying susceptible populations and need to be forcefully pursued before the arsenic MCL undergoes its next review cycle. The fact that they are not acknowledged in the documentation put forward by EPA provides no further encouragement to pursue these issues in the future. Consequently, we have taken this opportunity to comment on some of the research results that the Panel feels provide direction for future research in characterizing the risks of arsenic in drinking water.

Arsenic is not a classical direct acting carcinogen. It does not cause DNA adducts, nor does it induce point mutations although it can replace some of the phosphates in the sugar-phosphate backbone of DNA (Dixon, 1997). This can result in the cleavage of the sugar-phosphate/sugar-arsenate backbone and potentially in single strand breaks. This mode of action might account for the occurrence of deletions and translocations in the absence of point mutations in arsenic-induced cancer. Patrick (1964) demonstrated the incorporation of arsenic into DNA, protein, and lipid at the same rate as PO_4. Furthermore competition between these two ions has been said to uncouple oxidative phosphorylation (Frost et al., 1968). These data suggest a mode of action not yet fully explored.

AsIII can interact with thiols. This type of interaction may be important in the interaction with lecithin cholesterolacyl transferase (Jauhiainen et al., 1988) of potential relevance to vascular changes indicative of atherosclerosis.

Interactions with thiols are also significantly involved in the metabolism of arsenic. In serum, arsenic is transported bound to sulfhydryl groups of proteins, GSH, and cysteine. AsIII can form a complex with GSH (Delnomdedieu et al., 1994) and is more generally reactive with tissue than AsV. Moreover, arsenite (not ionized at physiological pH) can be taken up by liver cells and methylated, but not arsenate (ionized at physiological pH). In the kidney, however, arsenate is taken up, reduced, methylated, and released into the urine. The reduction of AsV can be accomplished by sulfhydryls. For example, glutathione can provide a reducing equivalent for AsV and the resulting AsIII can then oxidatively add a methyl through SAM (S adenosylmethionine) to produce the methylarsenic V.

There are only a few animal studies performed in the absence of a co-carcinogen that demonstrate induction of neoplasms by arsenic or one of its metabolites. The induction of bladder cancer in rats by DMA as reported by Wei et al. (1999) and Arnold et al. (1999) are of particular interest, since bladder cancer is one of the principal sites of concern in humans. These studies must be followed up. Arnold et al. (1999) have indicated that a non-linear mode of action is appropriate for DMA in the rat and hence for cacodylic acid (DMA) in the human. Genotoxic effects of arsenic appear to require substantially higher concentrations of DMA than would be observed systemically in animals provided DMA, since Moore et al. (1997) found concentrations of 5 mg/ml necessary to obtain a positive result in the MOLY assay. Also of interest is the observation that mice given a relatively low

level of arsenate, develop tumors in several organs that have counterparts in human epidemiology studies (but not in the bladder) (Ng et al., 1999). With these animal models there is now a much more reasonable path to pursue the mode(s) of action of arsenic and PB-PK analyses that may be responsible for these tumors.

The level of various arsenic metabolites in the urine, the serum, and in the target tissues and cells should be determined in these newly developed animal models. The most important questions are the concentrations and forms of arsenic responsible for each of the tumor types identified in human studies. When that information is obtained, truly useful pharmacokinetic models can be developed that will be very important in identifying the concentrations and species of arsenic formed in humans that are associated with carcinogenesis. This would help to determine the level of inorganic arsenic intake required to obtain the effective levels of arsenic metabolites under different conditions of human exposure. This will provide a much more comprehensive basis on which to determine the relative importance of drinking water and food sources of arsenic.

There are also genetic factors that increase the susceptibility to bladder cancer that might contribute to the background rate of tumor incidence that is independent of arsenic exposure. The prevalence of the GST-mu null and certain polymorphic forms of NAT2* (Bell et al., 1993; Eaton and Bammler, 1999) in the Taiwanese population (Chiou, et al. 1997) were not discussed by the NRC (1999) and, we presume they were not explored. These variables have been important modifiers of risks in smoking populations (Wen et al., 1994; Salagovic et al., 1999).

4. TREATMENT TECHNOLOGY AND COST ISSUES

4.1 Comments on Treatment Technology Issues

4.1.1 Charge Question 4: **Disposal Options.** Based upon a review of the attached materials, does the SAB believe that the EPA produced an accurate projection of the likely disposal options for arsenic residuals and the distribution of these options by treatment type? What are the SAB's views on the advantages and the limitations of the various waste disposal options? What effect, if any, would the SAB's analysis of these advantages and limitations have on the probabilities assigned? What are the SAB's views on which options will be more likely used by small systems (less than 10,000 people), and which will be more likely used by larger ones?

The Panel believes that, based on the information provided to it by EPA, that the Agency appears to have considered the spectrum of residual disposal alternatives. However, the Panel questions whether certain alternatives will be viable due to potential constraints placed on utilities. For example, the Panel believes that disposal of ion exchange (IX) or activated alumina (AA) treatment residuals to a publically owned treatment work (POTW) might not be acceptable in the majority of systems because of the high Total Dissolved Solids (TDS) concentration in those residuals. This is especially problematic in the southwest where treated wastewater is reused for irrigation and groundwater recharge and salt concentration is very important. Additionally, POTWs generally are opposed to receiving dilute organic wastes that can reduce the efficiency of biological treatment. This is the case in systems such as in Des Moines, Iowa. This would reduce the probability of selection for those alternatives which rely on these disposal options to near zero.

Additionally, the Panel feels that the assumed non-hazardous classification of the waste brines and sludges is questionable in the economic analysis. It is clear that in many cases in California the wastes would be classified as hazardous because of the waste characterization procedures used their and this could result in a public water supply choosing another alternative. Furthermore, the Panel has concerns related to the Toxicity Characteristic Leaching Procedure (TCLP) test which is used in other areas of the U.S. as the standard test for hazardous waste determination. The TCLP is designed to maintain a pH of 5-6, which represents the best cast scenario for arsenic binding to sludge. Therefore, while an arsenic-laden sludge may pass the TCLP test it may still leach arsenic into the groundwater under normal pH conditions found in some landfills. Additionally, characterization of lime softening (LS) sludge by the TCLP test is suspect because the target pH of the test (pH = 5) is likely to be overwhelmed by the acid neutralizing capacity of LS sludge.

4.1.2 Charge Question 5: Decision Tree for Treatment Technologies. Does the SAB agree with the principal "branches" of EPA's decision tree described in the attached documents and the likelihood that these options will be used for systems of various sizes with various source water characteristics? What views does the SAB have on EPA's description of the advantages and limitations of these treatment technologies? Would the SAB's views on the these advantages and limitations affect the probabilities assigned?

It was very difficult for the Panel to address this charge question without having the detailed documentation on the decision tree that was used by EPA to predict technology selection and cost. As a result the Panel was not able to follow, nor comment extensively upon, the "decision tree." Generally, the Panel feels the cost estimates predicted for the rule, on the basis of the Agency's decision tree analysis of applicable technology, appear to be low. From the limited information provided and from presentations to the Panel at the June 5-7, 2000 DWC meeting, the model seems to have certain deterministic and probabilistic components that make it quite complex.

In spite of the limitations noted above, the Panel does provide the following observations on some of the assumptions used in the model:

a) The list of best available technologies (BATs) seems to overstate the real situation. It is the opinion of the Panel that none of the technologies listed as BAT have been demonstrated in full-scale operation for arsenic removal. While it is true that some of the technologies are used in full-scale water treatment, they have not been operated optimally for arsenic removal. This optimization may result in a substantially different control strategy from the traditional operation.

b) The Panel is concerned that the list of BAT technologies may bias technology selection by community water systems (CWSs), and particularly to bias selection against some of the more promising emerging technologies [e.g., granular ferric hydroxide (GFH)].

c) The model does not appear to account for land acquisition cost. For groundwater systems using multiple entry points, this may be a substantial cost when wells are located on small lots of land within developed portions of a city.

d) It appears that the cost of replacement chemicals is not included in the cost of removing arsenic. In particular the cost of fluoride replacement when the resulting concentration is below optimum should be included in the cost of arsenic removal.

e) It is not clear that the monitoring burden and costs associated with point-of-use (POU) and/or point-of-entry (POE) systems is adequately represented in the costs for these technologies.

f) It is not clear that EPA has considered the need for increased training and certification of operators (or even availability of personnel) for a large number of very small systems. The Panel is concerned that this might lead to closure of some of these systems and increased reliance on private wells.

g) It is clear to the Panel that there are uncertainties contained in the model that result in uncertainties in the output. It would be more appropriate to present the output with a range of results than a discrete number. It is the feeling of the Panel that the range of uncertainty is larger for an MCL of 5 µg/L as compared to a value of 10 µg/L or 20 µg/L.

4.2 Other Issues Associated with Cost

4.2.1 Affordability and Risk Tradeoffs

In the previous section of this report, the Panel discussed its concerns with EPA's designated best available technologies (BAT) for arsenic removal. A related issue was raised during these discussions which focuses on whether the identified technologies are affordable to small community water systems. Even though the Agency notes that the listed BAT pass the affordability criterion and thus will not result in the use of variance technologies, the Panel still is concerned that if the technologies are too costly, they might force tradeoffs that do not maximize the gains to public health for persons in those communities where a co-occurrence of small system size, high arsenic water concentrations, and poor/susceptible population groups might exist.

