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April 18, 1979

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Gentlemen:

I am pleased to transmit to you the report of the Science Advisory Board's Subcommittee on Arsenic as a Possible Hazardous Air Pollutant. This report has been prepared by the Subcommittee to detail its deliberations and analyses following the two review sessions of scientific documents on arsenic prepared by EPA on May 22-23, 1978 and January 10, 1979.

Dr. Cantlon, Chairman of the Science Advisory Board, has authorized the direct release of the Subcommittee's report so that various groups within the EPA may use the scientific information contained therein for purposes of preparing new or additional documents on arsenic as a possible hazardous air pollutant. Dr. Cantlon has requested, however, that the report and the Subcommittee's experiences be discussed at the upcoming meeting of the Executive Committee, probably the morning of May 10, 1979. I am prepared to be present at that meeting, and would look forward to meeting with you concurrently or subsequently if you wish.

Sincerely yours,

R. Levine / J. Fahey

Ruth R. Levine, Ph.D.
Chairman, Graduate Division of
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Pollutant

U.S. ENVIRONMENTAL PROTECTION AGENCY
SCIENCE ADVISORY BOARD
EXECUTIVE COMMITTEE

A Report Of
THE SUBCOMMITTEE ON ARSENIC AS A POSSIBLE HAZARDOUS AIR POLLUTANT

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April 18, 1979

EPA Notice

This report was written by a Subcommittee of the Executive Committee of the Science Advisory Board of the U.S. Environmental Protection Agency. The Science Advisory Board is a statutory advisory body to the Administrator and provides independent scientific advice. This report has not been reviewed by the Environmental Protection Agency and, therefore, cannot be construed to represent official Agency policy. Mention of any trade names, products, or commercial items does not constitute an endorsement.

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I. INTRODUCTION

The Clean Air Act Amendments of 1977 require that the Administrator of EPA determine whether several chemical substances and radioactive materials are sufficiently dangerous, at the concentrations at which they are currently found in ambient air, to warrant special regulation. Specifically named chemical substances were (elemental) arsenic and (elemental) cadmium, coke oven emissions, and polycyclic organic matter (POM). Implicit in the naming of arsenic and cadmium are the inorganic compounds of each. The organic compounds of arsenic may also be of concern.

To determine whether these previously named substances need regulation, various EPA program offices, mainly the Office of Research and Development (ORD) and the Office of Air Quality Planning and Standards (OAQPS), were to supervise the preparation of several documents to assess the effects of a given substance on human health, the exposure potential of various airborne levels of the substance by selected population groups at risk, and the risk of cancer production from exposure. The program offices requested that the Science Advisory Board review the scientific merits of the documents prior to Agency development of appropriate regulatory or nonregulatory policies and strategies with respect to airborne levels of the substance.

The Science Advisory Board's approach to the review of these air pollutant documents has been to form subcommittees of specialists to review the materials and present their findings in discussions with the documents' authors at public meetings. These subcommittees are asked to consider the information presented and determine whether the analyses of such information make a cogent, scientifically-based set of arguments upon which a defensible regulatory or nonregulatory policy may be based.

This report deals with arsenic. The Science Advisory Board Subcommittee on Arsenic as a Possible Hazardous Air Pollutant (hereafter referred to as the Subcommittee) was established under the Chairmanship of Dr. Ruth R. Levine of the School of Medicine of Boston University. The membership of the Subcommittee is Appendix A.

Two sets of arsenic documents are discussed herein. The first set, prepared in spring 1978 and reviewed by the Subcommittee in public session on May 22-23, 1978, is referred to as the original draft set. The second set of documents, prepared in autumn 1978 and reviewed by the Subcommittee on January 10, 1979, is referred to as the revised draft set. Each set of documents has three parts: a health effects document, an exposure document, and a cancer risk assessment document (referred to as either "CAG document" or "cancer risk document").

When the original draft set of documents was reviewed, the Subcommittee suggested many revisions to make the documents more scientifically useful for supporting various EPA regulatory options. Because of the considerable interest in those recommended revisions, the Subcommittee issued a public statement of its findings and recommendations, corrected on June 12, 1978. The corrected public statement is Appendix B.

With the exception of the exposure document, the Subcommittee is no more satisfied with the revised set of documents that with the original set. The exposure document incorporated most of the Subcommittee's recommendations to provide an updated picture of population exposure to airborne arsenic from various arsenic sources.

A section on mutagenesis was the major revision in the health assessment document. The majority of the Subcommittee's recommendations were not incorporated into the revised health effects document.

The cancer risk document, although completely revised in content and analysis, incorporated very few of the Subcommittee's suggestions. Because of problems in statistical methodology, the Subcommittee considered this document to be less useful to the Agency (EPA) than the original draft version.

The Subcommittee found the revisions to be either insufficient in scope and detail or of limited usefulness to EPA decision makers. As a result, the set of documents failed to address and clarify specific, still unresolved issues. EPA decision makers tend to rely most heavily on the health effects document; thus, most of the Subcommittee's discussions dealt with that document. Probably the most serious problems the Subcommittee had with the health effects document, both the original and revised versions, were the way in which the literature cited on arsenic was evaluated, the omission of critical references without explanation, and the use of secondary sources for critical data. All of these resulted in a document which appears to obfuscate a very difficult and controversial literature. Subcommittee Members found the material poorly organized and found that there would be difficulty in following the logic, argumentation, and inferences about the meaning of the health effects data on arsenic in humans. Furthermore, the scientific revisions were inadequate in scope and detail. Specific inadequacies are discussed under various issues of concern to the Subcommittee.

