California Air Resources Board

Proposed Identification of Inorganic Arsenic as a Toxic Air Contaminant

Part C
Public Comments and ARB/DHS Staff Responses

State of California
Air Resources Board
Stationary Source Division

May 1990

PART C

PUBLIC COMMENTS AND RESPONSES TO THE INORGANIC ARSENIC REPORT

Prepared by the Staffs of the Air Resources Board
and the Department of Health Services

May 1990

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Comment Letters Received on the Preliminary Draft Version
of Inorganic Arsenic Parts A and B

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Ted Smith
Executive Director

April 7, 1988

Mr. Robert Barham
Toxic Air Contaminant ID Branch
Air Resources Board
Attn: Inorganic Arsenic
P.O. box 2815
Sacramento, Ca 95812

Dear Mr. Barham:

I have just received and reviewed the Draft Report on Inorganic Arsenic and would like to make several comments:

1. The information regarding the Semiconductor Industry is woefully out of date and inadequate. On Page A-61 Table II-3 relies upon a 1981 study done by CDIR using data from 1979 that pertains to only 23 companies. I am enclosing a report that we prepared last year entitled "Modeling Toxic Gas Releases Using a Simple Screening Model" which documented arsine storage at 25 facilities in the county, based on incomplete data from Hazardous Materials Inventory Statements for the period 1983-1985. In addition, I am enclosing a copy of Table A-5 from Appendix A of the 1984 Toxic Use Survey compiled by Steve Hill at the BAAQMD which lists 26 companies in the county (while there is a good deal of overlap, there are also several companies which do not appear on both lists). There are two other sources of easily available data-- the Santa Clara County Health Department (as well as other health departments throughout the state) are collecting inventory data on Acutely Hazardous Materials pursuant to AB 3777; filings to date in this county (still quite sketchy) indicate 13 companies storing 18,580 cubic feet of Arsine (in varying concentrations) and this information should be nearer completion in the near future. Lee Escobel is collecting this information for the county (408 299-6060). In addition, the Sunnyvale Department of Public Safety has developed a data base which includes all known arsine storage in their city and is available through Lt. Reuben Grijalva at (408) 730-7213. Palo Alto and Santa Clara may also have this information available by now.

2. I am also enclosing a copy of an affadavit prepared by Dr. George Alexeef of the Department of Health Services who presented information to the San Diego County Air Pollution Control District about arsine in a regulatory proceeding there last year. Much of the information that he presented and many of the references that he cites do not appear to be included in Part B of your draft report and should be incorporated.

3. EPA conducted its Integrated Environmental Management Program in Santa Clara County over a two year period and found an increased risk of cancer from arsenic exposure (copies of their Stage I and Stage II reports are available from EPA Region 9 in San Francisco.) During that process it was discuovered that many semiconductor companies do not even bother the scrub or use emission controls of any kind for arsine emissions because it is expensive and traditional controls are not very effective (arsine is not very water soluable). Most of those firms that do have controls believe that they are only slightly effective -- in the range of 25% effeciency (this information was reported by Steve Pederson, the IEMP representative from the Semiconductor Indsutry Association).

I hope that this information is useful and I would be glad to answer any questions that you may have. Current data is, unfortunately, still incomplete, but it is getting better. SARA Tile 3 information will soon be available, as will more complete data from AB 3777 and AB 1985/87. I hope that your data can be updated periodically as reporting systems become more sophisticated.

Sincerely,

Ted Smith

Ted Smith

Encl.

CalMat Co

P.O. BOX 2950, LOS ANGELES, CALIFORNIA 90051 (213) 258-2777
3200 SAN FERNANDO ROAD, LOS ANGELES, CALIFORNIA 90065

CalMat

April 28, 1988

Mr. Robert Barham, Chief
Toxic Air Contaminant Identification Branch
Air Resources Board
Attention: Inorganic Arsenic
P.O.Box 2815
Sacramento, CA 95812

Re: Comments on Part A Preliminary Draft Report

Dear Mr. Barham:

Several comments are made with respect to potential emissions of inorganic arsenic from portland cement manufacturing plants.

I. (pp. A-90, A-91). Data on actual As emissions from portland cement kilns in California are not available to CalMat, although I believe that such emissions tests have been performed on the CBR-Lone Star Cement Kiln in Davenport, California and the National Cement kiln at Los Robles, California. However, it must be emphasized that it is impossible to separately measure kiln stack As emissions from coal combustion and from the cement clinker raw materials. Arsenic from both sources, fuel and feed, will indistinguishably occur adsorbed or chemically combined on/in the emitted PM.

The use of an emissions factor for a coal-fired industrial boiler to characterize cement kiln emissions is inappropriate and technically invalid. The presence of large tonnages of chemically active clinker and raw materials within the kiln system substantially reduces the amount of As which will occur in the exhaust gas stream being cleaned by the dust collector (the cement clinker product, far more active and voluminous than boiler bottom ash, will remove most of the As from the kiln system).

Finally, the use of an emissions factor for ESP outlet gases to characterize baghouse outlet gases is questionable. Especially for low-sulfur western coals and dry-process kilns, the baghouse emissions are substantially lower on both a total particulate and a fine particulate basis than emissions from an ESP.

My suggestion is that cement kiln As emissions related to coal combustion be treated in the same section as cement manufacturing. This would avoid double counting and would be technically valid.

II. (p. A-92). The report states that in 1984 approximately 3,030 tons of PM were emitted from California cement manufacturing, "excluding emissions from fuels". While this total amount of total PM emissions for the eleven California cement plants operating during 1984 may be realistic (275 t/yr/plant), for the reasons stated before, I find it difficult to understand how the "emissions from fuels" could have been distinguished and excluded from the total PM emissions.

There are three types of PM emitted from traditional cement manufacturing point sources with respect to potential trace metallic elements:

1. raw materials preparation (primarily crushing, grinding, and homogenizing)

2. calcining and clinkering (rotary kiln emissions which include coal combustion)

3. cement preparation (clinker cooling, finish grinding, and distribution).

Each of these types of PM will have a significantly different average trace concentration of As and each production process will have a substantially different average PM emission rate for each of the California cement plants. Average concentrations will change as the fuel and raw materials change, which is common. To make even the roughest estimate of As emissions from cement manufacturing, three emission factors (corresponding to each type of PM) are required. The total PM emissions also would have to be allocated among the production processes according to the type of PM emitted.

With respect to the rotary kiln emissions alone (calcining and clinkering, which would include coal combustion), use of the average As concentration in kiln baghouse dust to determine an emissions factor may be technically valid. However, the average As concentration must be weighted according to 1984 clinker production by each California plant, not the arithmetic average of USBM analyses of California kiln dusts (CARB, 1986e).