The SAB previously commented on issues related to this concern when it commented on the Agency's efforts to develop a national affordability criterion for the U.S. (SAB, 1998). In that advisory the SAB called attention to the fact that there was no Agency definition of "national affordability" and it anticipated difficulties in utilizing a national criterion in a rule that disproportionately impacts small systems. The DWC comments here relate more to concerns about how affordability might affect community and individual behavior and potentially force trade-offs that do not seem to have been considered by EPA.

The Panel is encouraged that under the approach used to determine the need for variance technologies that inequitable situations will not be created across systems of various sizes, that is, that some systems will not be required to use technologies that lead to a greater risk than in other systems. However, the Panel believes that the situation might be more complex than that which is addressed under the affordability criterion itself. The Panel concern is with how individual households at the lower end of the income distribution within an area might be limited in their ability to make tradeoffs that influence their overall health status because of the involuntary allocation of additional income to lower arsenic levels in their drinking water.

A number of scenarios are possible. For example, it is possible that these same households might, as a consequence of nutritional or other factors resulting from their economic situation or because of an increased susceptibility, sustain a greater risk from elevated arsenic levels. In this case, it would be reasonable to expect that the result of any disproportionate cost they would sustain in paying for decreases in drinking water arsenic would be a greater than average gain in benefits and the two might offset one another in a cost-benefit analysis. However, there could also be a situation in which some of the increased arsenic risk, or other risks might be linked to nutritional factors. In these cases, allocation of income to arsenic might preclude addressing nutritional factors that could possibly result in even greater gains to the individual's health. It is important to note that this situation would apply to large as well as small communities, because not all of the 13 million Americans that live below the poverty line live in communities served by small water system. The Agency should consider the impact of these multiple tradeoffs as it promulgates a final MCL and decide how they influence the final risk picture in such communities.

The key to the above concern is who eventually has to pay for arsenic removal and what actions they will take as a result. In most areas, households will have to pay for the cost of arsenic removal. Too high treatment costs could shift these populations away from a small CWS to untreated sources of lesser quality and treatment that could influence risks realized from microbial and other contaminants, including arsenic. To avoid such outcomes the Agency and States might need to consider how their loan and grant funds are used to help communities comply with the rule.

It is also not apparent to the Panel how the economic impact of other regulations promulgated or in place might influence this problem. Arsenic control is but one of many issues that face drinking water system as a result of new and potential rules (e.g., radon, disinfection byproducts, long-term enhanced surface water rule, filter backwash, etc.). Compliance with this constellation of rules presents additional tradeoffs that need to be considered in the evaluation of risks and in the use of the funds available for drinking water treatment.

The Panel encourages the Agency to consider the issue of affordability in a broader context than that addressing the limited issue of the affordability criterion and the use of variance technologies.

4.2.2 Need for Performance Data on Arsenic Technologies and the Possibility of Adaptive Management

The Panel recognizes that selection of the MCL is within the policy domain of EPA and that it is not just a scientifically derived number. In setting a Maximum Contaminant Level, EPA must consider costs of implementing the rule and the benefits of decreased health risks. Considerable uncertainty exists in the calculation of both costs and benefits for this rule. Even so, it was the unanimous opinion of the DWC that the MCL needs to be reduced from its current level of 50 µg/L. Each member of the DWC has his/her own views about why the MCL should be more or less restrictive.

Uncertainties in the health data exist and cause some to suggest that an even more cautious MCL selection is appropriate while others suggest a higher MCL is warranted because the Agency neglected many cautionary statements provided in the NRC document about the shortcomings of the Taiwanese data for estimating risks in the U.S. The Panel believes that the uncertainties in applying risk estimates from the study population in Taiwan to estimation of cancer and non-cancer risks from arsenic in the U.S. are very large. Some of this concern over the uncertainty could be resolved if the Agency would extend the analysis of the potential effects of the uncertain risk factors, thus following the advice of the NRC to perform additional formal risk assessments on these data that consider how these factors may have modified the responses to arsenic.

The Panel believes that there is uncertainty in both the health effects and the limited technology and cost analysis information that it was provided by EPA. This could result in substantial uncertainty in the final national cost and benefit estimates for reducing the arsenic MCL from 50 µg/L to 5 µg/L. Further, this uncertainty is substantially greater at low values of the MCL (see the illustration in Fig 5 which uses an uncertainty factor of 30% as an example). As such, it appears that the outcome of mandating such technologies across the country before reliable information on their performance is available will be difficult to predict. The Panel suggests that the Agency consider whether it might be appropriate to gather performance data for technologies identified by their decision tree as it has done in some earlier situations. For example, such a rationale was used in the Information Collection Rule (ICR) which required collection of data on the performance and cost of certain treatment technologies during the Microbial/Disinfection Byproduct regulatory process. These data, which were not available on a national basis, were needed before these treatment technologies were to be implemented by utilities across the country.

When the uncertainties that arise from reliance on the Taiwanese data are combined with the apparent overestimation of the lung cancer risks in the Agency's benefit analysis and the substantive costs of implementing the lowest MCLs considered by EPA the Panel believes that EPA could judge that it has sufficient grounds to consider an alternative MCL for arsenic under the discretionary authority of the 1996 SDWA Amendments. There are technological uncertainties and they impact on implementation costs. These considerations could be addressed by implementing the reduction in a phased manner, that is allow a lesser reduction of the MCL, initially.

The recommendation for a stepwise approach could be supported by the following rationale:

a) Setting the initial MCL at a level intermediate between the current MCL and a long term target would require the utilities with the highest level of arsenic to implement arsenic treatment first. The resulting reduction in the number of systems that have to initially comply will greatly reduce the cost of this rule. More importantly, it would allow for the gathering of "real life" data on the performance and cost of various technologies for arsenic removal without establishing a regulation that runs the risk of

imposing very substantial costs on the nation prior to determining the full impact of doing so.

b) It is noted that these arsenic treatment systems will utilize the same technologies set as BAT by the EPA, and most of them (such as IX and AA) will produce waters that have arsenic levels at or less than 3 µg/L virtually all the time. Therefore, if the later rulemaking activity sets a lower MCL, these systems will be able to comply with these lower MCLs without further incremental costs. Any subsequent lowering of the MCL will simply increase the numbers of systems that will be required to treat to control arsenic.

c) In addition, the installation of these treatment systems will also allow the EPA and the industry to evaluate the validity of the assumption that the solid residuals from these technologies can be disposed in municipal landfills. This issue has a significant impact on the national cost of an arsenic MCL.

d) The feasibility of financing, designing, constructing, and commissioning of a large number of treatment systems is in question. A stepped rule will allow for a more practical implementation schedule.

e) Under the assumption of linearity, the efficiency of risk reduction is greater (i.e., the costs per unit risk reduction are lower) at the higher arsenic concentrations, in other words, the first increments of arsenic reduction below 50 µg/L are more cost-effective than further reductions, at least for small systems (Figure 3B). If future research establishes parameters for a sublinear dose-response curve, then the differences in efficiency at the upper ranges of the exposure distribution relative to the lower ranges of the exposure distribution would be even greater than the differences under a linear-dose response curve.

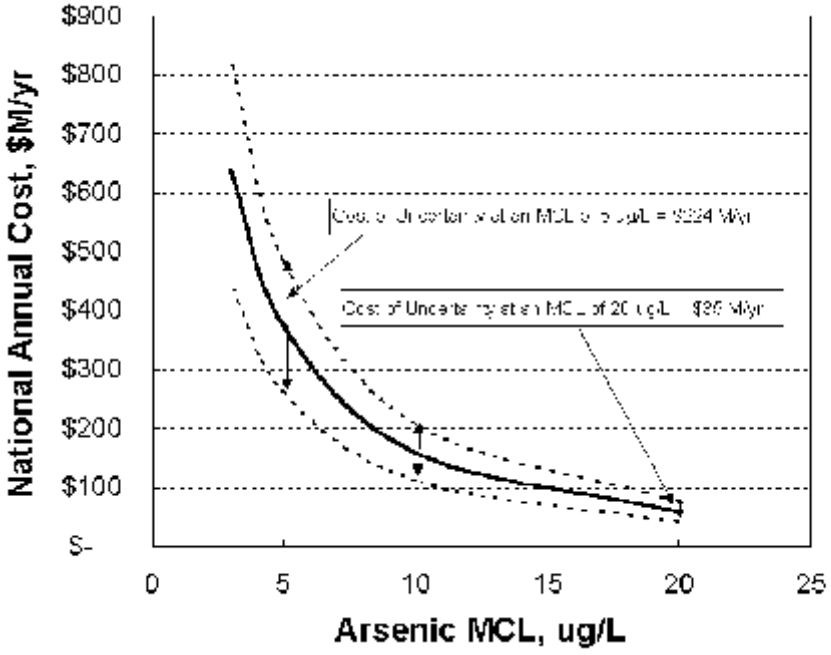

Figure 5: Cost of a 30% Uncertainty (as an example) in EPA's National Cost Estimate