At the January 10, 1979 meeting, the Subcommittee received a completely revised section of Chapter 3 of the health effects document dealing with experimental carcinogenesis. This additional material could only be discussed in a cursory manner at the meeting. Substantive review would require additional Subcommittee time once the Members returned to their home institutions. The Subcommittee noted, however, that this additional material exceeded in scope, detail, and length the total of all prior revisions of the health effects document received and reviewed by the Subcommittee. This only reinforced the view that previous revisions were inadequate.

The Subcommittee was charged to base its findings and conclusions primarily on the information presented, even though individual Members might be knowledgeable about data or analyses not cited in the documents. As a Member noted, one had to trust that the document's authors chose the relevant data, analyzed those data properly, and, drew reasoned and scientifically supportable inferences and conclusions from those data.

During the evaluation of the arsenic documents, the Subcommittee was continually reminded of the difficult and controversial nature of the literature on the environmental problems of airborne arsenic. EPA decision makers need documents that have clarity, focus, and a sense of direction. With the information on arsenic as presented in the two sets of documents, the reviewer is confronted with ambivalence, uncertainty, and possibly even confusion. The Subcommittee felt that its own conclusions must accurately reflect the current situation. It, therefore, framed two conclusions which are discussed in the next two sections. These discussions provide some of the Subcommittee's reasoning and analyses.

II. DISCUSSION OF CONCLUSION ONE

Conclusion One, as read into the Record on January 10, 1979, follows:

"All the available data lead to a consensus that there is a real association between exposure to arsenic and the development of cancer, both lung and skin cancer."

The conclusion is based on the data available in the open literature and is not necessarily one that the Subcommittee could draw from the selected literature cited in the health effects document. First, it is essential to establish the relationship between exposure to arsenic and cancer production under some set of conditions, e.g., occupational exposures, before one can consider whether environmental exposure to arsenic is a potential health hazard.

The Subcommittee has no doubt that exposure to arsenic, specifically inorganic arsenic compounds (both trivalent and pentavalent arsenic), raises the risk of lung and skin cancer. There may also be increased risks for liver cancer and some lymphatic cancers. (See the Federal Register, Volume 43, May 5, 1978, Part IV, p. 19584.) The uncertainties may be the levels of exposure, durations of exposure at various levels, dose-time response relationships, and mechanisms of carcinogenesis. The scientific literature provides an overwhelming collection of evidence that overall the association is real despite any specific deficiencies and limitations cited for individual studies.

The Subcommittee believes that it is important to address some other issues which have been mentioned as possibly casting doubt on the arsenic-cancer association.

A. The Subcommittee wants to resolve some of the problems that have resulted from responses within the scientific community to the perceived ambivalence of the expert committee of the International Agency for Research

on Cancer (IARC) in its 1972 monograph on carcinogenic risk to humans from arsenic (International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Volume 2. "Some Inorganic and Organometallic Compounds." Lyon: WHO, IARC, 1973). The IARC expert group evaluated studies up to 1972 on the possible carcinogenicity of arsenic in animals and the existing epidemiological data on human exposures to arsenic. That group expressed uncertainty as to whether the animal bioassay data support arsenic to be a carcinogen. The IARC expert group generally questioned cited studies, which showed a possible carcinogenic potential for arsenic, on the basis of inadequacies in experimental design (problems in the control groups of animals, numbers of animals used, dosing pattern), the small number of neoplasms detected, the very small overall sample sizes, or ambiguities in the descriptions and interpretations given by the original investigators. Nevertheless, the IARC accepted a carcinogenic role for arsenic:

> "The available studies point consistently to a causal relationship between skin cancer and heavy exposure to arsenic in drugs, in drinking water with a high arsenic content, or in the occupational environment."

The IARC group expressed less certainty with respect to lung cancer and thought that some observations of cancer of the liver were possibly "coincidental."

Clearly more studies and data were needed. In the six years since the IARC report, a large number of studies have been or are being completed. Based on the weight and direction of the results of these studies, there has been a change in the situation since 1973 with respect to the epidemiology of lung and skin cancer associated with human exposure to arsenic. This has been recognized by the Occupational Safety and Health Administration (OSHA) in rulemaking to reduce allowable airborne arsenic levels in the workplace. OSHA's rulemaking is based on an accepted association between exposure to inorganic arsenic and increased cancer risk. The reader is referred to the following major references for appropriate information and citations of work:

> Carnow, B. W. (ed.), "Health Effects of Occupational Lead and Arsenic Exposure." U.S. Department of Health, Education and Welfare. Washington, D. C., NIOSH Publication Number 76-134 (1976).

Fowler, B. A. (ed.), "International Conference on Environmental Arsenic: An Overview." Environmental Health Perspectives, Volume 19. U.S. Department of Health, Education and Welfare. Publication (NIH) 77-218 (1977).

Federal Register, Volume 43, May 5, 1978, p. 19584. (This is the final rulemaking of the Occupational Safety and Health Administration on inorganic arsenic in the workplace.)

Of the preceding three references, only the first two are cited in the revised health effects document. The proposed, rather than the final, rulemaking of OSHA is cited in the revised health effects document despite the availability of the final rulemaking two weeks before the original draft version was reviewed by the Subcommittee on May 22-23, 1978. The analyses presented in the final OSHA rulemaking were far more definitive than those in the proposed rulemaking and clarified important issues that should have been included in the revised health effects documents prepared by EPA.

B. The Subcommittee feels that regardless of the mechanism of cancer induction, i.e., whether arsenic is a primary carcinogen, a precursor, a promotor, or a cocarcinogen, the statistical validity of the association between human exposure and cancer production is real.

For risk assessment, the mechanism of cancer induction is immaterial since statistical association, specifically correlation as opposed to regression, does not prove cause and effect. Correlation demonstrates only relationship. The statistical weight of available studies, even those studies with marginal statistical results, lends overall validity to the association. The IARC did acknowledge cause and effect relationships between arsenic and skin cancer. (Very simply, the presence of arsenic elevates the risk of cancer induction.)

