



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

November 8, 1993

OFFICE OF THE ADMINISTRATOR
SCIENCE ADVISORY BOARD

EPA-SAB-DWC-94-004

Honorable Carol M. Browner
Administrator
U.S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

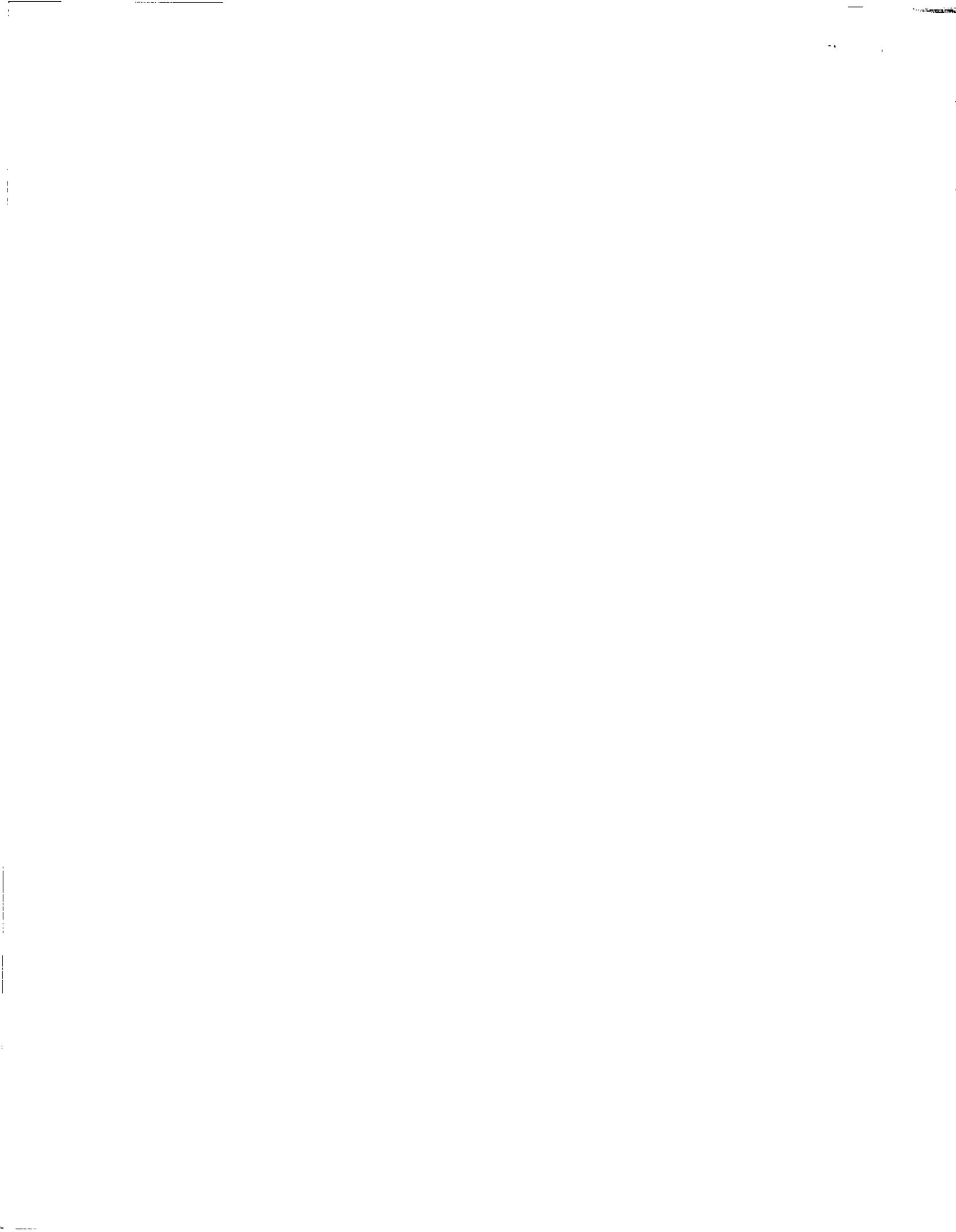
Subject: SAB Review of draft Drinking Water Criteria
Document on Inorganic Arsenic

Dear Ms. Browner:

On April 19-20, 1993, the Drinking Water Committee of the Science Advisory Board (SAB) reviewed the Agency's draft Drinking Water Criteria Document on Inorganic Arsenic. In general, this document addresses the important aspects of arsenic toxicology, as well as the principal mechanisms of the toxicity of different forms of arsenic. The Committee is concerned, however, that certain critical aspects of the dose-response and pharmacokinetic issues surrounding the potential cancer hazards from arsenic are not adequately integrated in the draft document. This letter summarizes the Committee's key concerns in this regard, which are developed more fully in the accompanying report. The Committee recommends revision of the document through an in-house risk assessment to achieve a more comprehensive evaluation and integration of the available data.

The carcinogenicity of arsenic is clearly a central aspect of any review of its potential health risks. The Committee believes that the currently available epidemiologic evidence supports the conclusion that an association exists between excess risks of cancer of various internal organs and exposure to *high levels of arsenic*. The Committee recommends, however, that the Agency develop a better understanding of several aspects of the relationship between arsenic exposure and cancer risk, as discussed below and in the attached report, before finalizing a quantitative risk assessment to underpin rulemaking activity.

Specifically, the Agency should clarify dose-response and pharmacokinetic relationships for arsenic in humans. The available data suggest that arsenic blood concentrations may only become elevated when the level of arsenic in water exceeds 100 $\mu\text{g/L}$, a level that is present only in a very small proportion of U.S. drinking water sources. This is a critical question because excess risks in the Taiwanese studies are the primary evidence for any quantitative risk



and risks in those studies have only been observed at arsenic water levels that are well in excess of this figure.

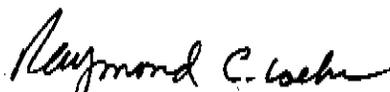
The Agency should also carefully take into account potential differences between Taiwanese and U.S. populations before using the Taiwanese findings to formulate a quantitative risk assessment for the U.S. These differences include the different nutritional status of the two populations, and, in particular, the high "background" blood levels of arsenic in the Taiwanese from *outside the areas where excess cancer risks have been reported*. The Committee recommends that the Agency undertake a further evaluation of background arsenic levels in the Taiwanese population and how they may affect the shape of the dose-response curve for arsenic carcinogenicity. Finally, the Committee supports the Agency's efforts to evaluate and include, in a revised Criteria Document, the findings of more recent epidemiologic studies, as well as any relevant re-interpretation of previous data.

With regard to non-cancer effects of arsenic, the Committee is not convinced that the use of an uncertainty factor of three in the estimation of the Reference Dose (RfD) is scientifically justified. The two reasons provided in the document as justification for such a factor are inadequate.

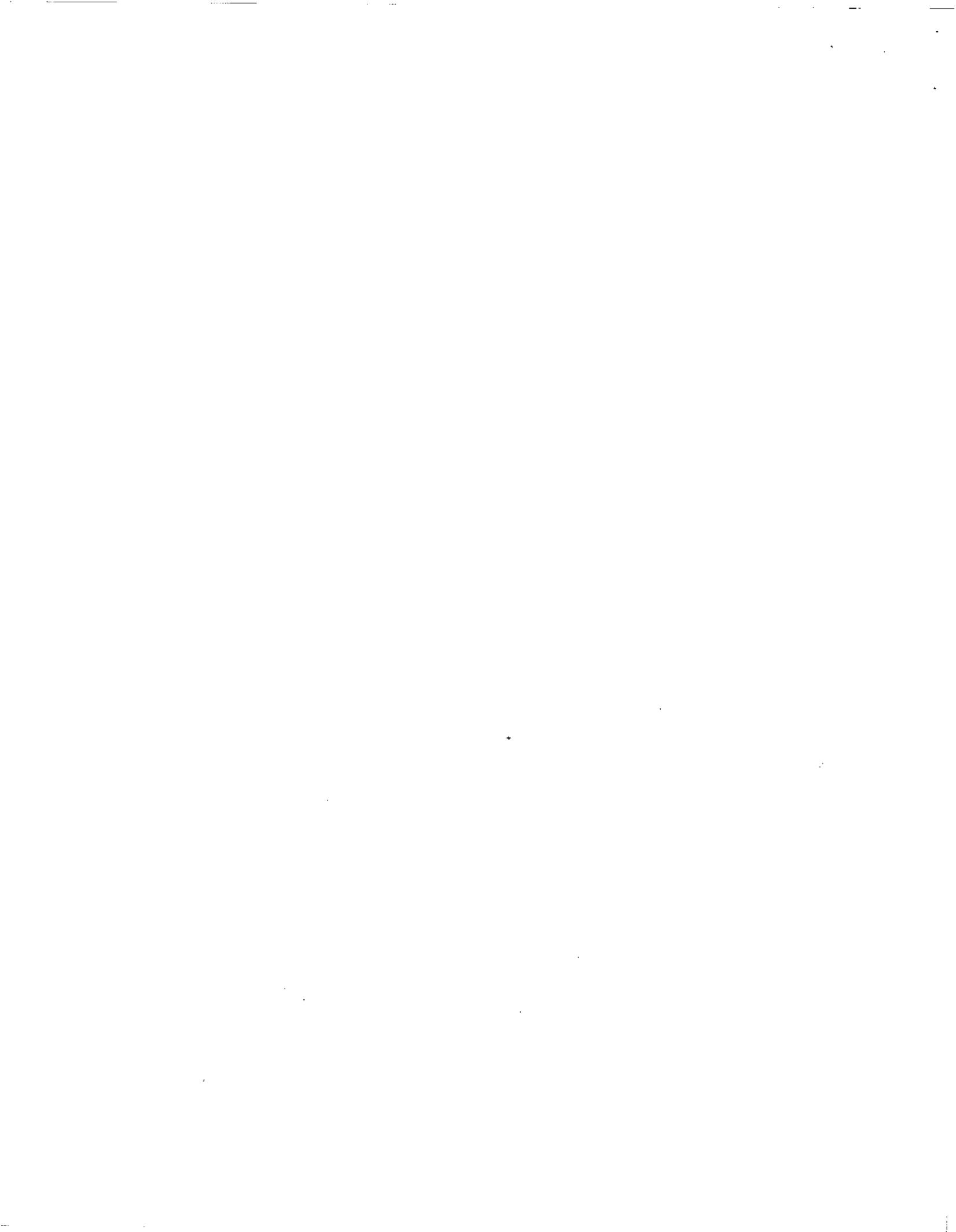
In summary, the Committee recommends that the Agency integrate all the available information through an in-house quantitative risk assessment for non-skin cancers from ingestion of arsenic in drinking water, taking into account concerns such as discussed above, namely potential exposures from other sources and the potential lack of linearity between blood levels of arsenic and arsenic levels in drinking water.