In my previous comments on the potential cement manufacturing cadmium emissions (Part C, Technical Support Document, Report to the Air Resources Board on Cadmium, December 1986), I calculated that the maximum 1981 total PM emissions from all California rotary kilns was 1855 tons (1981 total cement production was 7.9 million tons). Using the 1984 cement production of 8.7 million tons, total California PM emissions would be about 2,040 tons. Again, the total potential kiln As emissions, which includes coal combustion, would be based upon this 2,040 tons of PM and the weighted average As concentration in cement kiln dust (I am unable to calculate this average since I am not privy to plant identifications of the

USBM data nor individual plant clinker production for 1984).

Finally, as a caveat to using the As concentration in collected cement kiln dust as a surrogate for As in the actually emitted PM, emission tests performed by KVB in 1986 on one of our rotary kilns in Arizona did not detect any arsenic when burning about 5½ tph coal (along with natural gas). The As detection limit for these tests was 0.263 ppb, five orders-of-magnitude below the 62 ppm average determined from the USBM kiln dust data.

Sincerely,

David S. Cahn
Vice President Regulatory Matters

cc: P. Hawkins

FOX, WEINBERG & BENNETT
1714 MASSACHUSETTS AVENUE, N. W.
WASHINGTON, D. C. 20036

JAY L. KNOTT

TELEPHONE: 202-778-2300
TELECOPIER: 202-775-2330

May 3, 1988

Via Federal Express

Ms. Joan E. Denton, Manager
Substance Evaluation Section
Air Resources Board
1102 Q Street
Sacramento, California 95812

Re: Confirmation of Extension of Comment Period

Dear Ms. Denton:

This confirms our telephone conversation of May 3, 1988. We understand that Quemetco, Inc., a subsidiary of RSR Corporation, has been granted an extension to Friday, May 13, 1988, to submit written comments on the April, 1988 Draft Report on Inorganic Arsenic to the Air Resources Board ("ARB").

To the extent that Quemetco may wish to supplement its comments after May 13, we understand that it may do so, and that the ARB will review and address any such supplementary submissions. We also understand that the ARB likely will not address any such supplementary comments until the end of the comment period for the final draft report and the summary overview.

Your cooperation and assistance in this matter is appreciated.

Sincerely,

Jay L. Knott

JLK/mab

cc: Gerald A. Dumas
Homer P. Hine

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1714 MASSACHUSETTS AVENUE, N. W.
WASHINGTON, D. C. 20036

LYNN L. BERGESON

TELEPHONE: 202-778-2300
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May 12, 1988

Via Overnight Delivery

Mr. Robert D. Barham, Chief
Toxic Air Contaminant Identification Branch
Air Resources Board
P.O. Box 2815
Sacramento, California 95812

Re: Inorganic Arsenic

Dear Mr. Barham:

We are pleased to submit the attached Comments of RSR Corporation and its wholly-owned subsidiary, Quemetco, Inc. (hereinafter collectively "RSR"), on the California Air Resources Board's ("ARB") Draft Report on Inorganic Arsenic ("Draft Report"). Supplementing RSR's Comments are those of RSR's technical consultant, Dames & Moore, appended at Attachment 1 of RSR's Comments. Both sets of comments constitute RSR's Comments on the Draft Report.

The Draft Report is long and complex. Moreover, ARB's analysis regarding lead processing activities appears to be premised, in part, on data emission estimates and methodologies contained in a 1985 report prepared by the Radian Corporation ("Radian Study"). Due to the short comment period, we have concentrated our preliminary review on the Draft Report, rather than on the Radian Study, particularly focusing on discussions relating to what ARB refers to as "secondary lead smelting" activities. RSR believes that the Radian Study is conceptually flawed and factually inaccurate. To the extent any proposed findings presented in the ARB Draft Report rely upon the Radian Study, those findings are similarly flawed and inaccurate. RSR is now reviewing the Radian Study and the data on which the Study purports to be based, and may supplement the Comments it submits today with additional comments on the Radian Study.

RSR appreciates the opportunity to submit these Comments and looks forward to assisting the Board as it develops its analysis of the effects of inorganic arsenic.

Respectfully submitted,

LYNN L. BERGESON
JAY L. KNOTT
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1714 Massachusetts Avenue, N.W.
Washington, D.C. 20036

Counsel for RSR Corporation

mjt
Attachments

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LYNN L. BERGESON

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May 14, 1988

Via Federal Express

Mr. Robert D. Barham, Chief
Toxic Air Contaminant
Identification Branch
California Air Resources Board
1102 Q Street
Sacramento, California 95812

Re: Comments on Draft Report
on Inorganic Arsenic

Dear Mr. Barham:

Appended is a corrected set of RSR Corporation's, on behalf of itself and its wholly-owned subsidiary, Quemetco, Inc., Comments on the CARB's Draft Report on Inorganic Arsenic. The Comments submitted on Friday, May 13, contained minor typographical errors which have been corrected in the attached document.

Please substitute the Comments submitted on Friday with the attached. Your assistance is appreciated.

Sincerely,

Lynn L. Bergeson

mjt
Attachment

COMMENTS OF RSR CORPORATION ON THE CALIFORNIA AIR RESOURCES BOARD DRAFT REPORT ON INORGANIC ARSENIC

RSR Corporation, on behalf of itself and its wholly-owned subsidiary, Quemetco, Inc. (hereinafter collectively "RSR"), submits these comments in response to the California Air Resources Board ("ARB") Draft Report on Inorganic Arsenic ("Draft Report") circulated for comment on April 7, 1988. For the most part, RSR's comments are limited to those portions of the Draft Report relating to lead processing facilities. RSR may expand upon its analysis, however, and submit supplemental comments at a later date.

I. INTRODUCTION AND SUMMARY

Overall, RSR believes Part A of the Draft Report is seriously flawed, and that the ARB's preliminary findings relating to so-called "secondary lead smelting" activities cannot be supported. Among other serious defects, the data on which the emission estimates are based are inaccurate, and use

of a short-term model to calculate maximum annual average concentrations of inorganic arsenic is inappropriate.

Moreover, the data base in Part A is incomplete. ARB failed to identify all potential sources of inorganic arsenic emissions from lead processing facilities. In addition, it improperly attributed all measured emissions to a single lead smelter.

Finally, the Draft Report misapplies the term "secondary lead smelter" to any industrial activity involving lead processing. Misuse of this phrase unavoidably leads to the erroneous inference that secondary lead smelters -- as distinct from lead processing facilities, a broader category -- are a major source of inorganic arsenic emissions.

The draft conclusions contained in Part B of the Draft Report are generally well presented. These conclusions appear to rely, however, upon preliminary findings contained in Part A of the Draft Report. RSR may wish to submit additional comments on Part B pending review of ARB's revisions to Part A responsive to RSR's comments, and reserves the opportunity to do so.

II. RSR'S INTEREST IN THIS PROCEEDING

Quemetco operates a secondary lead smelter located in City of Industry, California. City of Industry is located in the South Coast Air Basin. ARB characterizes the Draft

Report as a summary of ARB's investigation to determine whether, pursuant to California law, inorganic arsenic should be identified as a toxic air contaminant. Draft Report, p. A-1. Secondary lead smelters may be a source of inorganic arsenic emissions. RSR believes ARB's findings could play a major role in setting future regulatory requirements applicable to the operations of RSR's California subsidiary. Accordingly, RSR has a significant interest in this proceeding, and offers the following comments on the Draft Report.