C. The Subcommittee believes that, although EPA does not regulate workplace exposure to arsenic but only potential ambient or environmental exposures, EPA cannot ignore the occupational literature as a guide to assessment of environmental hazard. Workplace exposure and worker health records, in many instances, provide the best data from which to develop dose-response curves for nonoccupational exposures. Especially important, as cited in reason #1 of the Subcommittee's supporting analyses of Conclusion One, is the OSHA record on regulating arsenic in the workplace. In general, the Subcommittee believes that consideration of the occupational literature is good scientific practice.

D. The Subcommittee believes that, although many arsenic compounds have been claimed to exhibit antitumorigenic or "carcinostatic" properties, this is not sufficient reason to declare arsenic compounds noncarcinogenic. The Subcommittee notes that some of the most potent anticancer drugs and medical techniques are themselves carcinogenic under different circumstances.

Several investigators have remarked about the carcinostatic properties of certain arsenic compounds and have decried the abandonment of arsenical medicines in the United States. The Subcommittee noted that most arsenical medicines are organics. "Fowler's solution" is an exception, since it is an inorganic arsenical medicine; the relationship between its use and the induction of skin cancer in patients is established. The issue of organic arsenicals as cancer causing agents is not completely resolved at this time. The OSHA rulemaking deals only with inorganic arsenic and exempts organo-arsenicals. (Organo-arsenicals are covered by other legislation, notably, the Federal Insecticide, Fungicide, and Rodenticide Act when the organo-arsenical is a pesticide product.) However, the Subcommittee does not believe that a substance with antitumorigenic effects is a priori noncarcinogenic.

E. The Subcommittee believes that the apparent lack of a suitable animal model for experimentally induced carcinogenicity does not reduce the validity of the association between arsenic exposure in humans and cancer production. In fact, the Subcommittee believes that this issue may no longer be a problem if one reviews the data from neoplasm studies in nonrodent species.

The Subcommittee is aware of the "lack" of suitable animal species for experimental induction of cancer with arsenic exposure. Most of the bioassay studies have been with rodents and the results have been equivocal. The Subcommittee believes that for reasons as yet unclear, rodents may not be appropriate experimental models for arsenic studies. It is to be noted (and appropriately cited in the revised health effects document) that the fate of arsenic in rats is unlike that in other mammals. Furthermore, Kraybill was cited in the OSHA final rulemaking to the effect that the right modes of dosing (inhalation) were not used. The citations of Halver's work by Kraybill (noted in the revised health effects document) in which liver hepatomas were found in trout exposed to carbarsone, an arsenic compound, were noted by the Subcommittee. Mawdsley-Thomas (Mawdsley-Thomas, L.E. "Neoplasia in Fish: A Review." in: T. Cheng, ed., Topics in

Comparative Pathobiology, Volume 1. Academic Press, New York, 1971) has reviewed the literature on neoplasms in fishes. His review strongly indicates the validity of using fishes as cancer bioassay test species in pollution-related situations.

The current evidence from epidemiological studies strongly suggests carcinogenicity in man from arsenic exposures. Lack of an experimental non-human animal model to show cancer production does not deny the relevance of human cancer risk inherent in the epidemiological data. The Subcommittee noted during its January 10, 1979 meeting that the drug thalidomide was removed from the marketplace as a human teratogen long before an appropriate animal model for the teratogenic endpoint was determined or study completed.

III. DISCUSSION OF CONCLUSION TWO

Conclusion Two, as read into the Record on January 10, 1979, follows:

"The data reviewed, and the manner in which these data are analyzed do not permit making a valid or definitive judgment at this time about the role of arsenic as a possible (nonoccupationally) hazardous (or nonhazardous) air pollutant."

The Subcommittee attempted to phrase Conclusion Two in an exact and unambiguous manner, but Conclusion Two has proven to be especially troublesome nonetheless. The Subcommittee developed the statement on the basis of the documents reviewed. The Subcommittee did not believe that it was impossible, in general, to make a judgment about arsenic; only that the documents prepared by EPA were by themselves inadequate to permit such a judgment. The Subcommittee felt that if its first recommendations had been incorporated into the revised draft documents to the maximum extent possible and, where not possible, an explicit explanation given as to why not, a definitive judgment on the role of arsenic as a hazardous or nonhazardous ambient air pollutant could have been made.

The Subcommittee did not intend to avoid making a decision, avoid its advisory responsibilities, or become a hindrance to Agency decision makers. As scientists asked to review data to substantiate conclusions concerning arsenic as a possible hazardous air pollutant, the Subcommittee could only base a decision on what was presented by EPA for its deliberations.

Agency officials were particularly concerned with Conclusion Two. First, Agency officials requested at the January 10, 1979 meeting that the conclusion be reread (four times) into the record to assure that the statement had been accurately heard by questioners and correctly recorded by the meeting reporter. Second, the Staff Officer of the Subcommittee received nearly fifty telephone calls on January 11, 1979, within the first two hours of the working day, for an exact reading of the conclusion and a constant stream of requests thereafter, from both within and outside the Agency, for an exact reading. The Subcommittee was asked by Agency officials several times at the meeting if the Subcommittee understood the political ramifications of its conclusion. The Subcommittee carefully responded that they made no political interpretations of the conclusions, and any political interpretations were not a consideration in their deliberations.

IV. SUBCOMMITTEE CONCLUSIONS AND RECOMMENDATIONS

The Subcommittee has every reason to believe that most of the suggestions and recommendations made for revision of the various documents are still valid and can be accommodated. The Subcommittee also believes that, without reconsideration of its suggestions and recommendations in further revision of the arsenic documents, the EPA decision makers charged with deciding whether or not to regulate arsenic will not have an adequate scientific basis for their decision.