The attached report discusses these and other issues in more detail. The Committee appreciates the opportunity to conduct this review, and we look forward to your response. We would also be pleased to assist the Agency in the review of a revised risk assessment of arsenic in drinking water.

Sincerely,


Dr. Raymond C. Loehr, Chair
Executive Committee
Science Advisory Board


Dr. Verne A. Ray, Chair
Drinking Water Committee
Science Advisory Board





United States
Environmental
Protection Agency

Science Advisory Board
Washington, DC

EPA-SAB-DWC-94-004
November 1993

REVIEW OF THE DRAFT DRINKING WATER CRITERIA DOCUMENT ON INORGANIC ARSENIC

**PREPARED BY THE DRINKING
WATER COMMITTEE OF THE
SCIENCE ADVISORY BOARD**



NOTICE

This report has been written as a part of the activities of the Science Advisory Board, a public advisory group providing extramural scientific information and advice to the Administrator and other officials of the Environmental Protection Agency. The Board is structured to provide balanced, expert assessment of scientific matters related to problems facing the Agency. This report has not been reviewed for approval by the Agency and, hence, the contents of this report do not necessarily represent the views and policies of the Environmental Protection Agency, nor of other agencies in the Executive Branch of the Federal government, nor does mention of trade names or commercial products constitute a recommendation for use.



ABSTRACT

On April 19-20, 1993, the Drinking Water Committee of the Science Advisory Board (SAB) reviewed the Agency's draft Drinking Water Criteria Document on Inorganic Arsenic.

The Committee found that the document generally addresses the important aspects of arsenic toxicology, but that it does not adequately integrate the available scientific information. They agreed that the methylated forms of arsenic are less toxic than the parent compound. They found that appropriate data were used to derive the Reference Dose (RfD) for arsenic, but recommended against the use of an additional uncertainty factor (UF) of three.

The Committee agreed that there is an association between excess risks of certain internal organ cancers and exposure to high levels of arsenic. They recommended, however, that EPA develop a better understanding of the relationship between arsenic exposure and cancer risk before completing an in-house quantitative risk assessment. In particular, they found a need to take into account possible differences between Taiwanese and U.S. populations, such as diet and background arsenic levels, before using the results of Taiwanese studies to assess risks for U.S. populations.

The Committee agreed that arsenic has not been shown conclusively to be an essential element. They recommended clarification of the use of the concepts of prevalence, exposure and use in the document, that the uncertainty surrounding arsenic exposures be estimated and reported, that issues of variability of dietary arsenic intake be addressed, and that the Agency also address potential ingestion of arsenic-laden dust by infants and toddlers.

Key Words: Arsenic, Cancer, Risk Assessment, RfD, Non-Cancer Risk, Exposure, Essentiality, Exposures, Taiwan, Skin Cancer, Uncertainty Factor.

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SCIENCE ADVISORY BOARD
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Review of Draft Drinking Water Criteria Document for Inorganic Arsenic

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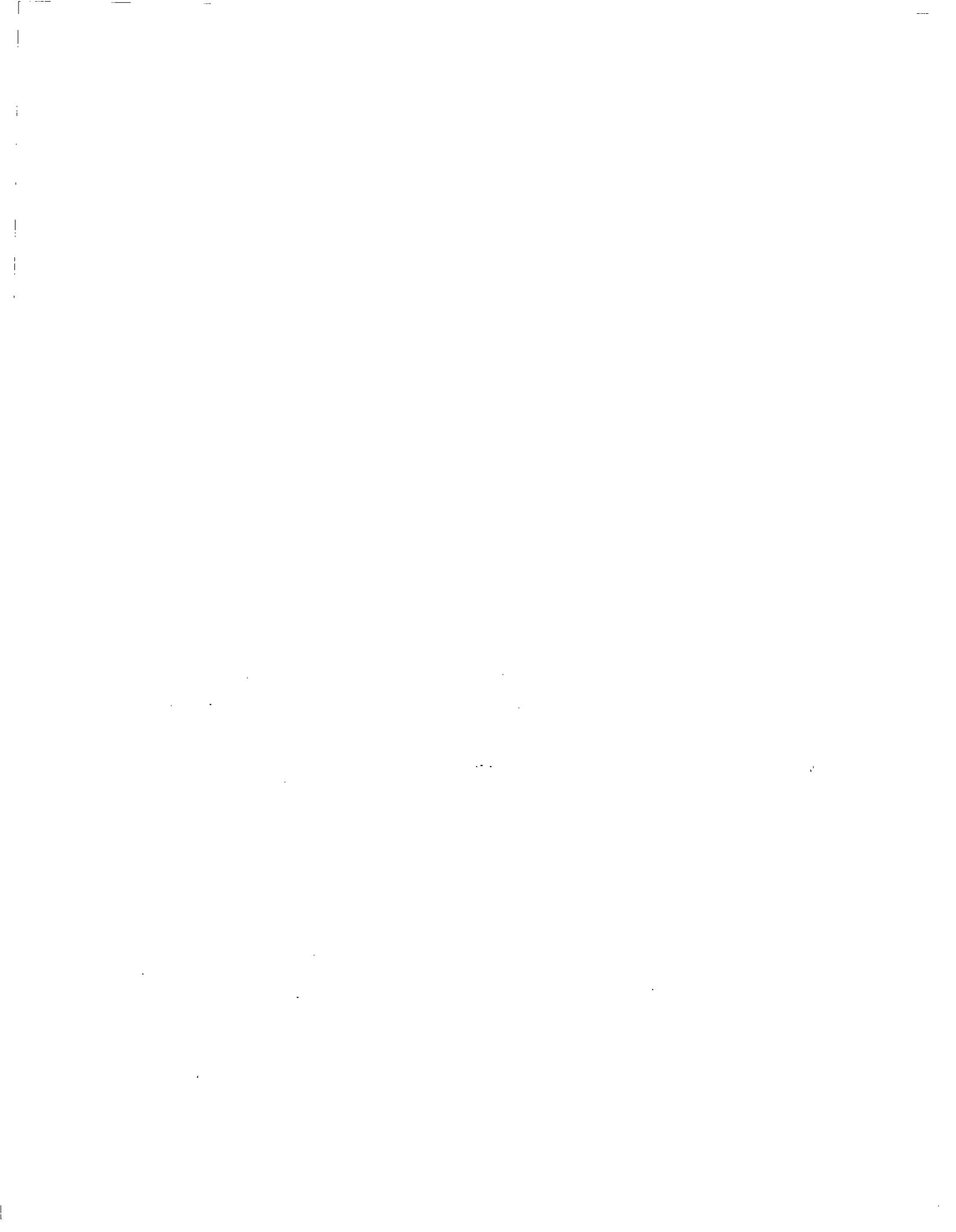


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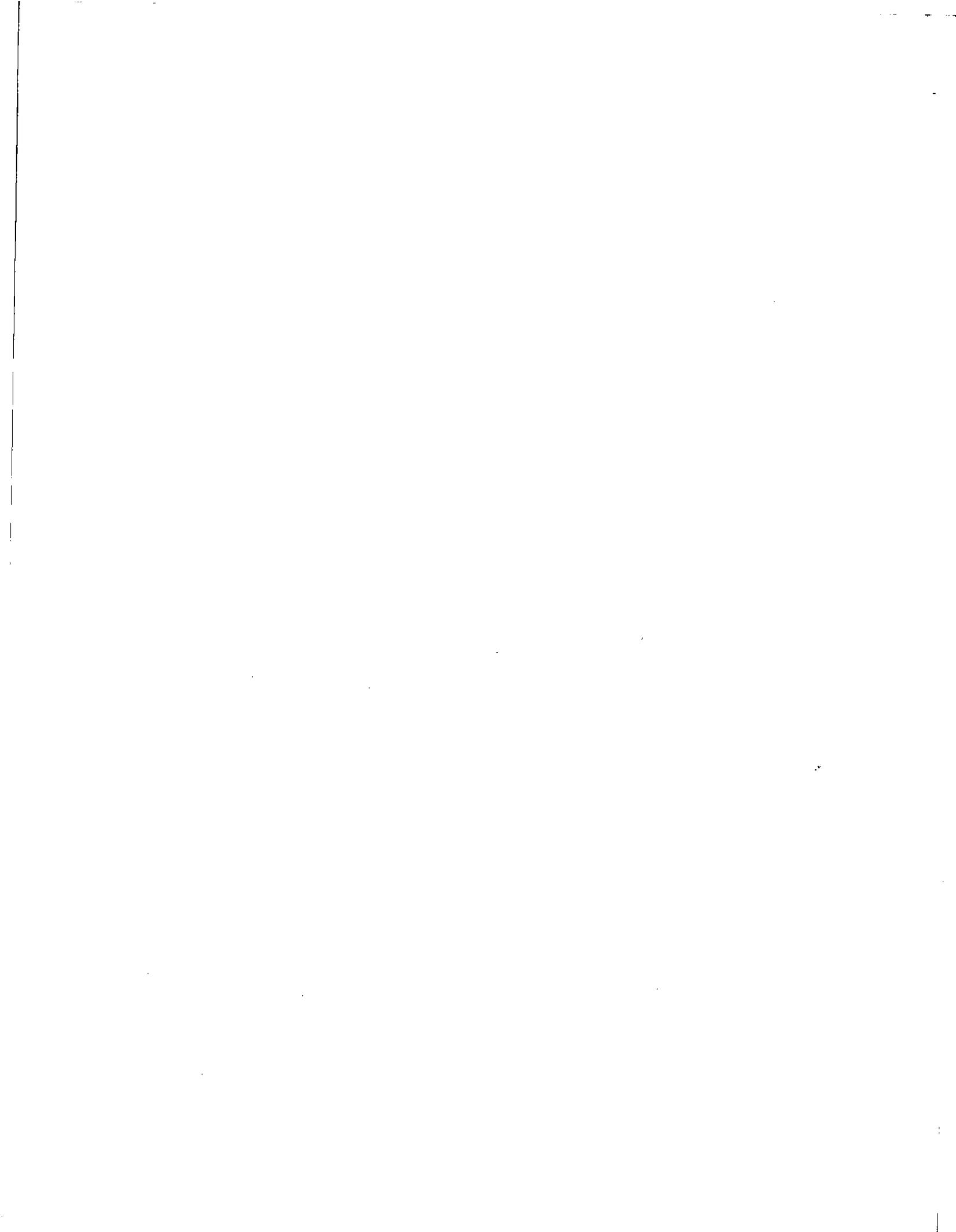
1. EXECUTIVE SUMMARY

In general, the Committee found that the Criteria Document addresses all the important aspects of arsenic toxicology, but that it does not adequately *integrate* the general toxicity data, the available information on carcinogenic and noncarcinogenic endpoints, and the current knowledge of metabolism and detoxification mechanisms for arsenic.