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ATTACHMENT A

A MINORITY REPORT ON ARSENIC IN DRINKING WATER: THE UNIQUE SUSCEPTIBILITY OF CHILDREN TO ARSENIC

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********SUBMITTED TO THE US EPA'S SCIENTIFIC ADVISORY BOARD ON ARSENIC IN DRINKING WATER ON SEPTEMBER 1, 2000********

I. *SOME PRINCIPLES OF PEDIATRIC AND DEVELOPMENTAL TOXICOLOGY*.

Some basic principles of pediatric-developmental toxicology are presented below. In the following section **(II)**, the unique susceptibility of young children to arsenic is outlined, within the context, phrased simply, that children are not young adults; differences in diet, metabolism, body weight, variable age groups, consumption of water, toxic effects of metal pollutants in a rapidly growing organism, and exposure estimates per unit of body weight are essential ingredients of risk assessment in

children. In brief, determination of safe levels of exposure to arsenic should take into consideration physiological factors that can place the fetus, infant and young child at greater risk of harmful health effects than adults. Differences in size, maturity of biochemical and physiological functions in major body systems, and variation in body composition(water, fat, protein and mineral content) all can modulate the severity of toxicity to any toxicant in a rapidly developing fetus-infant-child, *including arsenic*. Because newborns are the group most different anatomically and physiologically from adults, they can exhibit the most pronounced quantitative differences in sensitivity and susceptibility to environmental toxicants, including *arsenic*(1-6).

Furthermore, uncertainty factors are widely used to establish guidelines for human exposure. This is often accomplished by dividing the no-observed-effect-level(NOEL) by an uncertainty factor of 100 in animal studies. This factor comprises two separate factors of 10-fold each: one allows for uncertainty in extrapolating experimental data to humans; and the other accommodates variation within human populations. To provide added protection during early development, a third uncertainty factor of 10 is applied to the NOEL to develop the RfD. Because there exist uncertainty factors relating to susceptibility and vulnerability during early fetal, neonatal and childhood developmental toxicity, an additional 10-fold factor is used by EPA and FDA when testing data relative to children is incomplete. This is not a new or additional uncertainty factor but an extended application of uncertainty factors *routinely used by agencies of the U.S. Government*(7-9). In risk assessment, when there is some level of uncertainty relating to the overall quality of available data, *an additional factor, typically 3-fold, is included as a "modifying" factor*. In summary, there are unique risks and increased susceptibility of the fetus, young infant and child to damage from environmental chemicals, including arsenic. These risk assessment paradigms are recognized broadly by the U.S. government. Arsenic fits directly into the above paradigms.

II. *THE UNIQUE SUSCEPTIBILITY OF YOUNG CHILDREN TO EXCESSIVE TOXICANT EXPOSURES*:

The NRC/NAS(10) recognized that a margin of safety may be needed when conducting risk assessments of arsenic, because of variations in the sensitivity of individual subpopulations.

Some general concepts followed by specific examples in different organ systems are provided below.

Children are a unique population; and their risks can differ qualitatively and quantitatively from those in adults(10,11) *These differences include organ systems that are primarily affected by arsenic, such as the central nervous system, cardiovascular development, reproductive and developmental organs and cancinogenesis*(10).

Physiologically, respiratory and circulatory flow rates, as well as cellular proliferative rates, in many organs, are greater in children versus adults. From a metabolic standpoint, some enzymatic pathways are more efficient in the young(the P450s peak in adolescence) and others are far less effective in young children, such as glucuronidation. Developmental changes in cell permeability, binding and storage modulate the distribution and excretion of xenobiotics. The amount of water

intake(see below) and dietary status differ in young children compared with adults. From an environmental standpoint, living space and habits, specific to neonates and young children, are highly specific for these young age groups. Clearly, variations in chemical sensitivity and exposure exist in children in contrast to adults; and developmental changes from fetal to newborn to postneonatal to adolescence periods are superimposed on genetic and environmental variables in the young child, which are evidently different from those in adults. Moreover, early exposure in infancy to toxicant metals, such as lead(12) or arsenic(13) can lead to latent adverse health effects that become manifest later during adulthood.

Excretory capacity, in relation to the kidney, undergoes a considerable amount of maturation with aging. Renal clearance is reduced at birth and gradually matures over the first few years of life; and similar maturation in the liver, in the metabolism of xenobiotics, also occurs with aging.

In terms of water intake, body mass and cellular proliferation, in the brain, for instance, the differences between young children and adults are marked. 1) *The body surface:body mass ratio declines by about 66% from infancy to the adult years*; 2) Brain growth is extremely rapid in the first two years of life. About 75% of all brain cell types are present by the age of two years; and the brain represents a considerably larger portion of an infant's body mass compared to that in adults. Cerebral blood flow is also far more robust: a ten year-old has a flow rate of about 50L/Kg brain weight compared to about 40L in a 65 year-old adult. Thus, the younger the child, both brain mass and cerebral blood flow are considerably greater in contrast to adult values; 3) *The Tolerance Assessment System(TAS), used by the US EPA, indicates unequivocally that infants and young children consume the highest amount of water per unit body weight during their entire lifetimes.* An infant, a 1 to 6 year-old, a 7-12 year-old children consume 28 grams of water/Kg body weight/day, 30 grams of water/Kg body weight/day and 17 grams of water/Kg body weight/day, respectively, in contrast to an adult who typically consumes about 10 grams of water/Kg body weight/day. Obviously, the intake of arsenic from drinking water will be greatest within the pediatric age group**(**11**).**

In addition to all the above differences between children and adults, it can be concluded that infants and young children, *in contrast to adults*, have different exposures to toxic metals in water, have different life expectancies, absorb and maintain unique internal doses of a toxic metal from similar external exposures and respond differently and specifically to the same internal dose of a toxic metal.

III. ***THE CENTRAL NERVOUS SYSTEM(CNS):***

Development of the human CNS involves the production of 100 billion nerve cells and 1 trillion glial cells(5). Once produced, these cells undergo migration, synaptogenesis, selective cell loss and myelination. This progression occurs unidirectionally. Thus, inhibition at one developmental stage can cause alterations to subsequent processes. Developmental stages occur in temporally distinct time frames across different brain regions thereby making the brain heterogeneous in response to agents that interfere with specific processes. Unlike other organ systems, the unidirectional nature of CNS development limits the capacity of brain tissue to compensate for environmentally induced cell loss.

Maintenance of this rigid temporal and spatial schedule allows the brain to develop its various functions. It is this developmental complexity that underlies the sensitivity of the CNS to environmental insults and emphasizes the unique characteristics of development which place children at special risk from environmental exposures. In 1984, the US EPA indicated that children may be more susceptible to arsenic-induced CNS damage(14**).** For example, severe CNS deficits were observed in children exposed as babies to arsenic-contaminated powdered milk formulas. Follow up of these babies into childhood revealed an increased incidence of severe hearing loss, abnormal EEG patterns, and an increased prevalence of mental deficiency, seizures and other indices of severe brain damage.

IV. *THE REPRODUCTIVE SYSTEM:*

Toxicant exposure is known to affect critical events in the development of the reproductive system(15). Once exposure has sufficient influence on essential reproductive events, adult reproductive competency is reduced or abrogated. Critical windows of development are limited temporally and characterized by occurrence of sets of organizational events that constitute periods during which exposure can have effects on later reproductive competency. Environmental exposures can influence fertility to early embryo loss. Although early embryogenesis is a critical target of toxicants, preconceptional and even postnatal exposures may also adversely affect the reproductive system and progeny outcomes.

V. *THE CARDIOVASCULAR SYSTEM:*

Three to eight weeks following fertilization is the critical time period of organ(heart) formation. At that time, stem cell populations for organ morphogenesis are established and inductive events of differentiation occur(16). During this time, structural defects in the heart can ensue. It is this very narrow time frame when the anlage of the heart is first established. Moreover, later adverse effects can occur as various cell types begin to differentiate.

VI. CARCINOGENESIS:

The relevance of carcinogenesis to at risk children is discussed on pages 5 and 6 (Section **VII.4**).

VII. *THE IMPACT OF ARSENIC ON CHILDREN:*

1) The NAS/NRC document on arsenic(10) concluded that the current MCL of 50 ug/L does not achieve EPA's goal for public health protection and, therefore, requires downward revision as promptly as possible. Similarly, Morales, Ryan et al., (13) also concluded that 50 ug/L of arsenic is associated with a substantial increased risk of cancer; and this MCL is not sufficient to protect the public's health. For adults, EPA found that the safe level of arsenic, to avoid non-cancer diseases, is 0.3 ug/kg/day(U.S EPA. IRIS online: Arsenic, inorganic: 4/10/98, 0278, off the internet 5/15/00**).** To extrapolate this value to young children requires dividing the above intake by a factor of at least 6-10(see above and below). Morever, if the daily intake of arsenic by an adult is about 21 ug/day, and

the water intake is about two liters, this equals arsenic at a concentration of about 10 ug/L. For Superfund sites of which I am familiar, (Palmerton and Throop, PA and Kellogg, ID), this places arsenic in the category of an hazardous toxicant at Superfund sites for adults, without any consideration for the increased susceptibility of young children. As defined by EPA, any MCL above 5 ug/L is, at the very least, an hazard to human health and even more so for children(see below).