Specific recommendations, as given at the January 10, 1979 meeting, follow:

(a) Collect and analyze all existing data pertinent to the evaluation of the health effects of arsenic on nonoccupationally exposed individuals.

(b) Collect new data on concentrations of airborne arsenic in the vicinity of point sources and collect estimates of absorption of airborne arsenic by exposed individuals.

(c) Require that a statistician sit on every working group in which data collection/analysis will occur to avoid some of the statistical problems that have arisen in the various existing documents.

(d) Reassess the role of arsenic as a possible hazardous air pollutant on the basis of newly collected and analyzed (reanalyzed) data, this reassessment to be made as expeditiously as possible.

V. DISCUSSION OF VARIOUS ISSUES ABOUT THE ROLE OF ARSENIC AS A POSSIBLE HAZARDOUS AIR POLLUTANT

The Subcommittee wants to be of maximum help to the Agency but is not charged with preparation of the documents needed to assess the role of arsenic as a hazardous air pollutant. Nevertheless, the Subcommittee feels that, since some important issues were not addressed in the documents (original or revised), others were not adequately addressed, and still others were incorrectly approached, EPA program officials would find it beneficial to have as detailed a picture of the Subcommittee's concern as it is possible to provide.

The highest priority issues are the use of ambient monitoring data, the assessment of risk for noncarcinogenic endpoints (especially neuropathology and teratology), dose-response analyses on teratology, and the use of incorrect statistical procedures with misinterpretation of the results. The various issues and a discussion of each follow:

A. ISSUE 1

To what extent are ambient monitoring data incorporated into the exposure analysis?

Most of the exposure analysis involved modeling. A particular model, CSTER (not an acronym but a computer code name), was used. This model assumes a geographical grid, and, within each grid space, a completely mixed atmosphere. Superimposed on the grid is a Gaussian diffusional input from and output to adjacent grid spaces. This models scales, for a particular emission characteristic, the atmospheric concentrations of arsenic in each grid space. When population distributions are superimposed upon the grid, human exposure can be estimated. A ratio of an actual emission strength to the assumed model source strength then scales the actual exposure.

While the modeling is not subject to criticism per se, the Subcommittee questioned the extent to which actual monitoring data were used in scaling or checking the model results. There seemed to be indications that monitoring data were available but not used. Most of the apparently unused data were attributable to industrial sources. The Subcommittee understands that Agency scientists may be somewhat hesitant to use monitoring data that are supplied by an industrial source that is subject to regulation based on analyses of its data submissions. Nevertheless, there should have been more positive approaches to such data. Modeling, while intellectually stimulating and often rewarding, loses reality when only hypothetically scaled ambient predictions are made and when no concordance is examined between scaled predictions and actual data, regardless of source (e.g., Region X, EPA, monitoring and enforcement data and other data available for the Tacoma, Washington area).

B. ISSUE 2

The use of statistics within all of the reports presents serious problems to Agency decision makers because of incorrect or inadequate procedures. Document credibility often hinges on how statistics are used. The documents in hand are examples of poor statistical practice.

The first statistical problem, found in the health effects document, is the presentation of data on airborne arsenic versus urinary arsenic in exposed individuals. Since the data are designed to show that exposures to airborne arsenic are reflected in particular urinary levels, airborne arsenic should be the independent variable in the regression, and urinary arsenic becomes the dependent variable. This is not how the document presents these data. The original literature on the airborne/urinary arsenic cited in the health effects document, exposure documents, and other sources, have the reverse. In the health effects document, measured values of urinary arsenic are plotted as independent variables against airborne levels of arsenic as dependent variables. The Subcommittee questions whether human excretion of arsenic is a major source of airborne pollution.

Once the presentation of the air/urine arsenic regressions was given, the analyses proceeded along incorrect lines. Use of the regression, as presented, to calculate what the level of airborne arsenic must be to achieve an exposure associated with a given urinary level requires some special statistical procedures called "inverse prediction." Inverse prediction requires that special confidence levels be assigned rather than standard error estimates when the regression is reversed. These estimates of special confidence levels

associated with a predicted value of an independent variable calculated from a measured value of a dependent variable, are often larger numerically than the standard errors associated with the original data from which the regression was created.

A second problem was a tendency in the original draft version of the health effects document to preselect data points for regression analysis and reject others as "outliers" because they did not look "attractive." In the original draft, the outliers were not outliers. Statistical significance of the original regressions depended on these data points being part of the set. When the recalculation of regression was performed without these points, the results were statistically nonsignificant. This point is raised because the particular practice is common within EPA and applies to other documents reviewed by some Subcommittee Members for Science Advisory Board groups. Such statistical procedures must be carefully justified each time they are used. They cannot be used routinely, or many of the analyses presented in pollutant criteria documents may be judged misleading or even invalid.

A third problem, this time in the CAG document, is in combining three studies which do not have comparable data because of differences in experimental design and parameter meaning, and in estimating a new parameter from these studies as a basis for risk assessment of lifetime exposure to arsenic. This becomes questionable when one of the component studies has a regression and correlation with a zero correlation coefficient (no statistical significance). The slope of the regression line which is nonsignificant was used as one of the numbers to calculate a geometric mean of all the component studies as the basis risk parameter. In any geometric mean where one term is zero, the n-th root of zero is zero, not some positive number. This was discussed at considerable length. A particular investigator's data were force fit to a regression line that passed through the origin. The variances associated with the data points relative to that line increased, and a zero correlation coefficient resulted from the force fit. If that is the case, then the force fit is itself not statistically significant. The Subcommittee believes it would have been better to treat each study separately, make all risk calculations required for each study, and compare the final results for concordance or nonconcordance. When nonconcordance was found, the authors should have explained the differences.