The document generally covers the principal mechanisms of the toxicity of different forms of arsenic, although the Committee recommends the inclusion of more discussion of the interaction of arsenic with lipoic acid. In their view, it would be an overstatement to assert that methylated metabolites of arsenic are non-toxic or almost so, and that it would be better to simply indicate that the methylated forms are less toxic than the parent compound. The Committee found that a number of important reports in the scientific literature were not cited and recommends that the Criteria Document be enriched with additional references.

The Committee found that appropriate data were used to derive the Reference Dose (RfD) for arsenic, but recommended against the use of an uncertainty factor (UF) of three for the RfD.

The Committee believes that the currently available epidemiologic evidence supports the conclusion that an association exists between excess risks of cancer of various internal organs and exposure to *high levels of arsenic*. There is a critical need, however, to better understand several aspects of the relationship between arsenic exposure and cancer risk before completing a quantitative risk assessment to underpin any rulemaking activity. First, it is crucial to clarify dose-response and pharmacokinetic relationships in humans. The available data suggest that arsenic blood concentrations may only become elevated when the levels of arsenic in water exceed 100 $\mu\text{g/L}$. This is a critical question because excess risks in the Taiwanese studies are the primary evidence for any quantitative risk assessment, and risks in those studies have only been observed at arsenic water levels that are well in excess of this figure.



The Agency should carefully take into account the differences between Taiwanese and U.S. populations before using the Taiwanese findings to formulate a quantitative risk assessment for the U.S. In particular, the Committee recommends that the Agency undertake a further evaluation of the background arsenic levels in the Taiwanese population and how they may affect the shape of the dose-response curve for arsenic carcinogenicity. The Agency should also try to reconcile the apparently contradictory findings regarding excess cancer risks from a study of smelter workers in the U.S. and the Taiwanese findings involving exposure in drinking water (and possibly other non-occupational sources). We also applaud the Agency's effort to evaluate and include, in the Criteria Document, the findings of more recent epidemiologic studies, as well as any relevant re-interpretation of previous data.

In summary, the Committee recommends that the Agency conduct an in-house quantitative risk assessment for non-skin cancers from ingestion of arsenic from drinking water, taking into account the concerns discussed above, such as exposure from other sources and lack of linearity between blood levels of arsenic and arsenic levels in drinking water.

The Committee agrees with the Agency's current view that arsenic has not been shown conclusively to be an essential element and does not consider the new data in the Criteria Document a sufficient basis to change this view.

The Committee found that the discussion of human exposures was a good beginning in presenting this information. They recommend that the Agency clarify the use of the concepts of prevalence, exposure and use in several points in the text, that the uncertainty surrounding arsenic exposures be estimated and reported, that issues of variability of dietary arsenic intake be addressed, and that the Agency also address potential ingestion of arsenic-laden dust by infants and toddlers.

2. BACKGROUND AND CHARGE

The Safe Drinking Water Act, as amended in 1986, requires the Administrator of the U.S. Environmental Protection Agency to publish Maximum Contaminant Level Goals (MCLGs) and promulgate National Primary Drinking Water Regulations for each contaminant which, in the judgement of the Administrator, may have an adverse effect on public health and that is known or anticipated to occur in public water systems.

In considering potential regulations, the Agency develops Health Criteria Documents which serve to define the health effects basis to be considered in establishing MCLGs and drinking water standards. These documents contain data on acute, subchronic and chronic toxicity to animals and humans to specific contaminants. In March of 1993, the Office of Science and Technology of the Office of Water requested that the Science Advisory Board review the draft Drinking Water Criteria Document for Inorganic Arsenic. The specific charge for the review by the SAB was transmitted March 29, 1993 (Appendix A). The SAB has also conducted two other recent reviews of arsenic-related issues in the recent past (USEPA, 1989; USEPA, 1992).



3. FINDINGS

The findings that follow are organized to reflect the questions posed to the Committee by the Office of Water (see Appendix A).

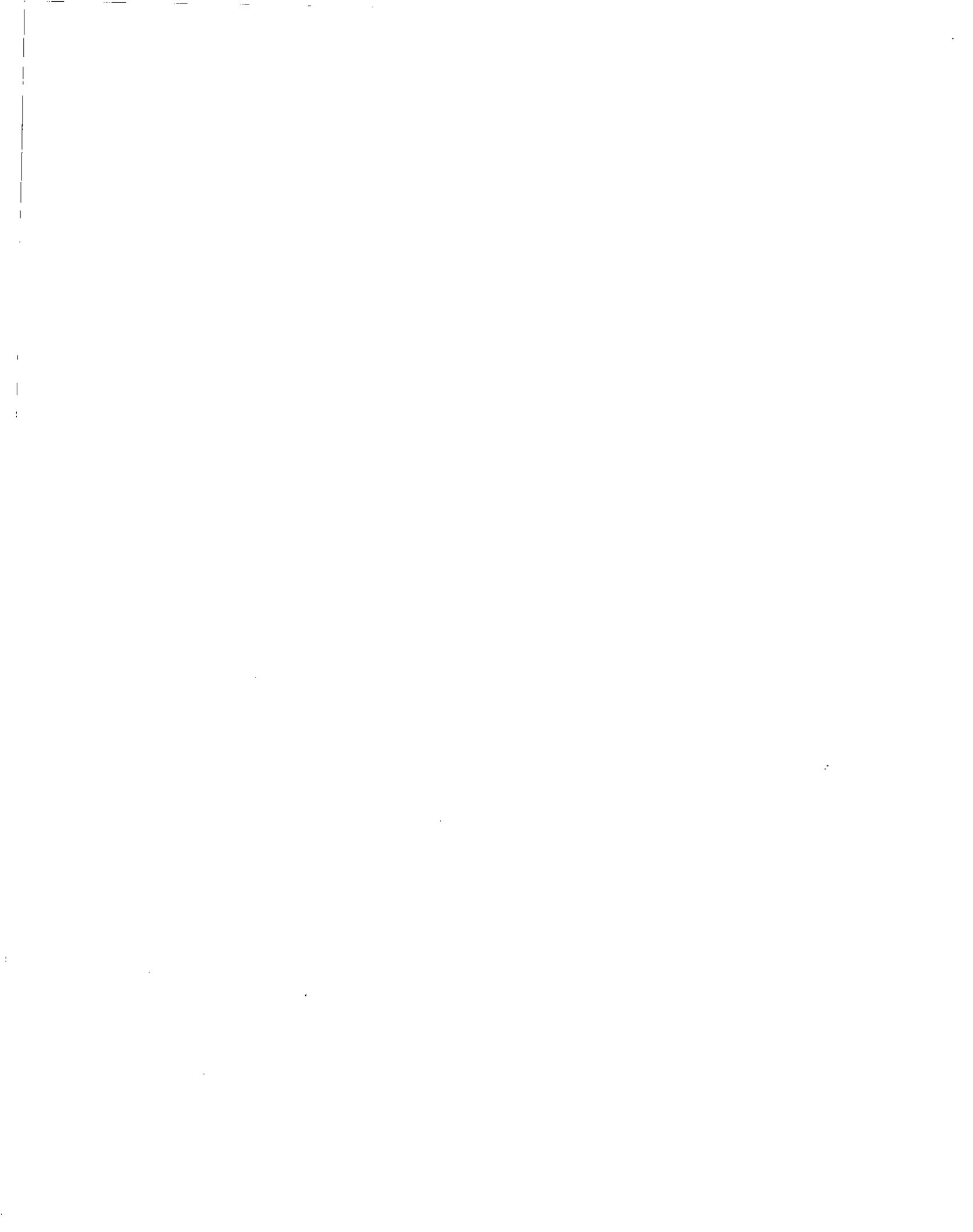
3.1 GENERAL TOXICOLOGY

Have all important aspects of arsenic toxicology been adequately discussed?

In general, the Criteria Document addresses all the important aspects of arsenic toxicology. It might be useful to cite a few general references referring to the history of arsenic toxicity. For example, it has been reported since ancient times that arsenic had a variety of effects, including the classical thirst and diarrhea, dilation of cutaneous blood vessels, darkening of skin pigmentation and perhaps even cancer.

A major shortcoming of the document is that it does not adequately integrate the general toxicity data, the available information on carcinogenic and noncarcinogenic endpoints, and the current knowledge of metabolism and detoxification mechanisms. For example, the data presented on page III-9 (Table III-1, reproduced in Appendix B) from the studies of Valentine *et al.* (1979), related to the relationship between blood and water levels of arsenic, suggest that there is not a linear relationship. Arsenic blood levels are reported low over a broad range of arsenic water levels (<6 - 123 $\mu\text{g/L}$), and elevations in blood arsenic were reported only at very high water arsenic levels (393 $\mu\text{g/L}$). How does this fit in with the data on blood levels in Danish and Taiwanese subjects (as noted in Heydorn, 1970). Are the relationships reported by Valentine sufficiently reliable? If so, what significance do these findings have for conclusions regarding carcinogenicity and general toxicity? The document fails to integrate or critically evaluate the available information in a manner that addresses these and other key questions.