2) In children, the arsenic dose per unit of body weight is about 6-fold times higher than in adults(17). Calderon et al.(17) concluded that the age-dependent difference in arsenic urinary concentrations can be attributed to the higher dose per unit body weight in children versus adults.

3) In a broad range of ages, children do not detoxify arsenic as efficiently as in adults (18, 19). The net result in children is that increased amounts of arsenic are available to produce toxic effects.

4) Toxic exposures to the fetus and in childhood are recognized determinants of cancer in adulthood(20-23); and such periods of latency have been demonstrated for hepatitis B exposure in infancy leading to hepatocellular carcinoma in adults(20). Morever, models exist of multi-step carcinogenesis incorporating initiation and progression to latent expression of disease. Toxicant exposure during conception or pregnancy can provide the initial mutational event that provides increased risk of cancer during adulthood. An adult will be at higher risk for cancer, once a germline alteration occurs; toxicant exposure can lead to somatic alterations postnatally with long latency periods(20-23).

Children have a general sensitivity to carcinogens that can be demonstrated by early biomarkers of cancer; and this may foretell an unique sensitivity in childhood even when cancer latency is long(22,23). It is important to point out that cancer biomarkers in young children vary considerably with ethnicity(22); and this observation may place specific ethnic groups of children at higher risk for developing arsenic-induced cancer as adults(22). Although there is presently an absence of longitudinal studies of excessively exposed young children to arsenic, ultimately leading to cancer in adulthood, the pathophysiological frame work exists in the fetus, infant and young child for such events to occur. Thus, the fetus, infant and young children should be considered to be at increased risk for developing arsenic-induced cancers after long latency periods.

5) To dismiss the Taiwanese data(24) in young and older children in this country is a simplistic approach to this country's pediatric population. The majority report posits that all American children, exposed to arsenic, have a nutritional status that is *complete* compared to the Taiwanese population. "If individuals in the Taiwan endemic zone were at added risk for arsenic effects by virtue of poor nutritional status, then individuals anywhere with this risk factor are of concern(25)." There are about 13 million American children who are living below the poverty line today in the United States(New York Times. 8/13/00) of diverse ethnicity(African-American, Hispanic and Native American children); and these subpopulations of American children, except, perhaps, for selenium, are more likely than not to be in poor nutritional status. Indeed, Smith(26) found the prevalence of skin lesions among men and children in a relatively small population, who had been drinking water containing excessive quantities of arsenic for decades within Northern Chile, was similar to the prevalence of these arsenic induced skin

lesions reported from Taiwan and West Bengal(27). However, the North Chilean population was nutritionally sound in contrast to malnutrition reported from Taiwan and West Bengal. Although the sample size was small in the North Chilean population, the findings were robust.

The above reality is especially operative for arsenic and nutritionally at-risk children in America. Many of the areas of the United States, which contain relatively high-risk fractions of particularly at-risk children, including Native American children, are also those areas where water arsenic levels are high, such as in desert areas of the Southwest. Arsenic-laced water consumption among risk groups in the Western United States would parallel the case for the Taiwanese, even if one were to accept that nutritional deficiencies were pivotal and determinative for carcinogenic and other non-cancer outcomes in the Taiwanese people.

Welch et al.(28) recently summarized data from the United States Geological Survey at an International Conference on arsenic exposure and health effects. Analyses were based upon over 17, 000 analyses of arsenic recorded by the USGS National Water Information System(NWIS). NWIS data revealed that Western areas of the United States have significantly higher rates of exceedences using any standard cut-point for arsenic (current or proposed EPA, current WHO) compared to water supplies in the East. These data are also in agreement with a related survey, namely, the National Arsenic Occurrence Survey(29).

Native American children living in the Western U.S., particularly reservation populations in desert areas of the Southwest are subjected to the poorest and most risk-producing factors for adverse effects of arsenic in America. They have higher rates of poverty and typically have higher rates of nutritional deficiencies in contrast to other demographic and socioeconomic subpopulations in the United States. Furthermore, a number of Native American tribes have contemporary diets that are clinically recognized as predisposing to diverse chronic diseases, for example, cardiovascular and cancer-based adverse health effects. These factors pose additive and, perhaps, synergistic risks together with excessive arsenic intake from water. This is especially relevant to areas of the Southwestern United States.

Ballew(30) recently described data for the Navajo in a “Navajo HANES”(Health and Nutrition Survey) a demographic and ethnic spin-off of the NHANES surveys, similar to the “Hispanic HANES” carried out in the 1980s as an adjunct to the 1976-1980 NHANES II. Navajo diets are typically low in important sources of vitamins and minerals(30), as are the diets of the Hopi and the Pima(31,32).

The U.S. EPA and SAB Committee cannot claim ignorance of the potential consequences of nationally high-risk Native-American children(and adults), because the 1997 Exposure Factors Handbook, widely used by risk assessors in various U.S. regulatory scenarios, includes coverage of this issue of intakes and diets of Native Americans(33). This multi-volume EPA document presents information for Native American tribes based upon data from four of these.

Overall, the SAB Committee and U.S. EPA must address the fact that, when one looks at high water levels of arsenic that simultaneously serve as a potential water source for nutritionally-deprived and otherwise at risk Native American children and adults(who are also likely to have increased intakes of water arsenic and consume animal herds who also drink arsenic-contaminated water), these populations would be similar to the Taiwanese in terms of exposure and nutrition. The article by Harris and Harper(34) should be consulted to examine the extent to which intakes of toxicant-contaminated media are remarkably different and much higher than non-Native American populations.

My own direct experience as a clinician working with Navajo includes recently published findings that arsenic and other chemical toxicants, in tandem with radionuclides, will, in fact, produce toxic harm in utero and post-natally in Navajo children(35,36). A detailed clinical and risk assessment evaluation of two Navajo sisters, exposed in utero and in early life to arsenic and other toxicants in pit waters was carried out. They were excessively exposed to arsenic during their pastoral family activities of herding the family's sheep on the Navajo reservation in Arizona. The net CNS result was a severe toxic peripheral neuropathy and CNS cortical disease.
Through direct interviews with Navajo family members, it was ascertained that many of the intake parameters(water, in particular), described by Harris and Harper(34) as potentially elevated, were in fact markedly elevated. This Navajo family spent its herding existence within an highly arid environment coming into contact and consuming higher amounts of arsenic contaminated water than typical children or even Native American children, who did not engage in pastoral activity.

In view of the above discussion, it is reasonable to conclude that the subpopulation of American children are at higher risk for arsenic-related disease than others from a nutritional standpoint, if the postulate(relating to malnutrition) is as strongly supported as it is in the majority report.

6) The recent article by Hopenhayn-Rich et al.(37) reported elevated late fetal, neonatal and postnatal mortality in a Chilean town(Antofagasta) with high levels of arsenic in drinking water compared to a control town(Valparaiso), where arsenic levels in drinking water were less than 5 ug/L. Similar results, reported from Bulgaria, including congenital malformations(38), from Texas(39) and from other parts of the United States, including congenital cardiovascular malformations, and spontaneous abortions, collectively support the view of increased susceptibility of the fetus and neonate to arsenic (40-42). Drinking water levels of arsenic decreased in Antofagasta from 1961 on, so did the prevalences in fetal mortality rate, neonatal mortality rate and postnatal mortality rates. In contrast, when arsenic water levels were elevated pre-1961, the combined mortality rate was 68 deaths per 1000 births.

More specifically, these data reflect a dose-response curve that is typically found in the field of toxicology(43-50). From 1974-1977, although mortality rates were still elevated in Antofagasta, a gradual decline in these rates was observed as drinking water concentrations of arsenic decreased from 860 to 110 ug/L. In the period of about 1978-1982, the mortality rates in both towns were similar; but the rate of decline in Antofagasta was far more pronounced over the preceding years than that in

Valaparaiso. Moreover, the rate of decline into the 1980s was the most pronounced for postneonatal mortality in Antofagasta, with more gradual reductions in neonatal and late fetal mortality. Arsenic levels in this town were decreased to 40 ug/L from the previous value of 70 ug/L. Statistically, Poisson regression analyses(with relatively few data points) were used to fit the mortality rates as a function of the estimated exposure to arsenic by log-linear models adjusting for location and calendar time(37). Arsenic values for Valparaiso were measured by the Chilean government and the authors; levels less than 5 ug/L were reported. Data collected from water companies during 1990-1994 found that arsenic levels in Valparaiso were below the analytical detection limit of 20 ug/L.

In the report by Hopenhayn-Rich and co-workers(37), data were analyzed in 4-year blocks of time, because there was considerable variation in annual mortality rates. Nonetheless, in the majority report, these originally reported data were analyzed year-by-year; and it was concluded that a dose-response curve was absent. It is scientifically unsound to re-calculate original data by artificially creating unreported data. Using the original data, as reported, analyses were carried out by linear regression, Spearman's rank correlations, and ANOVA. The p values from these three statistical methods ranged from <0.044 to <0.01 thereby indicating a typical toxicological dose-response curve as stated above(Rosen: Unpublished observations).