On February 9, 1979, the Chairperson of the Subcommittee met with EPA directors of the Cancer Assessment Group (Drs. Albert and Anderson). At that meeting, the CAG directors explained that the no threshold risk extrapolation policy for cancer risk assessment presumes that the origin is a valid datum without error or bias. Thus, if only one dose/effect datum were available, a force fit line through the origin could be drawn and used by CAG for its analyses. This was stated as EPA policy. The Subcommittee does not wish to enter into the debate on Agency policy. What is at issue is how statistics are misused in the step after the force fit line is constructed. If the force fit line does not give a nonzero statistically significant slope or if statistical properties of the slope cannot be calculated because of an inadequate number of degrees of freedom (i.e., insufficient number of data points), then that study should not be combined with others having valid statistics to produce an invalid combined assessment. The force fit study should be treated separately and, as previously suggested, the results of all risk assessments should be examined for concordance or nonconcordance.

A fourth problem, also in the CAG document, is the practice of merging data points, taking means of several points, and taking means of means. This practice reduces the number of degrees of freedom in resultant correlations. Although individual points may appear very close, when the number of degrees of freedom are reduced, the result may again be a nonsignificant or misleading regression. Subcommittee Members noted that often the data points which were combined, although numerically close, fit a geometric scale of exposures and thus provided a picture of several orders of magnitude in values of arsenic concentration. A geometric scale of doses and/or exposure is accepted practice in most toxicological protocols for risk assessment and dose-response relationship analyses. The procedure of merging data points is more prevalent at very low dose levels where scatter and variability in the data are greatest. But the procedures, rather than increasing reliability, lose vital information. Biological variabililty at low dose levels is expected and should not be masked by the procedures of data analysis.

C. ISSUE 3

Are there endpoints and adverse effects other than cancer for which risk assessments associated with arsenic exposure have to be considered?

The Subcommittee's answer is an emphatic yes. Risk assessment, even if only qualitative, for endpoints other than cancer is necessary to provide a balanced health risk assessment for regulatory purposes.

This is an important issue that arose at both Subcommittee meetings. At the May 22, 1978 meeting, the document authors were asked if they had reviewed data on arsenic effects on the central nervous system. The answer was "No, because data were unavailable." However, two relevant references were, indeed, cited in the original draft version of the health effects document and were also in the revised draft of health effect document. Yet neither reference was discussed in any detail or included in the discussion of risk assessment. Examinations of the references, with a view toward dose-response analyses of the data, were not provided in the health effects document; so the question of possible risk assessment could not be addressed and evaluated either qualitatively or quantitatively. Moreover, the Subcommittee Members are aware of additional data on the effects of arsenic on cardiovascular, renal, and central nervous system functions. A study including some of the most recently summarized data on neuropathology was sponsored by EPA ("Epidemiology Studies --Selected Non-Carcinogenic Effects of Industrial Exposure to Inorganic Arsenic." EPA report number 560/6-77-018, October 1977, Final Report, Office of Toxic Substances, U.S.E.P.A., Washington, D. C. 20460).

The Subcommittee feels it is also important to address the differential effects in the young versus the adult. For this reason, considerable analysis of the Chilean data on the children exposed to arsenic through drinking water is needed, not just citation and summarization of the results, as in the arsenic documents.

The issue of the paucity of analysis of the noncarcinogenic adverse health effects data with a view toward risk assessment was raised at the January 10, 1979; the Subcommittee was asked to provide the references for any data for endpoints or disease states other than cancer with respect to arsenic exposure. Because the need for risk assessment for noncarcinogenic endpoints is vital to EPA decision makers, the Subcommittee includes, herein, some useful references. The

Subcommittee expects, however, that citation of these references will be accompanied by analyses and critical evaluations for risk assessments. The Subcommittee, in fact had provided references for the revised health effects document only to find them cited in the bibliography but not in the text. In fact, the Subcommittee noted that 107 references listed in the bibliography of the revised health effects document were not cited in the text.

References:

Petren, K. "Etudes cliniques sur l'etiologie et les symptomes de l'empoissonement arsenical du a l'habitation ou des objets de l'emploie domestique." Acta. Med. Scand. 58: 217-230 (1923).

Chuttani, P.N., Chaula, L.S., and T.S. Sharma. "Arsenical neuropathy." Neurology 17: 269-274 (1974).

Jenkins, R.B. "Inorganic arsenic and the nervous system." Brain 89: 479-498 (1966).

Lequesne, P.M. and J.G. McLeod. "Peripheral neuropathy following a single exposure to arsenic." J. Neurol. Sci. 32: 437-451 (1977).

Frank, G. "Neurologische und psychiatrische folgesymptome bei akuter arsen-wassers toff vergiftunis." J. Neurol. 213: 59-70 (1976).

Freeman, J.W. and J.R. Couch. "Prolonged encephalopathy with arsenic poisoning." Neurology 28: 853-855 (1978).

D. ISSUE 4

Are there dose-response characteristics for arsenic as a teratogen?

Teratogenicity of inorganic arsenic compounds was discussed briefly at the January 10, 1979 meeting. The Subcommittee believes that significant data exist to show that inorganic arsenic is a teratogen. Teratogenicity has been demonstrated in mammalian species (mice, golden hamsters, rats) and bird species (chickens, mallards). Transplacental movement has been demonstrated in rodents and humans. The revised health effects document deals with teratogenicity through citations of the relevent work of Ferm, Hood and Bishop, and Petrokova and Puzanova. However, the revised health effects document does not present these discussions in terms of dose-response pharmacological and toxicological principles. The National Academy of Sciences document on arsenic (National Academy of Sciences. Arsenic. Washington, D.C. 1977), from which the citations appear to be taken, also did not present such analyses, although it cited some of the relevant numerical data. The Subcommittee suggests that Ferm's data and Hood and Bishop's data may lend themselves to such an analysis and that a dose-response relationship should be attempted.