The Committee believes that it is crucial that additional dose-response pharmacokinetic data in humans be obtained prior to any rulemaking. If there is a correlation between arsenic blood levels and cancer risks, as might be expected, the relationship between exposure levels and blood levels reported by Valentine



(1979) are of concern, because they suggest a nonlinearity between exposure and body burden. In reality the majority of people (>98th percentile) in the United States are exposed to less than 25 micrograms of arsenic per liter, which should not result in increased burdens of arsenic in blood according to the Valentine findings.

3.2 METABOLISM AND DETOXIFICATION

Does methylation affect toxicity? Are there sufficient data to conclude that the methylated metabolites of arsenic are nontoxic or almost nontoxic?

It is probably an overstatement to assert that methylated metabolites of arsenic are non-toxic or almost so. It would be better to simply indicate that the methylated forms are less toxic than the parent compound. The document makes clear comparisons between the different forms of arsenic for a variety of systems, both in vitro and in vivo, and it adequately includes discussion of environmental effects and mutagenicity potential.

The Committee has a serious concern about the significance of the reported non-linearities between arsenic concentrations in human blood and ingested water which are also discussed in Sections 3.1 and 3.5. The Agency should examine this issue more closely, as part of a larger critical review of the relationship between exposure, metabolism and dose.

In addition, the Committee recommends that several references and/or studies bearing on the issues of arsenic methylation and toxicity be critically incorporated in the Criteria Document. While the Committee is not suggesting that the conclusions be changed, a more balanced view regarding studies on the actions of methylated metabolites should be presented. Dimethyl arsenic acid (DMA) has been tested in mice and found to be negative for carcinogenicity (Innes *et al.*, 1969). Both morbidity and mortality due to DMA (nephrotoxic at 57 mg/kg/day for 4 weeks) have been reported (Murai *et al.*, 1993). Effects of DMA on DNA have also been reported (Yamanaka *et al.*, 1991; Tezuka *et al.*, 1993). Hopenhayn-Rich and co-workers present data that do not support the "methylation threshold hypothesis" for the toxicity of inorganic arsenic (Hopenhayn-Rich *et al.*, 1993). The 1988 report on arsenic by EPA is available in the open literature and



should be cited (Brown *et al.*, 1989). Finally, there are two papers by Sirachi in the Proceedings of the Western Pharmacology Society which should be cited as the primary references to his work.

These citations do not represent an exhaustive literature review. They simply illustrate the existence of additional, relevant literature that should be included in a comprehensive criteria document.

3.3 MECHANISMS OF TOXICITY

Have the relevant mechanisms been covered?

In general, the Criteria Document adequately covers the predominant mechanisms of arsenic toxicity. There should be more discussion of the interaction of arsenic with lipoic acid, however, because the formation of a stable ring is a key to understanding the interactions of arsenic with enzymes.

There are appropriate references to Voegtlin's work and also to the idea of arsenolysis. It should be noted that there are many studies dealing with the interaction of arsenic with sulfhydryl groups as well as the use of arsenic to study whether an enzyme is sulfhydryl-containing, and whether it has one or two sulfhydryl groups.

It should also be noted that the mechanisms of toxicity were more clearly articulated by Dr. Charles Abernathy during the Committee meeting than they are presented in the document. As discussed in Section 3.1 above, part of the problem is that much of the document reads like an annotated bibliography rather than a thoughtful evaluation and integration of the information in the available studies.

3.4 NONCANCER EFFECTS

**Were the appropriate data used to derive the RfD? Is the UF of 3 justified?
Are there other studies which should be considered?**



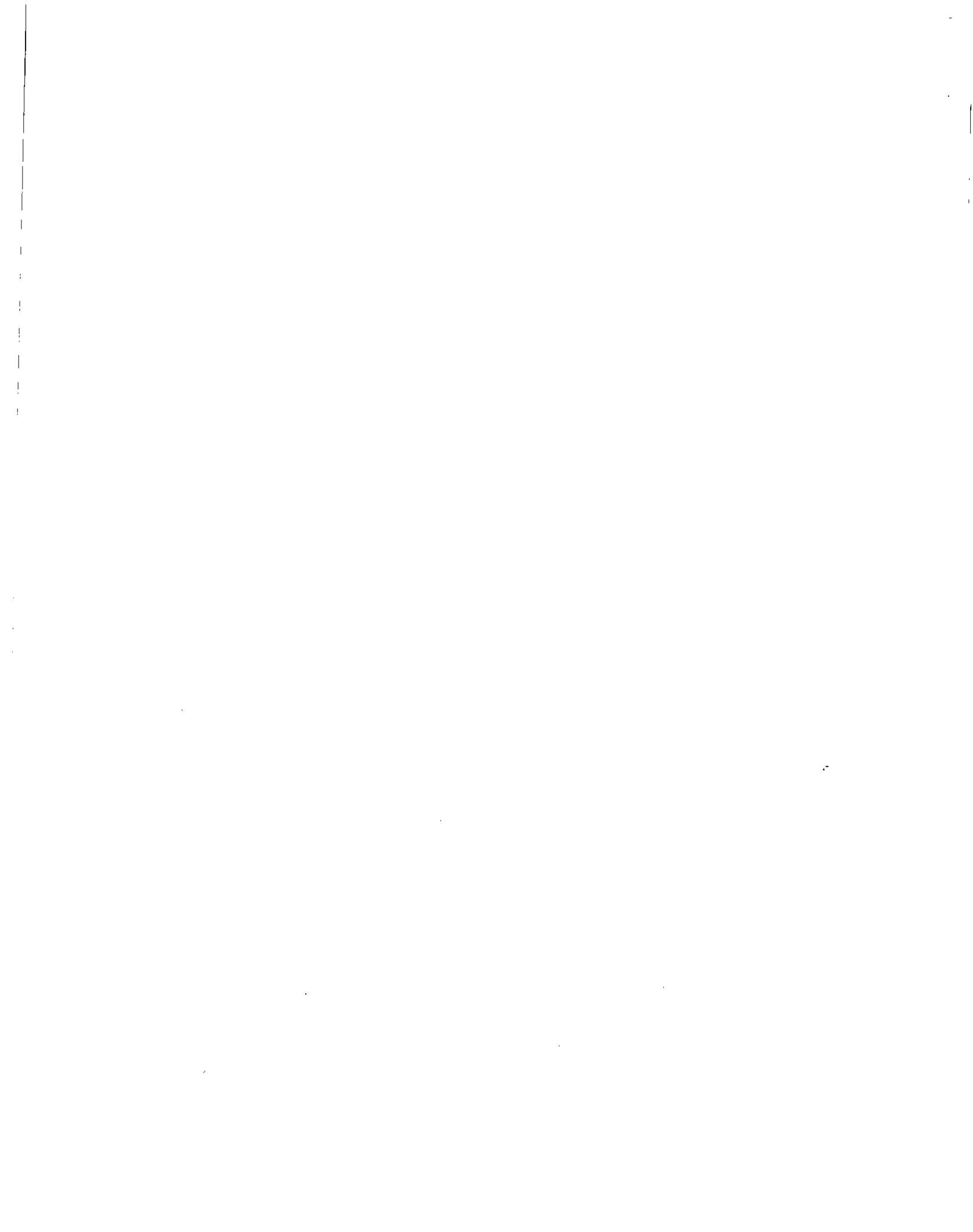
In general the appropriate studies were used to derive the RfD (Reference Dose). The document also cites additional studies whose results are generally consistent with those cited and would generate similar values for the RfD.

The draft document uses an uncertainty factor of three in the estimation of the Reference Dose (RfD). The Committee is not convinced that the use of this additional uncertainty factor is scientifically justified, and finds the two reasons provided in the document inadequate as justification. The two reasons presented in the document are: a) "to account for a lack of data that preclude reproductive toxicity as the critical effect;" and b) "to account for uncertainty that the NOAEL (No Observed Adverse Effect Level) accounts for all sensitive individuals."

In examining the first reason, the Committee finds no data to support it adequately. Certainly the better studies on developmental toxicity would support the conclusion of Hood and Harrison (1982) that acute oral arsenic administration is unlikely to have an effect at doses less than those which cause maternal toxicity. The data of Schroeder and Balassa (1967) on mice suggest a LOAEL (Lowest Observed Adverse Effect Level) of 0.35 mg As⁺³/kg/day. Those of Schroeder and Mitchener (1971) support a possible LOAEL for reproductive effects of the same value. Furthermore, these values are quite low compared to those associated with effects in humans and may have little application to risk assessment in humans.

The Chemical Manufacturers Association presented additional information at the Committee meeting which was relevant to understanding the reproductive and developmental effects of arsenic. These data have not been published in the open literature for proprietary reasons, but they are reportedly available to Agency staff from the Office of Pesticide Programs. These data seemed to support the concept that arsenic has no greater effects on reproduction and development than on other organ systems.