Hopenhayn-Rich(37) did acknowledge the possibility of confounders in ecologic studies, such as the design of their study. However, the distinct temporal pattern of infant mortality rates in Antofagasta compared to Valparaiso argued strongly against individual-level confounders; and the changes in the arsenic levels in the water was an "indisputable" event. The authors concluded that "the results of this study indicate that exposure to inorganic arsenic from public water supplies may be associated with increased risk of infant mortality. Specifically, these data suggest that arsenic exposure may represent a greater risk for late fetal mortality with lower, but still elevated, risk for neonatal and postneonatal mortality."(37).

The findings of Hopenhayn-Rich(37) are consistent withe the report of Concha et al.(51), which showed that ingested arsenic crosses the placenta during pregnancy, producing fetal exposure, as indexed by levels of arsenic in cord blood. The levels of arsenic in cord blood approached those measured in maternal samples. While this study appeared to show that arsenic metabolites were present, at this time, it cannot be ruled out that these metabolites were toxicologically inconsequential. In fact, these data gain increased support for their toxicological significance from the findings of Hopenhayn-Rich(37), which are consistent with animal studies summarized in the NAS/NRC report(10). As noted(10), animal species do show reproductive and developmental effects of arsenic evidenced by birth defects, impaired fetal growth, and reduced survival rates for fetal and newborn animals.

Collectively, it can be concluded that the above data indicate that young children are an uniquely susceptible population for adverse health effects of arsenic. Safety information based upon data from adults, in view of all the aforementioned differences between young children and adults, are

highly unlikely to effectively protect children, as a subpopulation most at risk. In the interests of public health, the population of the developing fetus, neonate and young infant
should be rigorously protected by considerable lowering of the MCL for arsenic to the very lowest level that is analytically reliable. A step-wise "phase-down" of the MCL will not protect this susceptible population.

VIII. *CONCLUSIONS*.

From a public health point of view, establishing new guidelines in drinking water for a potent toxic metal, namely, arsenic, requires protecting the most susceptible population. In this instance, the population includes the developing fetus, neonate, infant and young child. To protect this susceptible population *now*, the MCL for arsenic should be as low as analytically feasible. Any type of "phased-in" approach, above that which is analytically possible, will fail to protect a large population of susceptible young children.

IX. *THE MEDICAL AND PUBLIC HEALTH NEED FOR AN EPA DRINKING WATER HEALTH ADVISORY.*

I strongly endorse the need for the U.S. EPA to issue a health advisory for arsenic in drinking water. I do so within my knowledge of the current data base supporting the need for such an advisory. It is my understanding that EPA has issued such advisories on numerous occasions. These can be documented by anyone on the SAB Committee examining the online IRIS file for the many contaminants contained therein. An explicit section in each of these files refers to health advisories. In my informed opinion, the evidence for the need of such an advisory is compelling, as is my understanding of EPA's requirement to do so.

The evidence that compels such an advisory, particularly for those regions in the United States where water supplies of arsenic are elevated, is clear from the voluminous evidence for arsenic within its toxicological and epidemiological context. This evidence indicates that the current MCL is inadequate; and that currently available science dictates a drastic downward revision. While a substantial revision must follow along a feasible track for implementation, arsenic does not await imparting toxic effects while various regulatory frameworks become operative. *Children specifically will continue to be exposed while control measures are put into place by EPA.* Therefore, the U.S. EPA must take cognizance of the public health realities–that between on-going intoxication and practical needs for implementation time frames-by using
the advisory as a mechanism of public health awareness and education. The mechanisms for how an advisory is issued are, generally, in place and have been used extensively in the past. No deviance from this process is necessary.

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ATTACHMENT B

MEMORANDUM

To: **SAB Drinking Water Committee**

From: **Barbara Harper, PhD, DABT**
Yakama Nation Toxicologist

Date: **September 9, 2000**

Subject: **Endorsement of the Minority Report on Arsenic and Children**

I would like to lend my personal support for this report. The report describes a large body of evidence showing that children are a generally vulnerable or sensitive population. This has been recognized in a regulatory context through the use of an additional safety factor used for determining allowable trace concentrations of pesticides in food products intended for infants and children. Many children's health initiatives are being developed as well.

There was disagreement among SAB members about the interpretation of some of the arsenic epidemiology papers, including some of those which involved children. I personally prefer precaution when the data are substantialy suggestive of an increased effect in children, as I believe is the case with arsenic, rather than waiting for statistically conclusive evidence of adverse outcomes in children (i.e., I have a preference for making alpha errors when children's health is at stake).

In a risk ranking system (without economic considerations), the small systems with elevated arsenic serving the poorest populations would probably rank highest because their children are most vulnerable for a number of reasons. These systems may also serve unique populations with different exposure patterns (e.g., higher water intake) and different nutritional status, compounded by less access to health care, different underlying disease patterns, and so on. Many Native American Tribes fall into this category, as would migrant workers. The risk management question is whether they should be first in line to reduce their arsenic because their risk is greatest, or last in line because they can afford it least and because the water treatment technology may not be fully developed. The assertion that water treatment is solely self-funded is not strictly true - there are rural water system assistance grants and other special programs to improve rural and reservation water quality. Therefore, I would argue that a phased approach based only on economic reasons (large systems first, small systems later) is inadequately protective of the most at-risk communities, and additional approaches should also be considered.

I also support the issuance of a health advisory for selected situations, written with culturally sensitive language. The mechanisms of outreach may be different for different situations, especially for tribal, migrant worker, or other ethnic, linguistic, or disadvantaged communities. This may involve pediatricians in some situations, and other mechanisms in other situations.

This memo reflects my personal opnion and should not be interpreted as official tribal policy.

ATTACHMENT C

Response to Comments Entered into the Record on the DWC's EC-Review Draft of the "Arsenic Report" at the September 22, 2000 EC Teleconference Meeting

November 27, 2000

1. Introduction

The Science Advisory Board's (SAB) established a Panel to review portions of the EPA proposed rulemaking on arsenic from June to August, 2000. The Panel was comprised of members of the SAB Drinking Water Committee and five consultants added to provide expertise on special issues that were known to be important in the review. The Panel's report on "Certain Elements of the Proposed Arsenic Drinking Water Regulation" notes that the major background document it used as the source of information on arsenic's health effects was the NRC's *Arsenic in Drinking Water* (NRC, 1999) report that was developed by an NRC Subcommittee. In recognition of the importance of that report to their own deliberations, Dr. Louise Ryan, a member of the NRC Subcommittee on Arsenic in Drinking Water, was asked to serve on the SAB Panel reviewing the arsenic proposal. Dr. Ryan was selected because of her knowledge of the NRC report and because of her expertise in modeling issues that were considered to be key aspects in responding to the Agency's charge to the SAB. The Panel's conclusions agree with the major conclusions in the NRC report. In a few instances, the SAB Panel considered additional evidence that support its conclusions, and those of the NRC, when this new information provided additional insights into key issues.

As the Panel's arsenic report was being discussed by the SAB's Executive Committee (EC) on September 22, 2000, one member of the EC entered into the record comments on the SAB report that were originally made by a member of the public in response to EPA's proposed arsenic rule (Greer, 2000). These comments were suggested as carrying special weight because they were provided to the EC member by Dr. Alan Smith, an epidemiologist who also served on the NRC Arsenic Subcommittee (see Attachment 1 to these comments).

These comments raised objections to three points in the Panel's draft report, including statements about: 1) the direct applicability of the Taiwanese ecological data to U.S. risk assessment, 2) the detectability of a 1 in 100 risk level in epidemiological studies, and 3) the use of comparison populations in risk assessments based on epidemiology studies. The Chair of the SAB Panel considered these comments and discussed them with various members of the Panel in formulating the response provided below.

Comment Number 1:

Dr. Smith stated:

> "The letter states that, 'In the opinion of the DWC, the Agency misinterpreted some of the conclusions of the NRC report.' This point was elaborated with the statement that 'The NRC (1999) noted, there are several reasons why the Taiwanese data should not be accepted as being directly applicable to the U.S.' This is simply not correct and it is misleading to imply that such a statement was made in the NRC report. The following are pertinent quotes from the NRC report:
>
> > [a] 'Ecological studies in Chile and Argentina have observed risk of lung and bladder cancer of the same magnitude as those reported in the studies in Taiwan at comparable levels of exposure' (page 7).
> >
> > [b] 'Human susceptibility to adverse effects resulting from chronic exposure to inorganic arsenic is likely to vary based on genetics, nutrition, sex, and other possible factors. Some factors, such as poor nutrition and arsenic intake from food might affect assessment of risk in Taiwan or extrapolation of results in the United States' (page 8)...
> >
> > [c] 'A wider margin of safety might be needed when conducting risk assessments of arsenic because of variations in metabolism and sensitivity among individuals or subgroups' (page 244)... .
>
> In short, there may indeed be susceptible sub-populations. These would be present both in Taiwan and also in the United States. Added margins of safety may be called for, not reduced ones. The DWC has grossly distorted information in the NRC report without any good basis."