E. ISSUE 5

Are the low levels of arsenic which appear to be present in all individuals important when assessing the role of arsenic as an environmental hazard?

Although data on the environmental distribution of arsenic are discussed at some length in the various draft sets of documents, the issue of low levels of arsenic found in all human tissues is not addressed in either the health effects document or the exposure document. If individuals universally have low body burdens of arsenic and if these body burdens are not measurement artifacts, the correct lower limit of arsenic concentrations in dose/risk extrapolations is not necessarily zero, but some finite, measurable, residual value. Body burdens of arsenic below the lower limit of this residual level do not have the same biological significance as the residual levels because the latter act as "backgrounds."

There is a fifty year history of scientific interest in the body burdens of arsenic associated with "normal" or "unexposed" individuals. The literature begins with Billeter and Marfutt (1923), in Switzerland, and their analysis on a "fresh weight basis" of spleen and thyroid with lower limits of 0.03 - 0.06 ppm. Other data are those of Van Itallie (1932), in Holland, with comparable lower limits on nails. More recent data, all on a "fresh weight basis," are those of

Katsura (1957), Gerin and de Zorzi (1961), Boylen and Hardy (1967), Damsgaard et al (1973), and Mathies (1974), who provide lower limits of 0.001 ppm for heart, spleen, and brain; 0.006 ppm for liver, kidney, pancreas, blood, intestine (wall), and stomach (wall); and 0.15 ppm for bone. Reeves (1976) made an attempt to summarize some of these data but emphasized hair, and nails (tissues not indicative of current exposure but of past exposure) and urine and blood. Underwood (1977) cited data of Smith (1967), possibly because only Smith reported his analyses on a "dry weight basis," independent of the size and weight of the tissue. Moisture con4ent causes changes in tissue size and weight, and, when the moisture is blood, tissue levels may also reflect the arsenic content of blood. Smith suggests lower levels of 0.04 - 0.09 ppm (mg/kg) for body tissues.

Perusal of the literature shows that there is great variability in the data. This is to be expected because exposure levels are unknown and extremely variable. Another problem is the analytical methods for quantifying arsenic at trace levels in tissues. Analytical methods for trace quantities of arsenic have low reproducibility, as little as ± 30% at the 1 ppm level, depending on the matrices of the sample. This was acknowledged in the original draft of the health effects document but omitted in the revised draft. There seems to be little reason, therefore, to calculate and report mean values, median values, or other statistical parameters for these data. The range of values appears most descriptive with a note as to the great variability.

A corollary issue of trace body burdens is the question of whether they are of biological significance or coincidental; is arsenic necessary or just tolerated at some background level? Schwarz (1977) was concerned that trace body burdens of arsenic might imply biological necessity. The Subcommittee does not express a view on this conjecture but notes that biological significance is not restricted to metabolic necessity. Biological significance, however, may involve beneficial, but not essential, effects. Because trace levels of arsenic exist in all individuals, any health assessment document should note this and the fact that there is some question as to whether these levels have biological significance either in terms of essentiality of the element or beneficial, but nonessential, effects.

References:

Billeter, O. and E. Marfutt. "De la teneur normal en arsenic dans le corps humain." Helv. Chim. Acta. 6:780-784 (1923).

Boylen, G.W. and H.L. Hardy. "Distribution of arsenic in non-exposed persons (hair, liver, urine)." Amer. Ind. Hyg. Assoc. J. 28:148-150 (1967).

Damsgaard, E., K. Heydorn, N.H. Larsen, and B. Nielsen. "Simultaneous determination of arsenic, manganese and selenium in human serum by neutron activation analysis." Riso Report 271, Roskilde: Danish Atomic Energy Commission (1973) 35 pp.

Gerin, C. and C. de Zorzi. "The arsenic content in the organs of the human body." Zacchia 36 (Vol 24, Ser 2): 1-19 (1961).

Katsura, K. "Medicological studies on arsenic poisoning. Report 1: Arsenic contents of the visceral organs, bone, and hair of normal human individuals." Shikoku Acta. Med. (Shikoku Igaku Zasshi) 11:439-444 (1957) (in Japanese).

Mathies, J.C. "X-ray spectrographic microanalysis of human urine for arsenic." Applied Spectroscopy 28: 165-170 (1974).

Reeves, A. see B.W. Carnow (1976), p.240 (previously referenced).

Schwarz, K. "Essentiality versus toxicity of metals." in: Clinical Chemistry and Chemical Toxicology of Metals. S. Brown (ed.) Elsevier, Holland (1977).

Smith, H. "The distribution of antimony, arsenic, copper and zinc in human tissue." Forensic Sci. Soc. J. 7: 97-102 (1967).

Underwood, E.J. Trace Elements in Human and Animal Nutrition. 4th Edition. Academic Press, New York, pp. 424-429 (1977).

Van Itallie, L. "Arsenic content of hair." Pharm. Weekblad. 69: 1134-1145 (1932) (in Dutch).

F. ISSUE 6

Does arsenic at low levels have any beneficial effects on cell systems?

Most studies of arsenic metabolism in man have emphasized the nature of arsenic excretion products as a function of exposure to specific inorganic arsenic compounds. Virtually none of the research has emphasized trying to establish the form of arsenic within cells. Until the form of arsenic and the way in which it is bound in human tissues are ascertained, the questions of carcinogenicity of inorganic versus organic arsenic and toxicity versus beneficial effects will be conjectural.