With regard to the second reason, accounting for the most sensitive individuals, there are very few compounds which have a greater database in humans than arsenic. Certainly the document goes into detail about the Taiwanese reports (the basic study for setting the RfD) and the influence of factors such as malnutrition, age (young, old and in utero), association with other



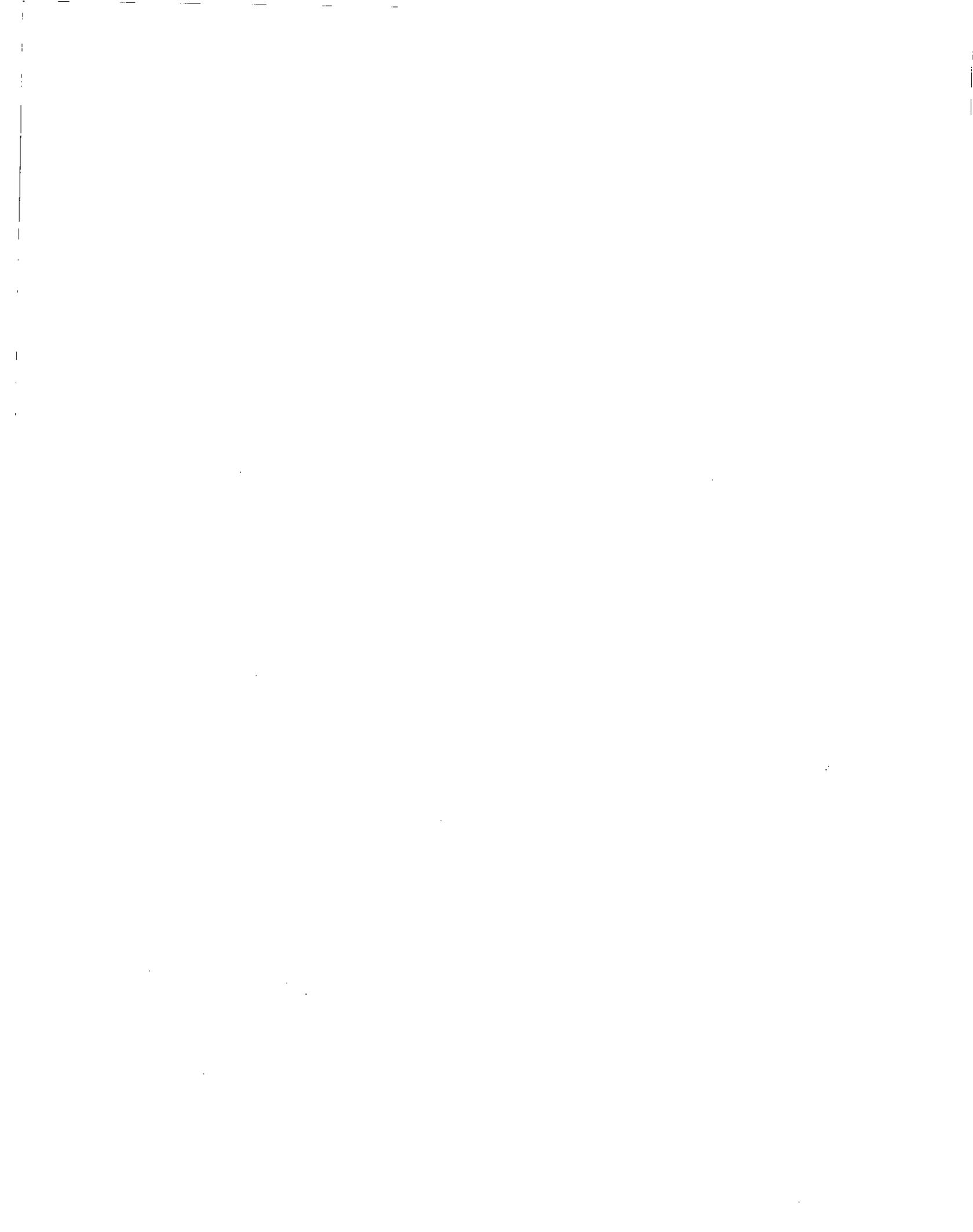
diseases such as blackfoot disease and accompanying exposures to other chemicals. Thus the second reason for using the uncertainty factor of three also has little substance. The Committee recommends against using this extra uncertainty factor of three in deriving the RfD.

3.5 CARCINOGENICITY

Was the most appropriate database used for the cancer quantifications? Do the data (or lack of) justify the use of the linearized multi-stage model (LMS) model (default position) in calculating a potency factor for arsenic? Is it justifiable to use the Taiwan data to set a Maximum Contaminant Limit Goal (MCLG) for the United States? Are there enough data to postulate that a "threshold" may exist for arsenic-induced carcinogenicity?

The Committee believes that the currently available epidemiologic evidence supports the conclusion that an association exists between excess risks of cancer of various internal organs and exposure to *high levels of arsenic*. However, the basis for calculating a potency factor for use in the United States is problematic and not clear and convincing for the low levels of exposure found in U.S. drinking water. The study of the Taiwanese population exposed to high levels of arsenic in drinking water provides the most persuasive evidence of excess cancer risks, because of the large size of the study population. Several published investigations of this population indicate that the mortality rates for cancer of the skin, lung, liver, bladder and kidney among arsenic-exposed groups are higher than the rates in control groups (Chen *et.al.*, 1985, 1988 a, b; Chen and Wang, 1990). Other studies with smaller sample sizes also tend to confirm the associations reported in the Taiwanese studies.

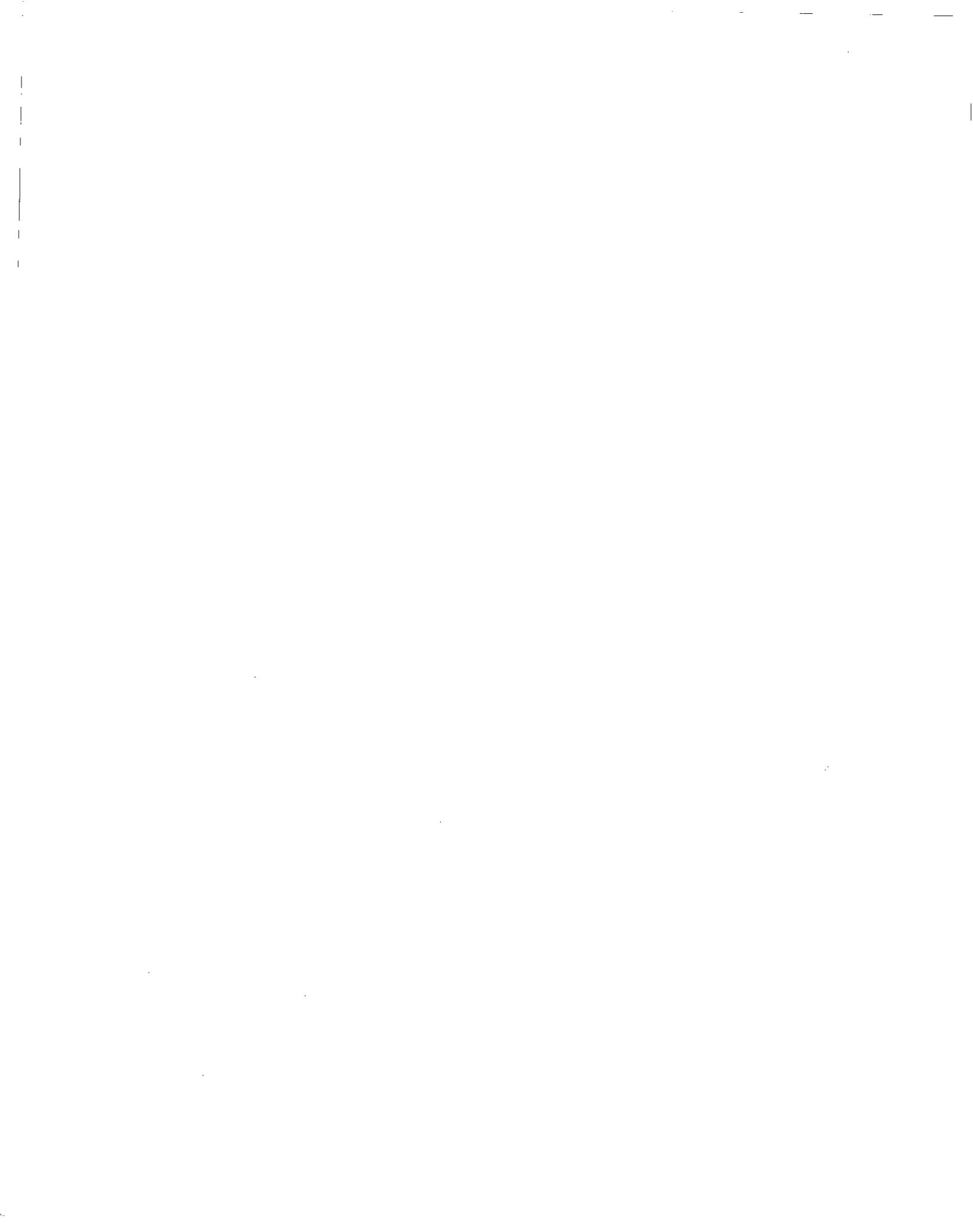
The Taiwanese database is certainly critical in developing arsenic risk estimations, but there are differences between the Taiwanese and U.S. populations which must be carefully taken into account when using the Taiwanese data to set U.S. standards. These differences include the different nutritional status of the two populations, and, in particular, the "background blood levels" of arsenic in the Taiwanese from outside the "endemic arsenic area," which is discussed in more detail below.



The studies reported among US smelter workers document an association of arsenic exposure (primarily airborne and dermal) and excess lung cancer risk, but a study by Enterline (Enterline & Marsh, 1982) did not observe excess risks of skin, liver or bladder cancers, in contrast to the Taiwanese studies, where exposure was primarily by ingestion. An excess for kidney was reported, but it was not statistically significant. Although the power of the Enterline study to detect risks of internal organs other than lung was quite limited, because of the size of the study population, a more thorough review of these data is warranted to see if the apparently contradictory findings can be reconciled. On the whole, however, the Committee feels that the available epidemiologic data support the conclusion that exposure to arsenic is associated with excess of skin and several internal cancers.

The criteria document should be revised to include the results of even more recent epidemiologic findings and re-interpretation of previous studies concerning the relationship between exposure to arsenic in drinking water and excess risks of internal cancers (Chen *et al.*, 1992; Cuziek *et al.*, 1992; Tsuda *et al.*, 1988). In this regard, the Committee is pleased that the Agency commissioned the review of two recent important articles bearing on these issues (Chen *et al.*, 1992; Smith *et al.*, 1992) by renowned experts in epidemiology and carcinogenesis models. The evaluation of these more recent data is imperative, because they address critical issues concerning the Taiwanese population, which is the largest population exposed to arsenic in drinking water that has been subject to epidemiologic study. Also, the conclusion that the risk of internal cancers from arsenic ingestion could be close to ten times the estimates for skin cancer (VIII-18) is premature at this point, and should be far more carefully scrutinized by the Agency.