Response to Comment No. 1:

The comment misinterprets the Panel's statement regarding "direct" applicability and ignores strong cautions contained in the NRC report about evaluating U.S. risk from arsenic. The Panel accepted the NRC's evaluation of epidemiological studies as providing strong and corroborating

evidence that arsenic is carcinogenic. Consequently, the first two statements are not at issue. However, the NRC was also quite clear about limitations on using such ecological data to predict risks:

> "First, there is no question that the ideal basis for risk assessment is a well-conducted epidemiological study involving accurate assessment of individual exposures. In the absence of such data, however, ecological data might be the only choice." Such analyses must be conducted with caution keeping in mind the potential for measurement error and confounding to bias the results. It is important to remember that any risk assessment based on ecological data must be cautiously interpreted because of the inherent uncertainty in the exposure-assessment methods used for such studies. In the case of the Taiwanese data, the fact that it came from a culturally homogeneous area provides some reassurance that confounding might not be too serious a concern. Our findings also suggest that additional caution might be needed when exposure concentrations are grouped into broad exposure categories. It is important to keep in mind that the considerable variability in the arsenic concentrations detected in multiple wells within some of the villages leads to considerable uncertainty about exposure concentrations in the Taiwanese data" (page 294 NRC).

The quote at item "b," is precisely what prompted the Panel to examine issues related to human susceptibility. The Panel discussed this in the report in some detail. In this regard it is important to point out that the NRC also restated the likely influence of these factors to risk in Taiwan and extrapolation to the United States later in their document on page 295, with a further note that these factors "...could not be taken into account quantitatively in this chapter." The Panel believes that one such important factor is the low selenium concentrations in Taiwan.

In this regard, the Panel concluded that:

a. There were several variables that are important for considering bladder and lung cancer risk, but the DWC recognized early that there were no data available that would allow us to compare the U.S. and Taiwan population that was studied. This would be an important area to follow-up on with targeted research.

b. Other sources of arsenic contributing to the risks of cancer in the Taiwan study population probably do exist and could be important if the appropriate data could be captured. At the present time, the uncertainties about how the form of arsenic influences toxicological responses prevents the Panel from resolving this issue. It was primarily for this reason that we suggested that Agency consider the incremental risk that is posed by arsenic in drinking water. Most Panel members support the NRC's indication that mechanisms plausibly associated with arsenic-induced cancer are sublinear (p. 300). However, the uncertainty about forms of arsenic and

their toxicity forced the Panel to accept the use of a linear model for estimating risks (as low as 1/1000), even though this was unsettling to many on the Panel.

c. The DWC noted and followed up on the data provided in the report on selenium status of the Taiwanese study population. Based upon four epidemiology reports identified by the Panel, it concluded that there may be sufficient information to make appropriate adjustments in the current estimate of risk. Two of these, discussed more fully below dealt specifically with selenium status and bladder and lung cancer.

In regard to statement "c," the Panel does not take direct issue with this statement. However, the Panel report expands on this issue in two respects: 1) we clearly accepted the possibility that there can be sensitive populations and examined these variables in some detail and 2) based on those variables having either qualitative information or quantitative data, the Committee suggests that the Taiwanese population studied may in fact itself be a sensitive population. Therefore, at least some of the additional margin of exposure appears to be captured in the source of the data that was used to estimate risks at low doses.

The SAB Panel's report does not take the position that there are no sensitive subgroups in the U.S. population. The Panel at least indirectly took the position that the Taiwanese study population appeared to be a "susceptible" subpopulation and explicitly recognized the possibility of children as such a sensitive population in its discussion of the Agency's proposed Health Advisory for mother's who might use drinking water with high arsenic levels to prepare infant formula. The Panel did not reject such an Advisory because it believes that these children could obtain higher doses of arsenic due to their greater intake of drinking water per unit of body weight. The Panel stopped short of fully endorsing the advisory because specific detailed information was not available on the proposed advisory and its implementation. The Panel believes that this Advisory will be different from the current health advisory program administered by the OGWDW because of the intended audience.

Comments Number 2 and 3:

Dr. Smith's comment number 2 stated that "The most serious error in the DWC report concerns the statement that: 'Further analyses of the Taiwanese data have been performed since the NRC report was issued that bring into serious question the use of the comparison populations outside the study area for estimating cancer risks due to arsenic. A study in Utah suggests that some U.S. populations may be less susceptible to arsenic.'" Further Dr. Smith states that "In the body of the DWC report it is stated that 'For one thing, if the lifetime cancer risk at the current standard (50ug/L) was really 1 case in 100 persons in the population, or greater, then there should be more evidence of effects in the U.S.'"

He goes on to state that "The above demonstrates a serious basic misunderstanding of epidemiological studies. To start with, the Utah study involved a highly select population from which no inference can be made about risk assessment." "There are no studies in the U.S., or anywhere else, conflicting with a 1 in 100 risk estimate. It needs to be understood that "...it is very hard to demonstrate if a 1 in 100 risk estimate truly exists." He concludes that "In short, the assumption that risks cannot possibly be as high as 1 in 100 has no scientific basis, and is in fact, very dangerous."

In comment number 3 Dr. Smith states that

> "It is imperative that any good arsenic risk assessment using epidemiological data should have a comparison population group that is clearly known not to be exposed to increased concentrations of arsenic in drinking water. While Morales et al. have conducted a good risk assessment in many aspects, no weight should be given to findings in their publication which do not include a comparison population known to be unexposed. Within the endemic area of Taiwan, only single samples from wells taken at one point in time were available. People migrate, they move to different villages, they do not drink from the same well for their total life. This means that within the endemic region, there is no comparison population known to be unexposed. Therefore, attention should be confined to the risk assessment results that were reported using external comparison populations."

Response No. 2 and 3:

Although many on the SAB Panel believe that their statement of concern as to why a 1 in 100 risk is not more noticeable in U.S. studies accurately reflects their feelings, they defer to the epidemiological expertise of Dr. Smith regarding the lack of sensitivity of such studies. Although deferring on this point, the Committee does not necessarily cede the point, rather the statement has been removed from the document because it does not materially add to their conclusions about the need for caution when applying the Taiwanese data to the U.S. situation.

Regarding the Utah study, the Panel did not attempt to use the Utah data for estimating cancer risks, partly for the same reasons cited by Dr. Smith. More fundamentally, however, we were not convinced that the population studied in Utah was any more representative than the Taiwanese in the study area modeled by NRC. Essentially, the Utah population was unlikely to have many of the co-carcinogenic exposures (e.g. smoking, dietary habits) that would be found in the broader U.S. population. The Panel came to the conclusion that the two populations may be at opposite ends of the spectrum in terms of susceptibility. This was the genesis of the statement that "some U.S. populations may be less susceptible to arsenic."

Specifically, in regard to the Panel's quote "For one thing, if the lifetime cancer risk at the current standard (50 ug/L) was really 1 case in 100 persons in the population or greater, then there should be more evidence of effects in the U.S.", Dr. Smith takes the position that the more than 1/100 risk that is projected from this population, based on the use of a comparison population, to a U.S. population is likely to be real and could be as high as 1/10. He dismisses the lack of parallel findings in the U.S. on the basis of the well-recognized insensitivity of epidemiological studies in resolving such issues. Dr. Smith also identifies the difficulties that are associated with the exposure assessments in this study. In contrast, the Panel took this analysis to suggest that there could be some substantive differences in the study population and surrounding areas of Taiwan. As indicated above, several differences were clearly identified in the NRC report (quote above taken from page 295 of the NRC report). It is important to recognize that these uncertainties call into question the accuracy of the dose-response evaluation as it is extrapolated to the U.S. population. Nevertheless, the Panel accepted the projection of an approximate 1/1000 risk of bladder cancer at the current MCL to exercise caution.

Moreover, the Panel concluded, based on the Morales et al. (2000) paper, that there was a similar incremental risk for lung cancer. These findings were the basis for the Panel's concurrence that the MCL should be decreased.

A key advantage in using data that are internal to the study population, is that it decreases the possibility of confounding. For example, from experimental data, arsenic is much more effective as a co-carcinogen than it is as a carcinogen. The study population was comprised of rural poor persons with relatively poor nutrition. Therefore, the Panel felt that it was important to explore potential differences in the study population in Taiwan and other parts of the world. Several differences were identified in the NRC report (pp.241-243 of the NRC report as cited above). One was the issue of how high the level of non-drinking water exposure to arsenic. There was evidence that relatively high exposures can exist from such sources, but the Panel concluded that for the meantime, this would be best ignored because of the uncertainties in the relative carcinogenic activity of varying forms of arsenic. Since the Agency had settled on linear extrapolation, it was suggested that this issue could be simplified by examining the incremental risk of drinking water for the purposes of the current rule.