III. SECONDARY LEAD SMELTERS

A secondary lead smelter is a facility included within Standard Industrial Classification ("SIC") Code 3341 (Secondary Smelting and Refining of Nonferrous Metals). This SIC code includes "[e]stablishments primarily engaged in recovering nonferrous metals and alloys from new and used scrap and dross." Office of Management and Budget, Standard Industrial Classification, p. 148 (1972). According to the United States Environmental Protection Agency ("EPA"), there are 28 facilities located throughout the United States properly included in SIC Code 3341. See "The Impacts of Lead Industry Economics and Hazardous Waste Regulations on Lead-Acid Battery Recycling: Revision and Update," USEPA (1987).

According to this EPA report, there are three secondary lead smelters located in the western part of the United States, each of which is located in California. Two of these secondary lead smelters are located in the South Coast Air Basin. The facility located in City of Industry -- the only source monitored by ARB for purposes of the Draft Report -- is the smaller of the two lead smelters.

IV. COMMENTS ON PART A OF THE DRAFT REPORT

A. The Draft Report Contains Factual Inaccuracies Regarding Lead Smelters

A fundamental problem underlying Part A of the Draft Report is ARB's failure to define properly "secondary lead smelting." The Draft Report states that "secondary lead smelting" is one of four "[m]ajor sources" of inorganic arsenic emissions in California. Draft Report, p. A-2. This is incorrect. RSR believes ARB meant to say that industrial operations involving lead processing -- including secondary lead smelting -- are a major source of inorganic arsenic emissions. ARB's failure to distinguish properly between secondary lead smelting activities and lead processing activities leads to the erroneous inference that secondary lead smelters alone are among the largest contributors of inorganic arsenic emissions in the State of California.

RSR requests that ARB correct the Draft Report to read, where appropriate, that there are three secondary lead facilities in California, not 30 as stated repeatedly throughout the Draft Report, and not 18 as stated on p. A-49, Table II-2.

RSR also recommends that ARB distinguish clearly in the Draft Report between secondary lead smelters and lead processing facilities. At a minimum, RSR urges ARB to replace the term "secondary lead smelter" with the term "lead processing facility," where appropriate, throughout the Draft Report. Section V of these Comments identifies specific references in the text that appear to be inaccurate, and suggests revised language to eliminate these inaccuracies.

B. ARB Has Improperly Excluded Other Sources of Inorganic Emissions From the Analysis

The definitional error discussed above is the probable basis for another serious flaw in the Draft Report. In referring to lead processing facilities as "secondary lead smelters," ARB has failed to include other potential sources of inorganic arsenic emissions in the analysis. ARB acknowledges that other sources of inorganic arsenic emissions exist, but makes no effort to identify those sources or quantify emissions from them. According to the Draft Report, for example, "there are six small companies within a five-mile radius performing different types of lead processing

activities which could be potential arsenic sources." Draft Report, p. A-29. Without knowing more about these other potential arsenic sources, RSR cannot determine whether they are either "small" companies or "small" sources. If any is in fact not a small "source," its omission from the data base would be a serious flaw, and ARB's preliminary findings regarding lead processing facilities would be arbitrary.

Moreover, in failing to identify other probable sources of arsenic emissions, all emissions were attributed improperly to the only facility monitored by ARB, a lead smelter. This is inappropriate.

To correct this deficiency, RSR recommends that (i) ARB identify all potential sources of inorganic arsenic emissions in the South Coast Air Basin; (ii) monitor emissions from these sources; and (iii) revise the Draft Report findings, where appropriate, by properly incorporating the new emissions data into the ARB analysis.

C. ARB's Reliance on the Radian Study Is Misplaced

ARB states in the Draft Report that emission rates obtained from a report prepared by the Radian Corporation were used "to estimate the annual average impacts of arsenic emissions from the smelter on public exposure." Draft Report, p. A-33. The Radian Study at issue is entitled "Control of

Arsenic Emissions from the Secondary Lead Smelting Industry-Technical Document" (May 7, 1985) ("Radian Study").

ARB's reliance on the Radian Study is misplaced. The Radian Study did not include actual emission data from the secondary lead smelter monitored in the Draft Report. Indeed, no emission data from any secondary lead smelter located in California is included in the Radian Study. Nonetheless, the emission rates used for dispersion modeling were taken by ARB from the Radian Study. At best, these rates are speculative estimates based on assumptions regarding, among other variables, process capacities that likely do not accurately reflect the monitored facility's capacities.

The inappropriateness of ARB's use of Radian Study emission estimates to predict annual ambient arsenic concentrations (700 ng/m^3) is highlighted by the inconsistency of that prediction with actual results of two ambient air studies conducted by ARB at the monitored facility in 1986 (approx. 60 ng/m^3 -- predicted annual average) and 1987 (approx. 20 ng/m^3 -- highest monthly average concentration). Further, the source emission inputs from the Radian Study used by ARB for modeling of the smelter facility (at least 138.6 lbs per year) are inconsistent with results from an actual source test at the monitored facility conducted by the SAI Corporation in 1981 (8 - 32 lbs per year).

To address this problem, RSR recommends that ARB seek to obtain actual emission data from all potential sources

of inorganic arsenic emissions located in the South Coast Air Basin.

D. The Radian Study Lacks Independent Scientific Verification

It is unclear whether the emission estimates reported in the Radian Study have ever been validated. The Radian Study was sponsored by EPA. The Study contains, however, a disclaimer from EPA providing that "[t]he opinions, findings, and conclusions expressed are those of the author and not necessarily those of the EPA." Radian Study, p. iii. Similarly, it is unclear whether the Radian Study has ever been subjected to peer review, and if so, whether it satisfies peer review standards.

RSR believes that ARB should determine in the first instance whether the emission estimates contained in the Radian Study are valid. If valid, ARB should so state in the Draft Report. If invalid, ARB's reliance upon the Radian Study to support any of its preliminary findings is arbitrary.

E. ARB's Use of the Industrial Source Complex Short-Term ("ISCST") Model is Inappropriate

ARB states in the Draft Report that it used the Industrial Source Complex Short-Term ("ISCST") model to calculate maximum annual average concentrations. The short-term model typically overpredicts annual averages and is more

appropriately used to predict maximum short-term, not long-term, concentrations. The use of the ISCST is thus inappropriate, and the Industrial Source Complex Long-Term ("ISCLT") model should be used instead.

In addition, the ISCST model requires extensive and accurate source-specific data to produce meaningful estimates. ARB's findings do not include such source-specific data. Since use of the model requires data inputs and assumptions of some sort, and ARB's Draft Report identifies no such data or assumptions, RSR is unable to determine whether those used are valid.