The Committee is concerned with several aspects of the quantitative risk assessment in the Criteria Document. In particular, the results reported by Valentine do not appear to have been taken into account in the risk assessment. Valentine noted that blood levels of arsenic remained constant at 3-5 ug/L over a range of drinking water concentrations from 6 to 123 ug/L. Arsenic blood concentrations were only elevated at very high levels of water arsenic (in one county, where the water concentration was 393 ug/L and the blood concentration was 13 ug/L). These data suggest strongly that until arsenic levels in the water exceed 100 ug/L, water is only a minor source contributing to increased blood



levels. The potential implication of these findings is that setting standards for water at a level lower than 100 ug/L would not be expected to significantly change the blood levels and body burden of arsenic in people.

Since regulations are likely to be predicated on the Taiwanese data, the characterization of the background levels is very important in allowing proper interpretation of the data. The basis for any quantitative risk assessment is the construction of a dose-response curve based on known exposures and cancer incidences. The Agency has attempted to calculate a potency factor for arsenic in drinking water based on tumor incidences and well water levels of arsenic observed in Taiwanese populations. However, average blood arsenic levels in Taiwanese living in areas where well water levels of arsenic are not particularly high (likely to represent the levels in the control populations of the epidemiologic studies) have been reported to be significantly higher (22 micrograms/liter) than blood arsenic levels observed in Danish or U.S. populations [2.5 micrograms/liter in Danish subjects (Heydorn, 1969) and 3-5 micrograms/liter in U.S. subjects (Valentine, 1979)]. This suggests that significant sources of exposure other than drinking water existed in Taiwan but do not exist in the U.S. The sources of arsenic exposure for the Taiwanese population must be characterized more thoroughly before meaningful estimates of risk from arsenic in drinking water can be prepared for the U.S. populations.

The Criteria Document presents a description of the risk estimates based on the data on skin cancer reported by Tseng *et al.* (1968). This description states that incidence data (p. VIII-17) were used, yet an earlier chapter discussing the same results reports that Tseng *et al.* calculated prevalence. This discrepancy needs to be resolved.

In summary, the Agency should integrate all the available information by conducting an in-house quantitative risk assessment for non-skin cancers from ingestion of arsenic from drinking water. As a key part of this assessment, the Agency should further evaluate the background arsenic levels and the sources of arsenic (other than water) in the Taiwanese population, how these factors may affect the shape of the dose-response curve, and the related issue of the lack of linearity between blood levels of arsenic and arsenic concentration in drinking water.



3.6 ESSENTIALITY

Have the newer studies shown that Arsenic is an essential trace element (ETE)? If Arsenic is recognized as an ETE, would this affect the Arsenic regulation?

Until recently, the Agency's view has been that arsenic has not been shown conclusively to be an essential element (USEPA, 1988), and the Committee has agreed. The Criteria Document is not convincing that this position should be changed. In the past, the Agency has held conferences and adopted position papers that fairly weigh this issue. These need to be more carefully reviewed in the present document. The new study(ies) by Uthus are not readily available for reading, they do not appear in good, peer-reviewed open literature, and their results have not been verified in other laboratories. This does not necessarily mean that they are incorrect in their conclusion, but they simply do not carry sufficient weight to justify a change.

3.7 HUMAN EXPOSURES

How do we use data on levels of inorganic arsenic in food and water? Is one route of exposure more important than the other?

The section on human exposure to arsenic is a good beginning on presenting information on what is known. The Committee has several suggestions for improving the presentation and the accuracy of the contents. These are as follows:

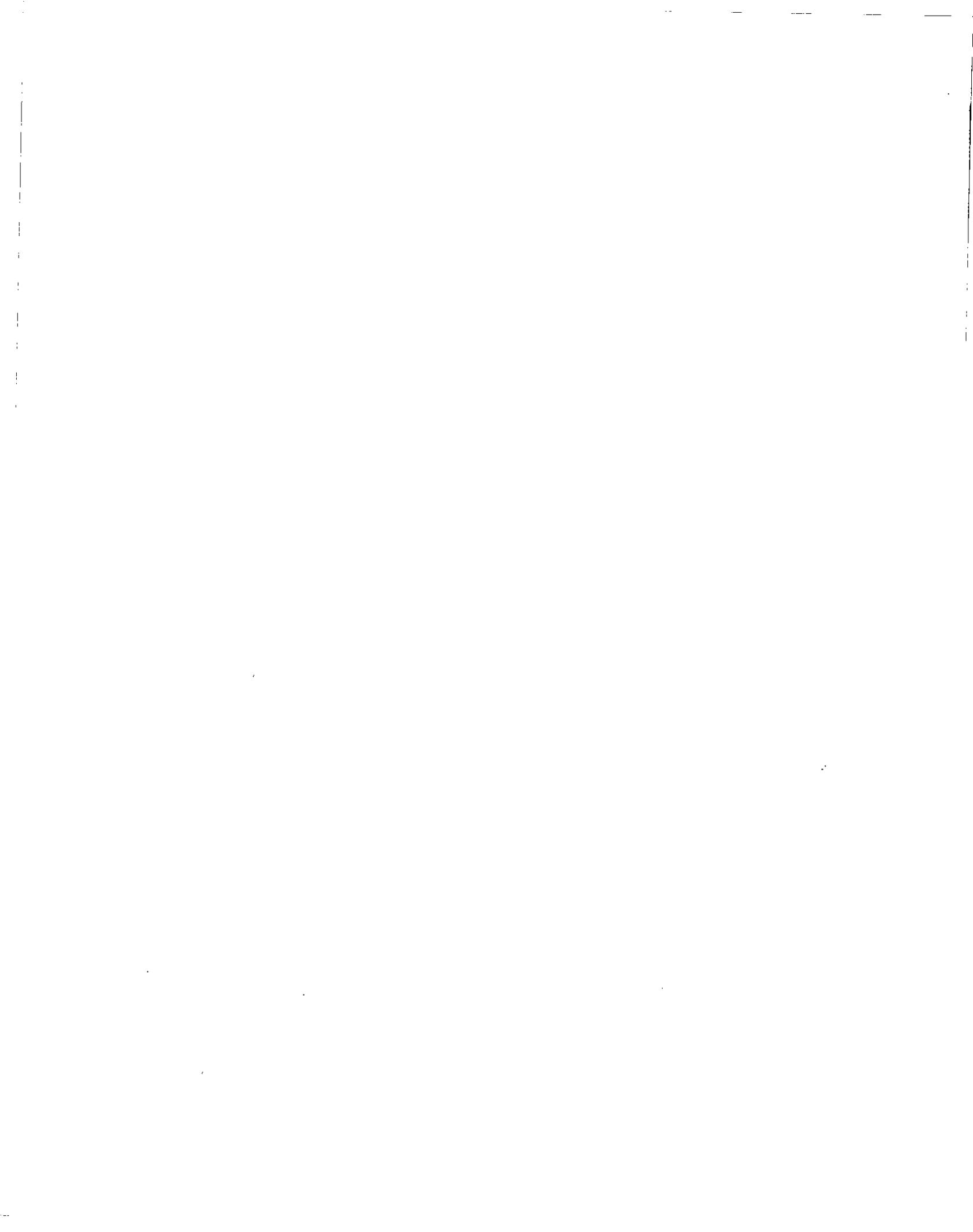
- a) p IV-1. subsection A. "Exposure from Public Drinking Water Systems" should be retitled "Occurrence in Public Drinking Water Systems." The information presented is prevalence; exposure is defined as a person coming into contact with the contaminant.
- b) Tables IV-1 to IV-4 should have "exposed" changed to "used," since exposure is concentration x quantity ingested which is not included in these tables.



- c) Subsection A should more clearly distinguish between what is prevalence data obtained from probability versus non-probability based sampling of the population (this presentation was attempted in Tables VI-1 to VI-4 by folding two databases together). This aspect is important when making inferences about *population exposure* to arsenic in drinking water.

A statement is needed indicating that a national or regional probability-based study to estimate frequency distribution of exposure to arsenic does not exist and therefore, that there is uncertainty as to the number of people exposed to arsenic at particular levels in drinking water.

- d) In addition to the use of a single 2-liter consumption value, distributions of exposure to arsenic in drinking water should be stated in terms of the ranges of water ingested by adults and children using, for example, the National Cancer Institute's water ingestion database.
- e) A short statement on the frequency distribution for dietary arsenic intake would also be useful, in addition to average values.
- f) The document is somewhat limited regarding pathways of exposure. The ingestion of arsenic-containing dust by infants and toddlers is an exposure route neglected by the document. The quantity of ingested house-dust in this population can range from 100 to 800 mg/day, and the quantity of arsenic thus ingested can be a significant contribution to total arsenic exposure (even at the low ambient air levels reported) along with drinking water and food. This factor may be important in calculating relative source contributions. A search for reports of arsenic levels found in house-dust should be made and included in the document, if available.
- g) The levels of arsenic in soil and anthropogenic sources should also be included in the chapter.



- h) The calculation of relative source contribution for arsenic from drinking water, food, and air should include a discussion or display of the uncertainty around the data used.
- i) On page IV-23 the level of arsenic (ug/L) in drinking water selected represents roughly the 98-99th percentile of frequency of occurrence in Tables VI-1 to VI-6. A justification for the use of the value chosen should be given.
- j) In Table VI-7, under large/very large systems, all zero entries are given. Is this correct? Or does this mean that there were no data? This should be clarified in all tables.