One variable that the SAB Panel felt should be considered more closely in the risk assessment is the poor selenium status of this study population (this is documented in the NRC report at pp. 241-243). There are data to suggest that selenium status influences bladder and lung cancer rates in human populations. The Panel was able to identify four publications that bear directly on the influence of selenium status on cancer risk without pursuing the issue exhaustively. To save time, only the two most relevant studies are summarized. One was a case control study in Washington County MD in which selenium status was measured in a cohort of 25,802 people that were followed over time. A nested case-control study found odds ratios of 2 in those individuals with lower selenium status (Helzsouer et al., 1989, Cancer Res. 49:6144-6148). The second study was part of a cohort study of diet and cancer in Holland. In a 3.3 year follow-up 550 incident cases of lung cancer were detected and selenium status of cases (370) vs. controls (2459) were compared. Again an odds ratio for individuals having higher levels of selenium was 0.5 with a significant inverse trend across quartiles of selenium status. These data suggest that the selenium status of the Taiwanese study population put them at greater risk from these two cancers. To state this differently, if the Taiwanese population is at all similar to other populations in the world with altered selenium status, they should have at least twice the background rate of bladder and lung cancer, irrespective of their exposure to arsenic. In turn, this suggests that the median susceptibility of this population for these cancers is greater than the median susceptibility of a U.S. population.

The SAB Panel report does not suggest that there are no subgroups in the U.S. population with greater sensitivity to arsenic. In terms of the data that were before the Panel, it was difficult to conclude that additional uncertainty factors are necessary to adjust between this Taiwanese population and the U.S. population. This does seem to be a different conclusion from that arrived at by Dr. Smith. However, it does not appear to be contrary to the substance of the NRC committee report. Consequently, the Panel felt that the use of Taiwanese data to estimate risks, without the comparison population, would capture the apparently higher susceptibility to arsenic-induced cancers in that population. This approch would provide an additional margin of safety for the general U.S. population.

The Panel also recognized that new data that are just becoming available will undoubtedly provide better insight into the appropriate models for low-dose extrapolation of arsenic risks, both cancer and non-cancer. Such information can be applied to improving on the shortcomings that the NRC Subcommittee identified in its report which stated:

> Regardless of the data set that is ultimately used for the arsenic risk assessment, the subcommittee recommends that a range of feasible modeling approaches be explored. The final calculated risk should be supported by a range of analyses over a fairly broad feasible range of assumptions. Performing a sensitivity analysis ensures that the conclusions do not rely heavily on any one particular assumption. (page 296 NRC).

Comment on the Figure provided by Dr. Smith

Dr. Smith includes the Taiwanese data in his figure that plots the nominal concentrations of arsenic in drinking water and tumor responses across several studies. This is an appropriate way to display these data, if you believe that there are no differences, other than arsenic exposure, in the Taiwanese population and the referent population. As discussed above, the NRC report also identified difficulties in using the comparison population (see page 292) which states:

> *"… the analyses presented in this chapter used age-specific cancer rates reported for the whole of Taiwan. Bias could be a potential problem, because the Taiwanese-wide data might not form an appropriate comparison group for the arsenic endemic region, which is a poor, rural area. Thus, the choice to use external information on baseline cancer rates represents a trade-off that to some extent can be explored using sensitivity analysis".*

The Panel concluded from this statement that the NRC Subcommittee was concerned that there were substantive differences between the study population and the rest of Taiwan, not to mention differences between this population and the U.S. In essence the validity of the comparison population as a "control" group that is postulated to differ from the study population by only the single variable under study must be questioned. The NRC Subcommittee repeatedly identified the unusual character of this population relative to the rest of Taiwan.

It is instructive to note the diverse behavior of the dose-response curves that Dr. Smith has plotted from different studies in the low dose range. The graph very strongly reinforces the extent of the uncertainties at the low end of the dose-response curve (i.e. in the range of 3-20 ug/L). The correlation coefficient of this line would not approach $R^2 = 0.8552$ if the concentrations above 200 ug/L were eliminated. In other words the high-dose data does not inform us much with respect to the nature of the dose response curve in this region. It is difficult to understand how Dr. Smith can argue that epidemiological studies in the U.S. do not have the power to detect a 1/100 risk, but that it has the power to resolve much lower risks from the epidemiology studies depicted in the graph. The latter fact has not been established. What occurs in this range simply depends upon the glasses that are worn. The Panel simply calls attention to the fact that effects have not been clearly documented in this range.

The Panel suggests that some serious attempt needs to be made to explore this question under controlled conditions. The Panel was impressed with the preliminary findings of Ng et al. (1999, In: Chapell et al. Arsenic Exposure and Health Effects, Elsevier, pp. 217-223) who were able to induce tumors in the lung, gastrointestinal tract, and liver of female C57Bl/6J mice at concentrations of arsenate of 500 ug/|L of drinking water. The tumors were produced in the same range of concentrations that were associated with cancer in various sites in the epidemiological studies. Equally encouraging were the independent findings of two groups that dimethyl arsenic was capable of inducing bladder tumors in rats. These findings appear to provide the experimental models necessary to explore the pharmacokinetic and pharmacodynamic variables that will be important for enabling biologically-based dose-response models envisioned in the SAB's research recommendations in 1989 and which were reinforced as being desirable in the NRC report (pages 293 and 296).

General characterization of the DWC Report

In summary, the majority of the SAB Panel viewed the uncertainties in the dose-response relationships associated with cancer and non-cancer effects of arsenic in a substantially differently than Dr. Smith. While we accept that the current MCL for arsenic is too high (as the NRC report points out, there is a margin of exposure that is less than 10 between those concentrations that produce effects and the current MCL based on the information that is available, as flawed as it might be), the Panel also recognized that this is an expensive rule. For that reason the Panel took the view that the great deal of existing uncertainty in the areas of risk assessment and in treatment costs in small systems could form the basis for the Agency's exercise of its discretionary authority in proposing this rule. This view was the basis for the Panel suggesting that the Agency consider an adaptive management approach to arsenic regulation (phased rule). There was one member of the committee and a consultant who dissented from this view. The Panel was careful to point out that this recommendation arose from considering the relatively large economic impact of this rule and that it was a risk management concern, not one that comes solely from scientific considerations of the risk.

ATTACHMENT 1

Comments from Dr. Alan Smith, University of California - Berkeley

NOTE: THE HEADER INFORMATION FOR THIS EMAIL WILL NOT COPY DIRECTLY TO THE WORD PROCESSING SOFTWARE; HOWEVER, IT INDICATES THAT IT IS FROM:

LGreer@nrdc.org
09/22/00 02:13 PM

Don

Here are the comments from Dr. Alan Smith of Berkeley, which were sent to my colleague Erik Olson at NRDC, who has been a long-time advocate on drinking water standards. Please pass them along to the rest of the executive committee as we discussed today.

Thanks, Linda
_____Forward Header_____
Subject: Fwd[2]: Arsenic drinking water standard
Author: Erik Olson
Date: 9/21/00 4:34 PM

linda: here's a short comment on the SAB report (and on EPA's proposed rule) from Dr. Alan Smith from UC Berkeley, who sat on the NAS arsenic committee and is probably the leading epidemiologist on arsenic in the world. -- erik

_____Forward Header_____
Subject: Fwd: Arsenic drinking water standard
Author: "Elena O. Lingas" <lingas@uclink4.berkeley.edu>
Date: 9/21/00 10:24 AM

Dear Mr. Olson,

The following comments were sent to the Water Docket earlier this week. Dr. Smith thought that you would be interested in seeing them.

Elena O. Lingas

>
> Date: Tue, 19 Sep 2000 16:20:58 -0700
> To: ow-docket@epamail.epa.gov
> From: "Elena O. Lingas" <lingas@uclink4.berkeley.edu>
> Subject: Arsenic drinking water standard
> Cc: ahsmith@uclink4.berkeley.edu
>
>
> 19 September 2000
>
>

> W-99-16 Arsenic Comments Clerk
> Water Docket (MC-4101)
> U.S. Environmental Protection Agency
> 1200 Pennsylvania Avenue, NW
> Washington, DC 20460
>>
> In addition to the comments previously submitted, dated 29 August 2000 and an
> erratum dated 1 September 2000, it has been suggested that we provide
> material for the EPA indicating how cancer risks, including lung cancer
> risks, could be estimated. In addition, I wish to comment on the Drinking
> Water Committee (DWC) report of the SAB.
>
> 1. Cancer risk estimation for arsenic in drinking water.
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> There is extensive information from several countries for use in lung cancer
> risk assessment, which is the main site for cancer mortality. We previously
> submitted a graph integrating data from Taiwan, Argentina, Chile and Japan.
> This includes results from a case-control study (Chile), a cohort study
> (Japan), and ecological studies (Argentina, Chile, Taiwan and Japan). We
> attach this graph again (Figure 1).
>
> Table 1 presents the risk assessment calculations which were part of our
> report to the Office of Environmental Health Hazard Assessment, California
> EPA. The lung cancer risk estimates for drinking 1 liter of water per day
> containing 50 ug/L were 7.8 per 1000 for men, and 9.9 per 1000 for women.
> Thus, the risk for lung cancer alone is on the order of 1 per 100.
>
> The methods used are standard risk assessment methods with linear relative
> risk extrapolation. This is the standard default. As can be seen in Figure
> 1, there is no basis for the incorporation of sub-linear or threshold models.
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> The use in calculations of 2.3 liters as the volume of water consumed per day
> was estimated from extensive interview studies in several countries (Table
> 2).
>
> As can be seen in Table 3, lung cancer related to arsenic was a more
> important cause of death in Taiwan, Chile and Argentina. This was
> particularly true for Argentina and Chile, both of which have populations
> which are similar to the U.S. population with regard to various
> characteristics, such as nutrition, ethnicity and lifestyle.
>
> Full details of the risk calculations are available in the report submitted
> to the California EPA.
>
> 2. The Drinking Water Committee Report.
>
> Rather than reviewing the full report, I will comment on three points raised
> in the cover letter to The Honorable Carol Browner.
>
> ? The letter states that "In the opinion of the DWC, the Agency
> misinterpreted some of the conclusions of the NRC report".
>
> This point was elaborated with the statement that "The NRC (1999) noted,
> there are several reasons why the Taiwanese data should not be accepted as
> being directly applicable to the U.S.".