To correct these deficiencies, RSR recommends that: (i) the ISCLT, rather than the ISCST, be used to calculate maximum annual average concentrations; (ii) the model utilize source-specific data from all potential sources of arsenic emissions; and (iii) any assumptions factored into the model be clearly stated.

F. The Part A "Introduction and Summary" is Misleading

The Part A "Introduction and Summary" is misleading. As currently drafted, it can be read to conclude that any exposure to inorganic arsenic emissions, regardless of concentration, is harmful.

Part A of the Draft Report is entitled "Public Exposure to Airborne Inorganic Arsenic in California." Part B

of the Draft Report is entitled "Health Effects of Inorganic Arsenic." The caption on page A-1 of the Draft Report, entitled "Part A Introduction and Summary," would appear to suggest that pages A-1 through A-5 of the Draft Report summarize only the findings of Part A. This summary, however, also refers to health effects actually contained in Part B of the Draft Report.

The potential for misinterpretation or confusion posed by the existing language can be cured by eliminating any reference to adverse health effects in the Introduction and Summary to Part A. Alternatively, ARB may wish to consider revising the caption on page A-1 of the Draft Report to read "Introduction and Summary" and summarize both the exposure information contained in Part A and the DHS health effects evaluation contained in Part B of the Draft Report.

G. Emission Measurements Should be Reported in Micrograms Per Cubic Meter

Throughout the Draft Report, emission measurements are reported in nanograms per cubic meter (ng/m^3). The more commonly used measurement, however, for air emissions is micrograms per cubic meter (ug/m^3). RSR believes that the Draft Report should conform with the more commonly used micrograms measurement. At a minimum, RSR recommends that ARB define whatever measurements it utilizes to avoid potential

confusion to readers unfamiliar with the difference in magnitude of the units in these measurements.

H. The Draft Report is Based on Inadequate Monitoring Data

The source-impacted ambient arsenic monitoring samples for the South Coast Air Basin were measured intermittently between May 17, 1986 and June 15, 1986. RSR believes these measurements, taken over a period of less than thirty days, are inadequate for calculating annual average arsenic concentrations.

Further, no meteorological data regarding the monitoring samples are included in the Draft Report. These data are essential in determining the likely source or sources of emissions and their respective rates. In order to comment meaningfully on these data, more information is necessary. Accordingly, RSR recommends that ARB include these data in the next version of the Draft Report.

I. The Draft Report Improperly Relies on Obsolete Meteorological Data

The Draft Report relies on 1972 meteorological data. It is possible that meteorological conditions have changed over the past sixteen years. RSR recommends that ARB replace the 1972 data with more recent meteorological data, if these data are available.

RSR also recommends that ARB obtain meteorological data from stations closer to monitored sources. Data from closer stations will better account for meteorological conditions uniquely impacting monitored sources.

V. SPECIFIC COMMENTS

RSR believes that data transmitted to the Scientific Review Panel must consist of only unbiased and independently verifiable facts. RSR believes there are a number of references throughout the Draft Report that do not meet this criteria. RSR has identified a representative sample of such references below, and has proposed changes to the Draft Report to eliminate the potential for misinterpretation or ambiguity. No attempt here is made, however, to identify all such references.

- Page A-5, last full paragraph -- "such as a secondary lead smelter" should be deleted.

- Page A-29, second full paragraph -- this paragraph should be deleted. Suggested insert: An analysis of arsenic sources in California indicated that industrial lead processing operations have the potential to emit large amounts of arsenic. Of the 30 lead processing operations located in California, one secondary

lead smelter in the South Coast Air Basin was selected by ARB for monitoring. There are also at least six other companies within a five-mile radius of the selected facility performing different types of lead processing activities which could be potential sources of arsenic emissions.

- Page A-30, first line, first full paragraph -- "[l]arge" should be deleted.

- Page A-31, first full paragraph -- the sentence "This is approximately 13 times the South Coast urban average," should be deleted.

- Page A-32, second paragraph, second sentence -- this sentence should be changed to read "[t]he smelter is the only source of arsenic in this area which ARB monitored, but it is likely possible that other unidentified sources in the area are contributing to the arsenic concentrations which ARB obtained."

VI. COMMENTS ON PART B OF THE DRAFT REPORT

The draft conclusions contained in Part B of the Draft Report are generally well presented. These conclusions appear to rely, however, upon preliminary findings contained in Part A of the Draft Report. RSR may wish to submit additional comments on Part B pending review of ARB's revisions to Part A responsive to RSR's comments, and reserves the opportunity to do so.

VII. CONCLUSION

Part A of the Draft Report is seriously flawed and scientifically unsupported. Based on the foregoing, RSR recommends that ARB defer submitting to the Scientific Review Panel those portions of the Draft Report involving lead processing facilities, properly address each of the deficiencies noted above, and reissue a revised Draft Report for public comment and review.

Appended for ARB's review are comments submitted by RSR's technical consultant, Dames & Moore.

Attachment

DAMES & MOORE A PROFESSIONAL LIMITED PARTNERSHIP
1550 NORTHWEST HIGHWAY, PARK RIDGE, ILLINOIS 60068 (312) 297-6122

May 11, 1988

Lynn L. Bergeson, Esquire
Fox, Weinberg & Bennett
1714 Massachusetts Avenue, N.W.
Washington, D.C. 20036

Dear Lynn:

Re: Comments on California Air Resources Board Draft Report on Inorganic Arsenic

This responds to your request for our comments on the California Air Resources Board's ("CARB") draft Report on Inorganic Arsenic Emissions. Dames & Moore's preliminary review of this Report has revealed the following areas where further additional analysis is warranted with respect to developing a more technically supportable assessment of ambient levels of inorganic arsenic:

- The calculation of maximum annual average concentration from sources should be based upon modeling with the ISCLT, not ISCST, dispersion model. The latter generally overpredicts annual averages and is more appropriately used to predict maximum short-term concentrations. The guidelines on air quality models (USEPA, revised 1986) state that when modeling for sources for which long-term standards alone are applicable, long-term models should be used.

- The CARB report did not provide detailed information pertaining to the dispersion modeling analyses performed. The detailed information should include emission inventory, version number of model employed, model options selected, and general discussion of the modeling methodology.

- The 1972 Ontario, California meteorological data employed by CARB should be replaced by more recent meteorological data, if available and from stations located closer to the monitored sources. Meteorological conditions vary with geography; the closer the meteorological station to the source, the better, assuming similarity in surrounding terrain and urbanization.

  Moreover, the meteorological data should be based on a 5-year period. The USEPA has recommended that 5 years of representative meteorological data should be used when estimating concentration

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with an air quality dispersion model. If a shorter period of record is being used, the meteorological data should contain appropriate worst-case conditions.

- o In assessing the impact on public health of facilities that emit carcinogens, the USEPA as well as many states calculate the maximum individual lifetime risk ("MILR") and compare with a threshold such as one in one million. The MILR is calculated by multiplying the maximum annual average predicted concentration off plant property resulting from the facility's emissions by the unit risk factor for the carcinogen. The unit risk factor for arsenic is 4.29×10^{-3}.