4. REFERENCES

- Brown, K.G., Boyle, K.E., Chen, C.W. and Gibb, H.J. 1989. A dose response analysis of skin cancer from inorganic arsenic in drinking water. *Risk Analysis* 9: 519-528.
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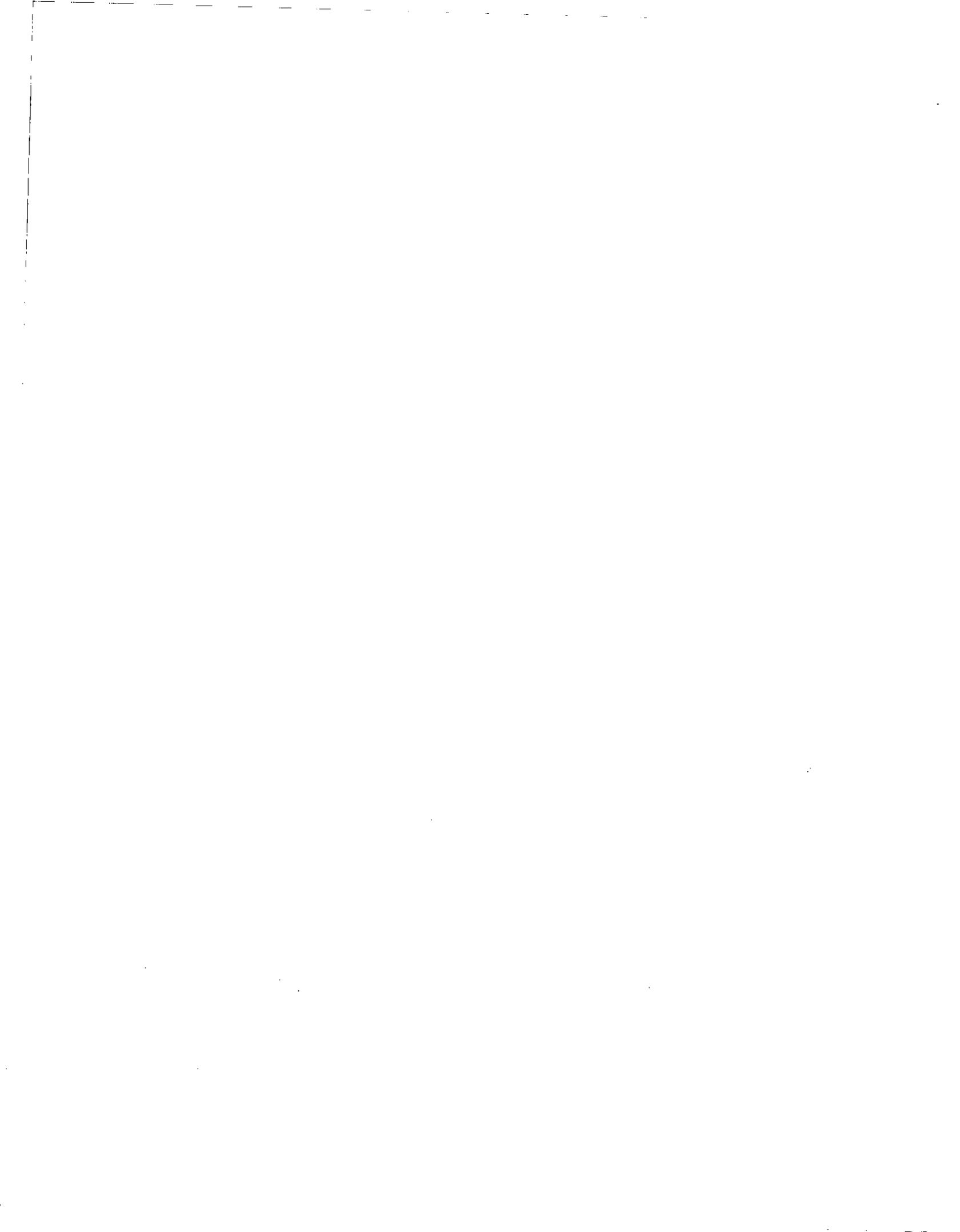
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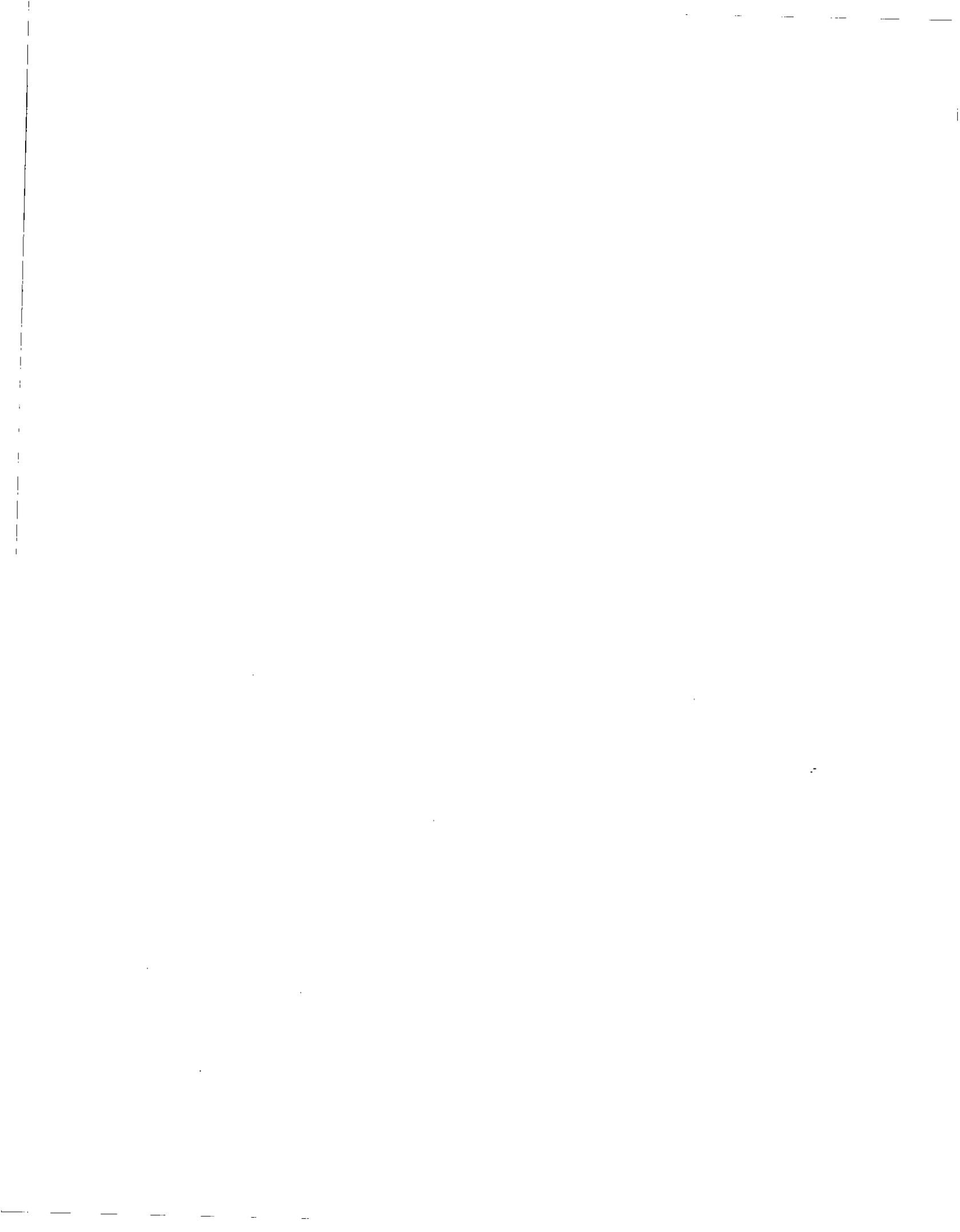
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APPENDIX A. CHARGE TO THE COMMITTEE





UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MAR 10 1993

OFFICE OF
WATER

MEMORANDUM

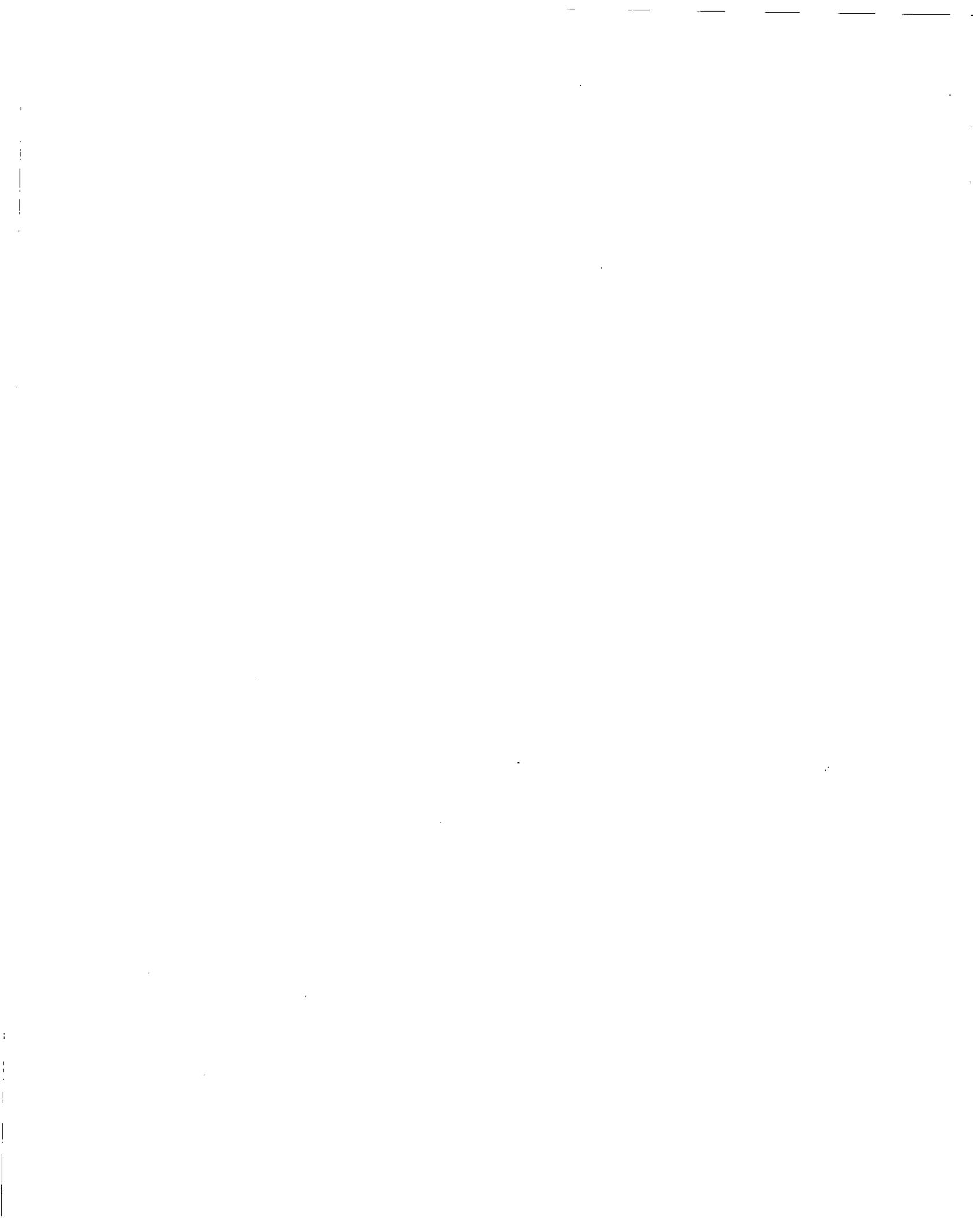
SUBJECT: SAB Drinking Water Committee Review of the Drinking
Water Criteria Document on Inorganic Arsenic -
April 19-20, 1993