Arsenic appears to have a potentially beneficial role in a number of animal species. Ironically, it was another part of EPA which alerted the Subcommittee to the data. In the Federal Register announcement, "Notice of Rebuttable Presumption Against Registration and Continued Registration of Pesticide Products Containing Inorganic Arsenic," (Volume 43, October 18, 1978, p.48267), EPA acknowledged and cited several references about possible beneficial effects of arsenic in mammals:

(a) Muth et al; Amer. J. of Vet. Med. 32:1621 (1971); describes that 1 ppm of sodium arsenate reduced myopathy of lambs on a selenium deficient diet.

(b) Nielsen et al; Fed. Proceedings. 34-923 (1957); reports on possible arsenic deficiency in rats on a 30 ppb arsenic level in the diet. The test animals had low rates of growth, rough hair coats, splenomegaly, decreased hematocrit, and increased osmotic fragility of erythrocytes.

(c) Anke et al: Trace Substances in Environmental Health, Volume 10; D.D. Hemphill (ed.) (1976); reports effects similiar to Nielsen's on possible arsenic deficiency in the diets of goats and swine.

In addition, there is a large literature on the importance of arsenic-selenium interactions in mammalian systems. Selenium is a cofactor in metabolic systems utilizing Vitamin E, is toxic in excess, is responsible for a number of animal diseases and has been implicated in some human diseases. In the 1930's, Moxon and his coworkers [Moxon, A.L. "The effect of arsenic on the toxicity of seleniferous grains" Science 88:81 (1938); Moxon, A.L. and K.P. DuBois. "The influence of arsenic and the other elements on the toxicity of seleniferous grains." J. Nutrition 18:447-459 (1939)] at the South Dakota Agricultural Station found that arsenic, added to the drinking water and feed of livestock, detoxified the selenium from seleniferous grains and selenium accumulator plants consumed by the livestock. Recently, Levander and his coworkers [Levander, O.A. and C.A. Baumann, "Selenium metabolism." Parts V and VI. Toxicol. Appl. Pharmacol. 9:98-105, 9:106-115 (1966).] at the Agricultural Research Service in Beltsville, Maryland, have examined some of the mechanisms of the arsenic-selenium interaction. They found that selenium detoxification by arsenic involves secretion of an arsenic-selenium complex into the bile.

G. ISSUE 7

What effect might possible beneficial effects of arsenic in human tissues have on the Agency's no threshold cancer risk extrapolation policy?

EPA has a policy to prescribe how to infer the effects of low dose exposures of a carcinogen from high dose bioassay data. This policy uses an assumption that carcinogens have no thresholds. This is not a question which the Subcommittee was asked to address, and, consequently, the Subcommitee did not address it. At the January 10, 1979 meeting, however, Agency officials questioned the Subcommitee on this issue, because they felt that perhaps the Subcommittee was recommending, in its Conclusion Two, that EPA abandon that policy. In addition, some scientists believe that beneficial effects of a substance, which is carcinogenic at higher exposure levels, might imply a threshold for the carcinogenicity.

The wording of Conclusion Two indicates only, one, that the data presented and reviewed in the arsenic documents did not include the possibilities that low levels of arsenic may have some beneficial effects in some species; and second, that the data presented on adverse health effects were insufficient and inadequately interpreted to permit drawing conclusions about the environmental levels at which arsenic is hazardous to humans. At the present time, as Kraybill noted in the OSHA rulemaking (previously cited), not enough is known about the mechanisms of carcinogenicity to discuss thresholds for this endpoint.

H. ISSUE 8

What is the significance for human carcinogenicity of equivocal results in animal bioassays of carcinogenicity?

Many of the animal studies of experimentally induced carcinogenesis produced equivocal results. Equivocal, in the sense used here, refers to a result which is not sufficiently statistically significant to displace a null hypothesis but is sufficiently marginal to be suspicious. In some instances, statistical procedures exist which allow one to test the combined effects of several studies with statistically marginal data to resolve the issue of whether one can ascribe an equivocal nature to the combined studies, or whether one can shade the overall evidence toward positive or negative inferences [c.f., Fisher, R. A. Statistical Methods for Research Workers. 12th Edition. Oliver and Boyd, Edinburgh (1954), 356 pp. (see section 21.1)]. Such techniques were not explored in any of the documents. However, the Subcommittee received a thoroughly revised section of Chapter 3 of the health effects document, dealing with carcinogenicity and including a reexamination of all of the animal bioassay studies. On the weight of the overall evidence, the authors concluded that the equivocal nature of the animal bioassay tests should be shaded toward a positive inference of carcinogenicity rather than a negative inference of noncarcinogenicity. The important issue is that equivocal results are not automatically positive or negative. Each case must be critically examined; such critical analysis should be an integral part of the assessment of the health effects of any pollutant.

I. ISSUE 9

Why have certain documents that have been published by the EPA and other Federal agencies and that are extremely relevant been ignored in the preparation of the criteria document for arsenic?

As previously indicated (ISSUE 6), the FIFRA document published in the Federal Register, Vol., 43, October 18, 1978, p. 48267 contained much data and addressed many issues that would have been entirely appropriate for inclusion in the Health Effects and CAG documents on arsenic. Also the OSHA document, Federal Register, Vol. 43, May 5, 1978, p. 19584, for example, provides analyses of data of such variables as time to tumor death, age at time of exposure and duration of exposures; the incorporation of assessments of risks associated with each of these variables were recommended by the Subcommittee in the review of the original CAG document (see Appendix B).

The Subcommittee finds it difficult to understand why the EPA ignored criteria documents prepared by one of its own subdivisions or by an agency of both the IRLG and Interagency Toxic Substances Data Committee with which the EPA is charged to maintain liaison. The Subcommittee concludes that almost one year could have been saved in the preparation of useful criteria documents for arsenic and the expenditure of much effort and funds been avoided, if the information in extant documents had been utilized.

The Subcommittee wishes to suggest that in preparing future criteria documents the EPA adhere to its broad coordination and policy development responsibilities under various environmental legislative authorities with particular attention to policies it describes in the Federal Register announcement of May 26, 1978 concerning the Interagency Toxic Substances Data Committee.