- o The arsenic modeling performed by CARB incorporated emission factors derived by the Radian Corporation. These emission factors were based on a study by Radian of smelting operations in existence at the time the Report was prepared. The correlation, if any, between smelting operations investigated by Radian and the lead smelter included in the CARB draft Report should be examined.

  The validity of the emission factors derived by Radian should be reviewed for their acceptance by the USEPA. Similarly, it is unclear whether the validity of Radian's emission factors has been subjected to peer review, and, if so, whether they meet peer review standards.

- o Fugitive arsenic emissions modeled by CARB were based upon a formula in the the Radian Corporation Report. It is questionable whether this formula is applicable to the monitored lead smelter. Because of the importance of the amounts of stack and fugitive arsenic emissions employed in the model, much more detail should have been provided in the CARB report with respect to assumptions used in applying the arsenic emissions from the Radian Corporation report to the monitored lead smelter (i.e., stacks versus fugitives). Further, the CARB report was unclear with respect to how the fugitive emissions were treated in the ISCST model. In the USEPA's report, "Estimating Releases and Waste Treatment Efficiency for the Toxic Chemical Release Inventory Form," it is stated in the section treating estimation of fugitive emissions that, whenever possible, fugitive emissions should be calculated by the use of direct measurement. Since fugitive emissions vary widely between different facilities, use of formulas developed from measurements taken at other facilities will result in estimates having considerable uncertainty.

- While the CARB report suggests that the ambient arsenic measurements may result from arsenic sources other than the monitored lead smelter, no other potential sources are specifically identified in the draft Report, nor are their respective emissions quantified. Other sources are believed to include a lead smelter and at least two lead acid battery manufacturing plants. At a minimum, estimates of arsenic emissions from these and all other potential sources of arsenic emissions should be included in the report.

- The South Coast Air Basin ambient arsenic samples, measured from May 17, 1986 to June 15, 1986, are inadequate for the purpose of estimating annual average arsenic concentrations. Variation of meteorological conditions throughout the year as well as operation of the monitored lead smelter should cause the concentrations in Table 1-5 of the CARB report to be used with great caution with respect to estimation of annual averages.

- In expressing ambient arsenic concentrations, the CARB report uses units of nanograms per cubic meter rather than the more common micrograms per cubic meter, thus giving the uninitiated reader an impression of higher levels than would otherwise be the case if micrograms per cubic meter were used.

If you have any questions or comments, please feel free to contact us directly.

Sincerely,

DAMES & MOORE
A Professional Limited Partnership

Perry W. Fisher/ekk

Perry W. Fisher, Ph.D.
Partner (Ltd.)
Certified Consulting Meteorologist

Steven A. Frey/ekk

Steven A. Frey
Project Meteorologist

PWF/SAF:dak

GEO Operator Corporation
A Subsidiary of Geothermal Resources International, Inc.

May 9, 1988

Mr. Robert Barham, Chief
Toxic Air Contaminant
Identification Branch
AIR RESOURCES BOARD
Attn: Inorganic Arsenic
P.O. Box 2815
Sacramento, CA 95812

Re: Comments on Part A - Public Exposure to Airborne Inorganic Arsenic in California

Attention Inorganic Arsenic Unit:

GEO Operator Corporation (GEOOC) has evaluated the "Geothermal Steam" section of the above-referenced document. It appears to GEOOC that the writer does not have a thorough understanding of the presence of arsenic in geothermal steam, nor of the terminology used industry-wide to describe geothermal wells and power plants. GEOOC would appreciate the opportunity to discuss this matter with representatives of the Air Resources Board.

Some specific comments are as follows:

The report states that

> "the arsenic emissions from geothermal steam utilities in Sonoma County are estimated to have been between 0.27 and 3.4 tons in 1984. The upper estimate is based on the assumption that arsenic trioxide, extracted from condensers at its maximum equilibrium vapor pressure along with water-vapor and noncondensible gases, plus the arsenic in cooling-tower drift, is emitted into the atmosphere; and the lower estimate is based on the assumption that only the arsenic in cooling-tower drift is emitted."

This assumption is inconsistent with GEOOC's chemical measurements which indicate that arsenic partitions into the steam condensate (liquid phase) at the power plant inlet and therefore probably also in the condenser. Thus power plant emissions are most likely limited to cooling tower drift. What small amount of arsenic which might remain volatile in the condenser is most likely removed from noncondensible gases by the Stretford system before it is emitted to the atmosphere.

GEOOC appreciates the opportunity to comment.

Sincerely,

JODY SPOONER
Environmental Coordinator
EN88-061.JS:cap

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1330 North Dutton Avenue, Suite A, Santa Rosa, CA 95401
Telephone: (707) 523-4778 Facsimile: (707) 575-8100

Freeport-McMoRan Resource Partners
Limited Partnership
Geysers Geothermal Company Division

May 9, 1988

Mr. Robert Barham, Chief
Toxic Air Contaminant
Identification Branch
Air Resources Board
Attention Inorganic Arsenic
P.O. Box 2815
Sacramento, CA 95812

Dear Sir:

Freeport-McMoRan Resource Partners/Geysers Geothermal Company (FMRP/GGC) as a geothermal steam producer and future power plant operator would like to comment on the preliminary Draft Report to the Air Resources Board on Inorganic Arsenic as it pertains to geothermal steam at The Geysers in Lake and Sonoma Counties.

Our comments will have to be of a general nature since we do not have access to the specific references used in the draft report. On Page A-50, Section 1. Geothermal Steam - the reference to twenty-seven wells in operation as of December 1985 appears to be in error. The total number of wells in The Geysers steam field is approximately four hundred. About 10 percent are condensate injection wells and the remainder produce geothermal steam. Currently there are twenty-five geothermal steam power plants operating at The Geysers.

The statement beginning at the end of Page A-51 and continuing on the top of Page A-52 "During the summer very little water is reinjected and virtually all of the geothermal steam drawn from the wells is released to the atmosphere through the cooling tower" does not reflect the facts. It is true that less condensate is injected in the summer; however, FMRP/GGC experience indicates that about 25 percent less condensate is injected in the summer than in the winter.

Also in the last paragraph of the geothermal section on Page A-52 there appears to be confusion between wells and power plants. Power plants, and not wells, are certified.

Thank you for the opportunity to comment on the inorganic arsenic report and we hope that our comments will be helpful in preparing the final draft report.

Yours very truly,

H. E. Nissen

H. E. Nissen

HEN/lm

cc: C. E. Woods

PACIFIC GAS AND ELECTRIC COM

PG&E + P. O. BOX 7640 • SAN FRANCISCO, CALIFORNIA 94120 • (415) 972-6501 • TELEC

JOHN F. McKENZIE
DIRECTOR
ENVIRONMENTAL PLANNING
ENVIRONMENTAL SERVICES DEPARTMENT

October 20, 1987

Mr. Jim Guthrie
Air Resources Board
Toxic Pollutants Branch
P.O. Box 2815
Sacramento, CA 95812

Dear Mr. Guthrie:

Geysers Arsenic Emissions Information

PG&E understands that the Air Resources Board (ARB) is considering identifying and regulating arsenic as a toxic contaminant. We further understand that you are preparing report on sources of arsenic emissions in California as pa that consideration. Finally, we understand that the c re internal ARB draft of this report calculates arsenic emiss from geothermal power plants as though all the arsenic in incoming steam is emitted.