FROM: Margaret Stasikowski, Director *MS*
Health and Ecological Criteria Division (WH-586)

TO: Donald Barnes, Director
Science Advisory Board (A-101)

Section 1412 (b) (3) (A) of the Safe Drinking Water Act, as amended in 1986, requires the Administrator of the U.S. Environmental Protection Agency to publish maximum contaminant level goals (MCLGs) and promulgate National Primary Drinking Water Regulations for each contaminant, which, in the judgment of the Administrator, may have an adverse effect on public health and that is known or anticipated to occur in public water systems. The MCLG is nonenforceable and is set at a level at which no known or anticipated adverse health effects in humans occurs and that allows for an adequate margin of safety. Factors considered in setting the MCLG include health effect data and sources of exposure other than drinking water.

This document provides the health effects basis to be considered in establishing the MCLG. To achieve this objective, data on toxicokinetics, and acute, subchronic and chronic toxicity to animals and humans are evaluated. Specific emphasis is placed on data published in peer-reviewed literature providing dose-response information. Thus, while the literature search and evaluating performed in the development of this document have been comprehensive, only the reports considered most pertinent in the derivation of the MCLG are cited in the document. The comprehensive literature data base in support of this document includes information published up to 1992, however, more recent data may have been added during the review process.



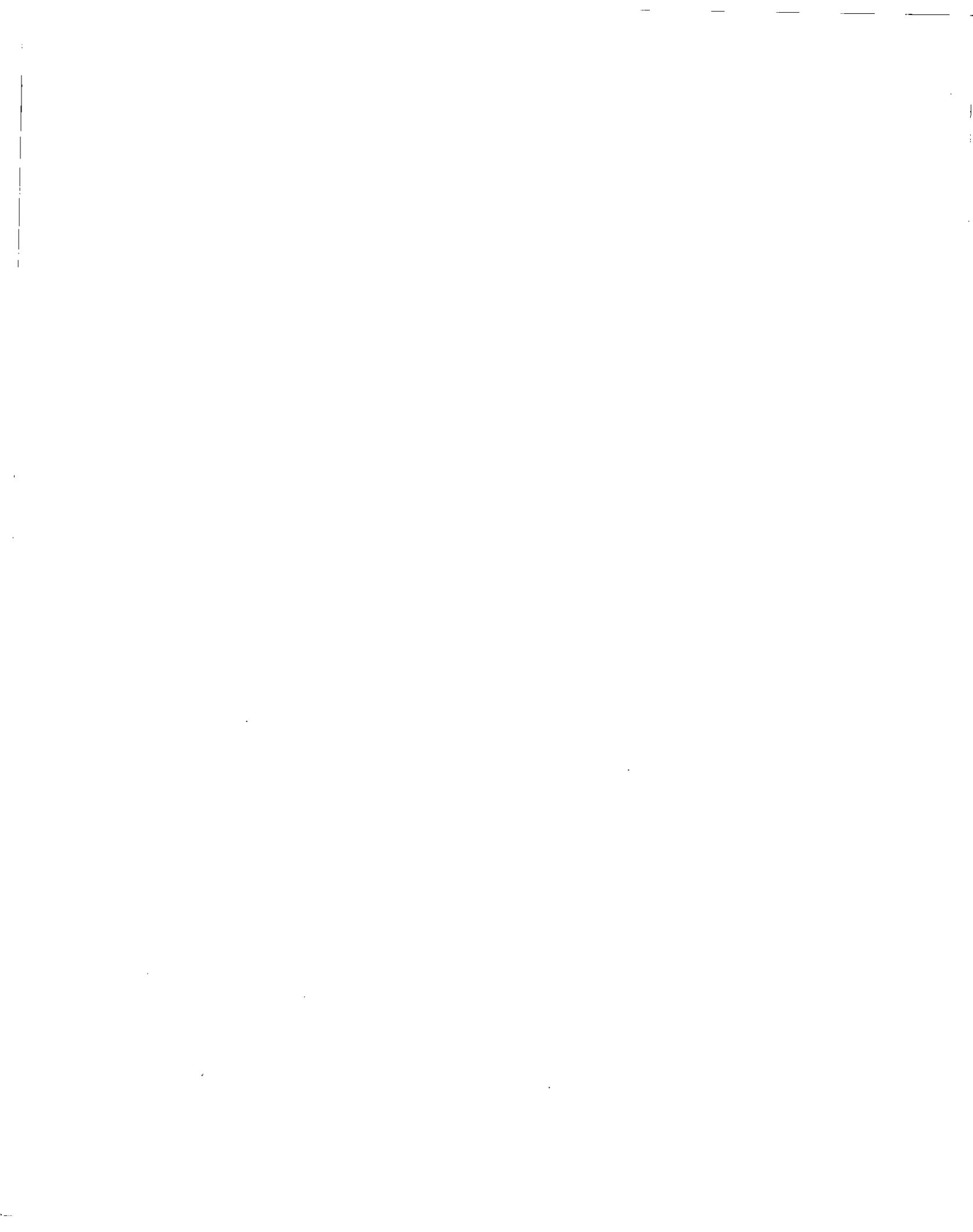
When adequate health effects data exist, Health Advisory (HA) values for less-than-lifetime exposures (1-day, 10-day, and longer-term, i.e., = 10% of an individual's lifetime) are included in this document. These values are not used in setting the MCLG, but serve as informal guidance to municipal utilities and other organizations when emergency spills or contamination situations occur. With adequate data, a Reference Dose (RfD) is derived to be utilized in the derivation of a Drinking Water Equivalent Level (DWEL) on which the MCLG is based. Also, provided is the U.S. EPA's determination of the contaminants carcinogenic potential. When the contaminant has been determined to be a human carcinogen, the estimated excess cancer risk associated with ingestion of contaminated water is included.

The Office of Water's Office of Science and Technology would like to receive your comments on the basis for the noncancer and cancer risk assessment for inorganic arsenic in drinking water.

For your information, we are also including external peer reviewers' comments on the internal cancer studies by Smith et al. (1992) and Chen et al. (1992).

Enclosure

cc: Manuel Gomez (A-101F)





UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MAR 29 1993

OFFICE OF
WATER

MEMORANDUM

SUBJECT: Review of Arsenic (As) Criteria Document (CD) by
Science Advisory Board (SAB)

FROM: Margaret J. Stasikowski, Director *[Signature]*
Health and Ecological Criteria Division (WH-586)

TO: Donald Barnes, Director
Science Advisory Board (A-101F)

During the April 19 review of the Arsenic (As) CD, we request that the SAB provide comments on the following areas:

1. General Toxicology. Have all important aspects of As toxicology been adequately discussed?
2. Metabolism and Detoxification. Does methylation affect toxicity? Are there sufficient data to conclude that the methylated metabolites of As are nontoxic or almost nontoxic.
3. Mechanisms of Toxicity. Binding of As^{+3} to sulphhydryl groups, arsenolysis (As^{+3}) and reduction of As^{+3} to As^{+2} prior to exerting toxicity have been covered. Are there any other relevant mechanisms?
4. Noncancer Effects. Were the appropriate data used to derive the RFD? Is the UF of 3 justified? Are there other studies that should be considered?
5. Carcinogenicity. Was the most appropriate database used for the cancer quantification? Do the data (or lack of) justify the use of the IMS Model (default position) in calculating a potency factor for As? Is it justifiable to use the Taiwan data to set an MCLG for the United States? Are there enough data to postulate that a "threshold" may exist for As - induced carcinogenicity?



6. Essentiality. Have the newer studies shown that As is an essential trace element (ETE)? If As is recognized as an ETE, would this affect the As regulation?
7. Exposure. How do we use data on levels of inorganic As in food and in water? Is one route of exposure more important than the other?
8. Other Areas. If the SAB feels that other data should be included, we will be glad to consider their suggestions.

If you have any questions concerning this request, please contact Dr. Charles Abernathy at 260-7571. Thank you very much for your assistance.

cc: Manuel Gomez (A-101F)



APPENDIX B.

Note to the Reader: This table is reproduced from page III-9 of the draft Criteria Document reviewed by the Committee.

Table III-1. Blood Levels of Arsenic in Response to Exposure From Drinking Water^a

Community	Water ($\mu\text{g/L}$)	Intake ($\mu\text{g/day}$) ^b	Blood ($\mu\text{g/L}$)
Edison	393 \pm 31 ^c	786	13 \pm 12
Hidden Valley	123 \pm 16	246	4 \pm 2
Fallon	98 \pm 2	197	3 \pm 2
Virginia Foothills	51 \pm 13	102	5 \pm 7
Fairfax	<6	<12	5 \pm 1

^aAdapted from Valentine et al. (1979).

^bAssuming a drinking water intake of 2 L/day for a 70 kg adult.

^cMean \pm standard deviation.



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