VI. APPENDICES

APPENDIX A

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APPENDIX B

U.S. ENVIRONMENTAL PROTECTION AGENCY
SCIENCE ADVISORY BOARD
SUBCOMMITTEE ON ARSENIC AS A POSSIBLE HAZARDOUS AIR POLLUTANT

Subcommittee Statement
(Corrected) June 12, 1978

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INTRODUCTION

On May 22-23, 1978, the Subcommittee on Arsenic as a Possible Hazardous Air Pollutant met in public session in Washington, D.C. to review documents related to the EPA's proposed actions on whether or not to "list" arsenic as a hazardous air pollutant under Section 123 of the Clean Air Act Amendments of 1978. The Subcommittee read into the public record a Statement of Recommendations on May 23, 1978 which provided the Subcommittee's consensus on the Agency's documents.

One part of the Subcommittee's Statement indicated that the document, Assessment of the Health Effects of Arsenic, was "not suitable in its present form to support the development of control procedures for arsenic as a hazardous air pollutant." In making this statement, the Subcommittee was not aware of the Agency's legal choices with respect to the use of documents to support air pollution standards and criteria. Only in the case of designating a national ambient standard for an air pollutant must the scientific documentation be in a "final form" which can withstand appropriate challenge. In those situations where the Agency is asked to "list" a pollutant as "a hazardous air pollutant" the decision to "list" or "not to list" does not depend on the scientific quality of background documentation. Theoretically the Agency could choose to "list" or "not list" without recourse to scientific documentation.

The Subcommittee desired to be of maximum constructive assistance to the Agency. Therefore, in order that the public record not be clouded by any misunderstanding on the part of the Subcommittee with respect to the Agency's needs and uses of scientific documentation on arsenic as a possible hazardous air pollutant, the Subcommittee has issued a revision of its Statement of Recommendations (June 12, 1978). This Statement of Recommendations, in its revised forms, has been communicated by the Staff Director of the Science Advisory Board to appropriate Offices of the EPA.

STATEMENT

The Subcommittee on Arsenic as a Possible Hazardous Air Pollutant (of the Science Advisory Board of the U.S. Environmental Protection Agency) has read and reviewed in detail the three documents submitted by the EPA:

1. Human Exposure to Atmospheric Arsenic

2. Population Risk to Arsenic Exposures

3. Assessment of the Health Effects of Arsenic

I. Human Exposure to Atmospheric Arsenic

This is a well-written document discussing the data available to quantify the exposure of United States populations to atmospheric arsenic. The general summary and the summaries of each chapter appear to be valid conclusions drawn from the assessment of the data presented. The modeling estimates are in good accord with the limited monitoring data available.

In order to make this document suitable as part of the scientific basis upon which the EPA can develop control procedures for arsenic as a hazardous air pollutant, we recommend the inclusion of a statement to the effect that:

> "Data essential for determining the potential hazard of arsenic emissions from certain point sources, such as glass manufacturing plants and cotton ginning operations, be collected and made available for critical analyses. There is is also a need for additional monitoring data from regions with primary smelters."

Also, the Subcommittee believes that the exposure assessment needs to include information on the possible exposure routes of arsenic in man through water and food with consideration of food chain relationships that may be relevant.

The Committee recommends that the final document contain data relevant to emissions from secondary smelters, since these point sources have not been discussed.

II. Population Risk to Arsenic Exposures

This is a well-prepared document given the paucity of the data available. The authors appear to have used the best of the data to arrive at dose-response relationships between standard mortality ratios (SMR) and crude estimates of the lifetime exposure to atmospheric arsenic.

The Committee recommends that the following additional analyses and asseessments be incorporated into the present document:

1. SMRs be estimated for regions of high ambient arsenic concentrations for populations both occupationally and non-occupationally exposed. This is essential because the Committee points out that the statistic of 15.6 excess deaths nationally from lung cancer attributable to arsenic exposure is not indicative of the true risk to United States populations in high risk areas in the vicinity of point source emissions. Indeed, the document should contain some statement regarding the level of confidence of this statistic.

2. Statistical studies of such variables as time to tumor death, age at time of exposure, and duration of exposure be carried out. The Committee believes that this is necessary to provide more insight into the problems of differential risk from arsenic exposure.

3. Recalculations be made of excess lung cancer deaths in the smelter areas studied by Blot and Fraumeni. *

4. Assessments of the possible synergistic relationships between arsenic and sulfur dioxide at ambient levels be extracted from modern and historical data.

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* Blot, W.J., Fraumeni, J.F. (1975) "Arsenical Air Pollution and Lung Cancer," *Lancet*: 142-144; July 26, 1975

III. Assessment of the Health Effects of Arsenic

Although this document does contain a compilation of useful material, it does not do justice to the data available. Moreover, this document in its present form is not as useful to EPA as it should be to support the development of control procedures for arsenic as a hazardous air pollutant. In order to make this document suitable, the Committee suggests that the following revisions be made:

1. The document should be reorganized to lend itself to logical evaluation of the data presented.

2. Since there is little or no critical analysis of the toxicological and epidemiological studies cited, such analyses should be made and included.

3. Since there is a lack of consistency in the presentation of much of the data, this deficiency should be corrected.

4. Many important and pertinent recent as well as early references have been omitted, and should be added.

5. Since the discussions of carcinogenesis, teratogenesis, and mutagenesis are inadequate and sometimes confounded, these sections need to be improved.

6. The summary should be rewritten to become an adequate presentation of the data on health effects of arsenic.

In summary, the Committee recommends that the document be substantively revised *under the direction of a qualified toxicologist* in order to correct its deficiencies and to incorporate additional data deemed essential.