PG&E believes that this calculation method will overestima Geysers arsenic emissions by at least a factor of ten. We concerned that the release of such an overestimate might u alarm the public. Attached is PG&E's best current estimat Geysers arsenic emissions, along with supporting informati request that you consider this information and incorporate into your draft report before releasing it for public comm

Annual arsenic emissions can conservatively be estimated f guaranteed maximum cooling tower drift rate, the average circulating water arsenic concentration and the designed f load circulating water flow rate. This is likely to still overestimate arsenic emissions since actual drift rate tes generally show lower actual drift rates, and since the uni not operate at full load all year long.

While arsenic drift calculations do not specifically addre potential arsenic vapor emissions, the maximum calculatabl emissions exceed the likely actual drift emissions by more enough to cover any potential vapor emissions.

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As a practical matter, Geysers arsenic vapor emissions are v low and difficult to quantify. Previous studies have led to following conclusions:

A. In the Geothermal Resources Council, TRANSACTIONS, Vol. July 1978, pages 579 -582, an article summarizing work sponsored by the National Science Foundation and the Department of Energy, and conducted by Battelle Northwes Laboratories, indicated that arsenic vapor was undetecta in the noncondensible gases. They concluded that arseni generally goes into the condensates/circulating waters a converts to the less toxic pentavalent form "as these wa are exposed to the atmosphere". They further concluded most of the arsenic remains in the water and leaves with blowdown, but that sludge deposition could also be impor

B. In conjunction with the "Jointly proposed PG&E and Calif Energy Commission (CEC) Staff Compliance Plan for Geyser Unit 17", PG&E sampled incoming and estimated outgoing arsenic in 1983 - 1984. Attached is a summary of those results. The Unit 17 data indicates that cooling tower blowdown water is the main carrier for arsenic leaving t power plant. Note also that as time passed, the unaccou for arsenic, believed to primarily represent sludge deposition, decreased.

C. James W. Cobble, in the attached August 1985 Electric Po Research Institute report EPRI AP-4214 Project 1525-6, concluded that arsine (AsH_3) "is thermodynamically unsta and "would not survive" the elevated temperatures seen i geothermal systems (see page 2-7); $AsCl_3$ only forms at l pH and higher chloride concentrations than those existin the Geysers (see page 3-17); and although As_4 and As_2 co directly volatilize at high temperatures, they would be n likely to react with water (see page 2-8). He postulate that arsenous acid $As(OH)_3$ is the most likely source of arsenic vapor emissions, and estimates vapor:water distribution coefficients for different temperatures (se page 2-12).

Attached is an example calculation of arsenic vapor emission based upon Mr. Cobble's assumed distribution coefficients, a highly unlikely, but conservative, assumptions that:

1. all of the arsenic in the circulating water is in the ar acid form;

2. the air passing through the cooling tower attains equili arsenous vapor concentrations; and

3. none of this air recirculates.

Note that even with such conservative assumptions, Geysers Unit 17 arsenic vapor emissions would be on the order of 0.03 lbs/year. Estimated maximum Unit 17 drift emissions are on the order of 1.2 lbs/year, and exceed estimated actual emissions by about 0.3 lbs/year. Vapor emissions of 0.03 lbs/year would therefore be insignificant.

Further note that Battelle was unable to detect any arsenic vapors in the condenser offgases -- even measuring to the 3 ppb detection level. Arsenic vapors are more likely to form in the condenser than in the cooling tower because:

a. At the turbine exit into the condenser, temperatures are higher, and pressures are lower than in the circulating water. Also, the arsenic is already associated with gaseous steam, and more likely to be in a trivalent state -- several compounds of which are volatile.

b. In the cooling tower, arsenic is initially dissolved or suspended in the circulating water, and the time for attainment of equilibrium vapor concentrations is short;

c. dissolved oxygen picked up by the circulating water in the cooling tower, as well as iron catalysts or peroxide added to the condensate for hydrogen sulfide abatement, can oxidize any trivalent arsenic to pentavalent arsenic. We are not aware of any pentavalent arsenic compounds which are significantly volatile.

In summary, for the above stated reasons PG&E does not believe that significant amounts of arsenic are emitted as vapor at Geysers, and believes that traditional drift calculations provide reasonably conservative estimates of Geysers power plant arsenic emissions. PG&E therefore requests that the ARB base its estimates of geothermal power plant arsenic emissions on cooling tower drift data and/or estimates.

Please call me, or Mr. J. Ted Holcombe (at 415-972-6910), if you have any questions about this material, or would like to meet with us to discuss it.

Sincerely,

Attachments

AN EXAMPLE OF THE INSIGNIFICANCE OF GEYSERS ARSENIC VAPOR EMISSIONS

In his August 1985 report entitled: "A Theory on Trace Arsenic in Geothermal Fluids", Electric Power Research Institute, James W. Cobble theorized that the most likely source of geothermal power plant arsenic emissions would be arsenous acid [$As(OH)_3$].

Using Mr. Cobble's theoretical $As(OH)_3$ vapor:water phase distribution coefficients, even with very conservative assumptions that:

1. all the arsenic is in the arsenous acid form;

2. the condenser offgasses and the cooling tower air flow attain equilibrium arsenic concentrations;

3. none of the air circulating through the cooling tower is recirculated; and

4. the arsenous acid vapor:liquid equilibrium concentration ratio at 50°C of 7.43×10^{-8} can be applied to steam at 105.5°F, and circulating water at 103.1 °F (about 40°C).

The maximum calculatable Geysers Unit 17 arsenic vapor emissions would still not exceed:

a. in the condenser offgases:

$$\frac{10015 \text{ lbs gas}}{\text{hour}} \times \frac{8760 \text{ hours}}{\text{year}} \times \frac{2.6 \times 10^{-8} \text{ lb Arsenic/lb condensate}}{} \times \frac{7.43 \times 10^{-8}}{\text{liquid/vapor}}$$

$$= 1.7 \times 10^{-7} \text{ lbs As vapor / year}$$

b. in the air passing through the cooling tower:

$$\frac{14.9 \text{ ACF air}}{10^{-6} \text{ min}} \times \frac{0.067 \text{ lbs}}{\text{ACF air}} \times \frac{8 \times 10^{-8} \text{ lbs Arsenic/lb circ water}}{} \times \frac{7.43 \times 10^{-8}}{\text{liquid/vapor}}$$

$$\times 5.256 \times 10^{+6} \text{ min/year} = 0.031 \text{ lbs As vapor / year}$$

Such maximum calculatable <u>vapor</u> emissions are only ten percent of the <u>difference</u> between full load and actual load arsenic <u>drift</u> emission estimates, and hence are <u>insignificant</u>.