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> This is simply not correct and it is misleading to imply that such a
> statement was made in the NRC report. The following are pertinent quotes
> from the NRC report:
>
> "Ecological studies in Chile and Argentina have observed risk of lung and
> bladder cancer of the same magnitude as those reported in the studies in
> Taiwan at comparable levels of exposure" (page 7).
>
> "Human susceptibility to adverse effects resulting from chronic exposure to
> inorganic arsenic is likely to vary based on genetics, nutrition, sex, and
> other possible factors. Some factors, such as poor nutrition and arsenic
> intake from food might affect assessment of risk in Taiwan or extrapolation
> of results in the United States"(page 8) (italics added).
>
> "A wider margin of safety might be needed when conducting risk assessments of
> arsenic because of variations in metabolism and sensitivity among individuals
> or subgroups" (page 244) (italics added).
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> In short, there may indeed be susceptible sub-populations. These would be
> present both in Taiwan and also in the United States. Added margins of
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> information in the NRC report without any good basis.
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> ? The most serious error in the DWC report concerns the statement that
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> "Further analyses of the Taiwanese data have been performed since the NRC
> report was issued that bring into serious question the use of the comparison
> populations outside the study area for estimating cancer risks due to
> arsenic. A study in Utah suggests that some U.S. populations may be less
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> from which no inference can be made about risk assessment.
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> 100 risk estimate. It needs to be understood that it is very hard to
> demonstrate if a 1 in 100 risk estimate truly exists. One example of this is
> that it took many studies (about 16) before an NRC report could conclude that
> lung cancer risks from passive smoking by non-smokers married to smokers were
> indeed increased and of the order of 1 in 100. In the case of arsenic in
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> of cancer mortality is about 20 per 100 (i.e. about 1 in 5 people die from
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> within the endemic region, there is no comparison population known to be
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>
> Again, for further information, feel free to contact my office at
> 510-843-1736 or the web page at http://socrates.berkeley.edu/~asrg, which
> contains information on our research.
>
> Sincerely,
>
>
> Allan H. Smith, MD, PhD
> Professor of Epidemiology
> School of Public Health
> University of California, Berkeley

<html>
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them.

Elena O. Lingas

<blockquote type=cite cite>Date: Tue, 19 Sep 2000 16:20:58 -0700
To: ow-docket@epamail.epa.gov
From: "Elena O. Lingas"
<lingas@uclink4.berkeley.edu>
Subject: Arsenic drinking water standard
Cc: ahsmith@uclink4.berkeley.edu

<font face="Times New Roman, Times" size=4>19 September 2000

W-99-16 Arsenic Comments Clerk
Water Docket (MC-4101)
U.S. Environmental Protection Agency

1200 Pennsylvania Avenue, NW
Washington, DC 20460

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Professor of Epidemiology
School of Public Health
University of California, Berkeley </blockquote>
</html>

Received: from uclink4.berkeley.edu ([128.32.25.39]) by mail.nrdc.org with SMTP
  (IMA Internet Exchange 3.14) id 0007588A; Thu, 21 Sep 2000 13:28:25 -0400
Received: from ehs-204-7 (ehs-204-7.SPH.Berkeley.EDU [128.32.252.91])
    by uclink4.berkeley.edu (8.10.1/8.10.1) with SMTP id e8LHTEJ20679
    for <EOlson@nrdc.org>; Thu, 21 Sep 2000 10:29:14 -0700 (PDT)
Message-Id: <4.1.20000921102128.00a29ee0@uclink4.berkeley.edu>
X-Sender: lingas@uclink4.berkeley.edu
X-Mailer: QUALCOMM Windows Eudora Pro Version 4.1
Date: Thu, 21 Sep 2000 10:24:11 -0700
To: EOlson@nrdc.org
From: "Elena O. Lingas" <lingas@uclink4.berkeley.edu>

Subject: Fwd: Arsenic drinking water standard
Mime-Version: 1.0
Content-Type: multipart/mixed;

Attachments to the Email from Dr. Smith:

a. File Name: SMITHTABLS
(Originally in the email this was called <Tables for water docket.doc>)

Table 1: Estimate of Excess Lung and Bladder Cancer Risk Due to Arsenic in the Drinking Water

	Males	Females
Slope of excess lung cancer relative risk (RR-1) versus exposure per ug per liter as obtained from Figures 4 and 5	0.0046	0.0076
Estimate of background lifetime lung cancer mortality risk per 1000 persons based on U.S. rates in 1996 from Table 6	79	52
Approximate adjustment of average daily water consumption of 2.3 liters per day to 1 liter per day (1 liters/2.3 liters) from Table 7	0.43	0.50
Estimate of lifetime added lung cancer risk per 1000 persons exposed to 50 ug/L	7.8	9.9
Estimate of lifetime added lung cancer risk per 1000 persons exposed to 10 ug/L	1.6	2.0
Ratio of excess lung cancer plus bladder cancer deaths divided by excess lung cancer deaths from Table 9	1.3	1.6
Estimate of lifetime added lung and bladder cancer risk per 1000 persons exposed to 50 ug/L	10.1	15.8
Estimate of lifetime added lung cancer risk per 1000 persons exposed to 10 ug/L	2.1	3.2
Estimate of lifetime added lung and bladder cancer risk per 1000 persons exposed to 50 ug/L for both sexes combined	13.0	
Estimate of lifetime added lung and bladder cancer risk per 1000 persons exposed to 10 ug/L for both sexes combined	2.7	

Table 2: Drinking water consumption in liters per day from various epidemiological investigations of arsenic outside the U.S.

Country-Reference	Drinking water consumption (liters/day)
Chile-Ferreccio, personal communication^	
Total	**2.4**
Males	**2.6**
Females	**2.2**
Chile-Biggs et al., 1997	
San Pedro-high	**2.5**
Toconao-low	**2.3**
Chile-Moore et al., 1997a	
High and low exposure groups	**2.6**
Argentina-case control*	
Total	**1.9**
Males	**2.0**
Females	**1.7**
India[#]	
Total	**2.4**
Males	**2.6**
Females	**2.1**

^findings from participants in the lung cancer case-control study of Ferreccio et al., (submitted)

***preliminary findings from an on-going bladder case-control study; data from 28 females and 149 males**

[#]preliminary findings from an on-going skin cancer case-control study; data from 73 females and 143 males

Table 3: Excess Deaths (observed minus expected) from cancers related to arsenic in drinking water

Country Cancer Site	Men			Women		
	Excess deaths	Ratio of excess lung/bladder cancers	(Excess lung cancer deaths plus bladder cancer deaths)/Excess lung cancer deaths	Excess deaths	Ratio of excess lung/bladder cancers	(Excess lung cancer deaths plus bladder cancer deaths)/Excess lung cancer deaths
Argentina*						
Lung cancer	307	4.4	1.2	84	7	1.1
Bladder cancer	70			12		
Chile (Region II)[+]						
Lung cancer	401	5.1	1.2	105	1.9	1.5
Bladder cancer	78			56		
Taiwan[#]						
Lung cancer	228	1.5	1.7	177	1.1	1.9
Bladder cancer	152			157		
TOTALS						
Lung cancer	936	3.1	1.3	366	1.6	1.6
Bladder cancer	300			225		

*Hopenhayn-Rich et al., 1996; 1998(high exposure group); [+]Smith et al., 1998; [#]Chen et al., 1985

b. File Name: SMITHFIG1

(Originally in the email this was called <Figure 1 for water docket.doc>)

Please provide a fax number to obtain this Figure.

ATTACHMENT D

ACRONYMS AND ABBREVIATIONS

BAT	Best Available Treatment
CWS	Community Water System
DWC	Drinking Water Committee
GFH	Granular Ferric Hydroxide
LS	Lime Softening
MCL	Maximum Contaminant Level
MHI	Median Household Income
POE	Point of Entry
POTW	Publically Owned Treatment Works
POU	Point of Use
PQL	Practical Quantitation Limit
SAB	U.S. EPA Science Advisory Board
SDWA	Safe Drinking Water Act Amendments of 1996
TCLP	Toxicity Characteristic Leaching Procedure
TDS	Total Dissolved Solids