The insignificance of any vapor emissions is independent of the actual arsenic concentration. Both drift and vapor emissions are, under the all arsenous acid assumption, equally proportional to the arsenic concentration. Of course, vapor emissions are in reality proportional to dissolved concentrations of specific arsenic compounds, whereas drift emissions are proportional to total dissolved or suspended arsenic. Furthermore, Unit 17 has very efficient drift eliminators. The ratio of drift emissions to vapor emissions, and hence the insignificance of vapor emissions, would be greater for units with less efficient drift eliminators.

Table 1

ESTIMATED GEYSERS POWER PLANT ARSENIC EMISSIONS
DUE TO COOLING TOWER DRIFT

Geysers Unit Number	Design Full load Circulating Water Flow in gal/min	Arsenic concentration in the circulating water in ppm	Guaranteed maximum cooling tower drift rate (emissions as % of circ flow)	Maximum (full load) annual arsenic emissions via drift in lbs/yr	Average annual Capacity Factor for 1982 thru 1986 in % of full load	Actually measured cooling tower drift rates in % of circ flow	Estimated remaining cooling tower drift rates in % of circ flow	Best estimate of actual arsenic drift emissions in lbs/yr
1	12,000	.50	.020	5	59.8		.02	3
2	14,000	.31	.020	4	65.4		.02	2
3	29,000	< .05	.020	1	57.9		.02	< 1
4	29,000	.05	.020	1	67.5		.02	< 1
5	49,000	.08	.020	3	60.1	.0032		< 1
6	49,000	< .05	.020	2	59.3	.0037		< 1
7	50,000	.13	.020	6	71.3		.004	< 1
8	50,000	.32	.020	14	69.8		.004	2
9	50,000	.72	.020	32	70.1		.004	5
10	50,000	.66	.020	29	70.6		.004	5
11	100,000	< .05	.005	1	53.9		.005	< 1
12	100,000	.67	.008	24	70.5	.0011		3
13	123,200	.60	.009	33	70.8	.0029		0
14	152,750	1.96	.020	182	82.0		.004	30
15	68,250	.26	.020	16	34.0	.0016		< 1
16	165,000	est .64	.002	9	100.3		.002	9
17	165,000	.08	.002	1	82.7	.0019		< 1
18	165,000	.87	.002	8	87.3	.0024		9
20	165,000	est 6.40	.002	93	89.9		.002	83
TOTAL				Approx 464				< 167

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NOTES AND ASSUMPTIONS FOR TABLE 1

1. Arsenic concentrations for Units 1-13, 15, and 18 are based on December 1983 analyses performed by Multi-Tech Laboratory of Santa Rosa.

2. Arsenic concentrations for Unit 14 and 17 are based on analyses performed by PG&E in August 1986 for Unit 14 and in 1983-1984 for Unit 17.

3. Arsenic concentrations for Units 16 and 20 are estimated from quarterly main steam analyses performed in 1985-1987 by PG&E.

4. Capacity factors for Units 16-20 reflect full years of operation only. For these units, the first full year was:

Unit 16	1986
Unit 17	1983
Unit 18	1984
Unit 20	1986

5. Actual measured drift rates were determined from cooling tower drift rate tests conducted by PG&E according to the Environmental Systems Corporation of Knoxville, Tennessee's manual for drift droplet size and flux determination.

6. Estimated drift rate for Units 7-10, and 14 are based on the manufacturer's guaranteed drift rate and on the drift rates PG&E measured for Units 5, 6, and 15. The actual drift rate measured for units with guaranteed drift ≤0.02 percent averaged 0.0028 percent. The highest drift rate measured at any of PGandE's towers was 0.0037 percent. Therefore, the drift rate for Units 7-10 and 14 is estimated to be less than 0.004 percent.

7. Estimated drift rates for Units 1-4, 11, and 16 and 20 are taken to be the manufacturers guaranteed drift rate. Sufficient information to make a better estimate is unavailable.

Table 2

PACIFIC GAS and ELECTRIC Company
GEYSERS UNIT 17

Summary of letters to the
CALIFORNIA ENERGY COMMISSION
on the mass balance of
ARSENIC

Letter Date	Estimated Arsenic in lbs/hour			
	Incoming	Drift	Blowdown	Other
3/14/83	0.038	0.00001	0.006	0.032
7/19/83	0.05	0.00007	0.04	0.01
11/4/83	0.10	0.0003	0.08	0.02
1/12/84	0.06	0.0001	0.05	0.01
4/30/84	0.08	0.0001	0.06	0.02
8/7/84	0.03	0.0002	0.05	-0.02
10/30/84	0.04	0.0002	0.04	0.00
1/7/85	0.05	0.0001	0.05	0.00

Note:

1. The main steam supply, the condensate, and the circulating waters were sampled in close succession, and concentrations of arsenic in those samples were determined by hydride atomic absorption (see Standard Methods for the Examination of Water and Wastewater, 15th ed, 1981).

2. Drift rates are calculated based on design flows.

3. Incoming arsenic is calculated using the power plant steam flow instrumentation readings recorded at the time of the steam sample.

4. Blowdown arsenic is calculated using a direct measurement of flow over a weir.

5. "Other" represents the net difference remaining.

6. These analyses were submitted in accordance with the compliance monitoring plan, Section 2-5, for the Geysers Unit 17 Application for Certification [79-AFC-1C].

JTH 10/87

Pacific Gas and Electric Company

One California Street, Room F-1601
San Francisco, CA
415/972-7746
Telex 972-6888

Mailing Address
P.O. Box 7640
San Francisco, CA 94120

Victor C. Furtaco, Ph.D.
Manager
Environmental Services

May 9, 1988

Mr. Robert Barnum, Chief
Toxic Air Contaminant Identification Branch
Air Resources Board
Attention: Inorganic Arsenic
P.O. Box 2815
Sacramento, CA 95812

Dear Mr. Barnum:

PG&E COMMENTS ON DRAFT ARSENIC EXPOSURE AND RISK ASSESSMENT

PG&E appreciates this opportunity to comment on the draft assessment. To assist you in finalizing this assessment, PG&E has assembled comments from a variety of sources.

Comments from Dr. Dean Carter and Dr. Steven Pike are presented in Attachment A. These comments focus on the need to revise Part B to either:

1. lower the current combined arsenic risk estimate by a factor of 20 to 40 to better account for the differences in the types of arsenic compounds and particle size distributions found in historical occupational exposures versus current ambient air exposures; or to

2. estimate pentavalent arsenic risks separately from trivalent arsenic risks — with pentavalent arsenic risks being estimated to be at least ten times lower than trivalent arsenic risks.

They also suggest reconsideration of the possibility of a threshold of no significant adverse effects since arsenic sulfhydryl bonding is an equilibrium process that supports the concept of a threshold, and evidence suggests a linear threshold model would fit the data better.

Comments from Dr. Kenny Crump are presented in Attachment B. These comments focus on the need to revise Part B to:

3. either replace the unsound and not understandable smoking interaction model, or at least develop a range of estimates that is more consistent with the data available; and

4. show the range of risk that would result from use of the Environmental Protection Agency (EPA) additive risk model assumptions.

Dr. Crump also suggests that Part B be revised to:

5. discuss/investigate more fully the implications of the Lee-Feldstein (1986) data and the non-linear relation estimated by Enterline et al.;

6. reconsider or better justify the conclusion that the use of cumulative exposure may substantially underestimate risks from environmental exposures; and

7. discuss whether evidence from the epidemiological studies is consistent with no risk from environmental exposures of concern.

Comments from Dr. Paul Solomon are presented in Attachment C. These comments focus on ambient air monitoring. Dr. Solomon suggests that As(III) vapor emissions are likely to be detected by particle monitors located at least 500 meters downwind.

Comments by Ted Holcombe are presented in Attachment D. These comments focus on the alarmist and conjectural nature of some of the statements in Part A, and on the significance of ingestion exposures and ingestion threshold theories on inhalation exposures.

The highlights of a recent draft toxicological evaluation of arsenic by Dr. William Marcus, EPA Office of Drinking Water, are presented in Attachment E. Part B should be revised as needed to incorporate the statements and references cited in the highlights.

PG&E believes the 30-day comment period on this draft risk assessment severely limits the public's ability to comment. Given that this draft was released for public comment on April 7, 1988, after 32 months of preparation by the agencies, additional review time would seem appropriate.

If you have any questions about these comments, or if the Scientific Advisory Panel would like Drs. Carter, Crump, Pike or Solomon to present oral testimony, please call me at (415) 972-7746, or Ted Holcombe at (415) 972-6910.

Victor C. Furtado

Attachments

Enviro

2200 E. RIVER ROAD, SUITE 123 • TUCSON, ARIZONA 85718 • 602 577-0818

May 4, 1988

Mr. Ted Holcombe
Pacific Gas & Electric Co.
Room 1658
1 California Street
San Francisco, California

Dear Mr. Holcombe,

Attached you will find comments prepared by Dr. Dean Carter and me regarding the Report on Arsenic in the Ambient Air prepared by the California Department of Health Services for submission to the Scientific Review Panel on Toxic Air Contaminants dated December 30, 1987. Our comments recommend:

1. Lowering the unit risk estimate for inorganic arsenic by at least a factor of 20 to 40 by incorporating differences in potency of As(III) compared to As(V); by recognizing that As(V) is the predominant species present in ambient air, and incorporating physical chemical properties of particles such as size and solubility into the risk estimates.

2. Addressing the physiological implications of the physical chemical properties of particles on such parameters as lung capture, retention, and bioavailability in the calculation of the unit risk estimates.

3. Incorporate the possibility of a threshold below which no significant adverse effects are likely to occur (considering the possibility that arsenic may be an essential metal) and fit the data to such a model.

You will be receiving Dr. Kenny Crump's comments under separate cover and will find that his comments will recommend among other modifications:

4. Abandoning the contorted and unsound DHS approach of "inferring data" to fit their model to account for a presumed interaction between smoking and arsenic in the production of lung cancer that is intermediate between linear and multiplicative.

5. DHS should reconsider the use of an additive risk model considering the weak arguments presented for using the relative

risk model in the derivation of their unit risk estim
DHS's decision contrasts with the EPA's finding that additive
models fit the data better than relative risk models.

Please feel free to contact Dr. Carter, Dr. Crump or me direc
you have specific questions relative to our comments.

Very truly yours,

Steven Pike, M.D.

Enc.

Review of California DHS Draft Report on Inorganic Arsenic

I. The risk assessment should incorporate the difference in potency of Arsenic III compared to Arsenic V in developing the unit risk estimate. Existing data are sufficient to warrant a unit risk at least ten times lower for Arsenic V than for Arsenic III. [Comments by Dean Carter, Ph.D. and Steven Pike, M.D.]

In Section 2.1.2 DHS suggests that inhalation of ambient arsenic may be more toxic than ingestion of an equivalent amount of dietary arsenic. DHS reasons that lack of methylation (detoxification) in the lung may be responsible. It is important to note that it is the trivalent arsenic that is taken up by hepatocytes for methylation and not the pentavalent. Speciation of arsenic plays an important role in metabolism, As(V) requiring reduction to As(III) to undergo methylation. Since the target for this risk assessment is the effect of arsenic on cells of the lung, a closer look at the effects of As(III) and As(V) on cells is warranted.

Section 7.1.1 cites reports in which arsenite As(III) inhibited DNA repair of damage caused by UV radiation in bacteria, while arsenate As(V) at five times the concentration had no effect on DNA repair.

In Section 7.3 concentrations of arsenate (As(V)) ten times greater than arsenite (As(III)) were required to inhibit mitogenesis. Furthermore, mutation of frequencies were negative in the mouse cell thymidine kinase (TK) locus assay when treated with As(V). Section 7.3 also reports positive responses for chromosomal abnormalities in mammalian cells exposed to As(III); As(V) was not tested.

In Section 7.3.1 DHS cites work reported on human lymphocytes exposed in vitro to sodium arsenite (As(III)) which resulted in chromatid breaks and gaps, but was negative when tested with sodium arsenate (As(V)).

It is apparent that there is at least a ten-fold difference in the potency of As(III) compared to As(V). When considering the lack of evidence of the lung's ability to metabolize As(V) to As(III) and detoxify As(III) by methylation, failing to factor in speciation of arsenic in considering toxicity combined with failing to consider ratios of As(III):As(V) in ambient air, risk is overestimated by at least a factor of 20 to 40.

II. The risk assessment should factor the relative contributions and potencies for the development of cancer that vary with particle size, solubility, and the proportion of As(III):As(V) in ambient air. The magnitude of such effects should be estimated and incorporated into the calculation of the unit risk for arsenic. Consideration of these factors will lower the resultant risk estimates. [Main comments by Steven Pike, M.D., some comments by Dean Carter, Ph.D.]

In Section 11.4.2C DHS recognizes that assuming ambient air and occupational exposure involve similar As(III):As(V) ratios may overestimate risk. Arsenic trioxide (As(III)) is probably nearly the exclusive form of exposure to the Anaconda and Tacoma smelter workers. Andreae, 1980 reports that nearly all the arsenic emitted from the Tacoma smelter is arsenic trioxide (As(III)) and that rainfall samples from the Anacortes, Washington site were 88% arsenite (As(III)) strongly supporting the argument that the Tacoma smelter is the dominant source of arsenic at this site. This result should be contrasted with the environmental ratio of As(III):As(V) reported in Appendix C of Part A [Solomon, 1987] to be close to 1 (i.e., equal mixture of both species, approx. 50% As(III)). However, this ratio was determined from samples collected in the City of Industry and thus may not truly reflect the ratio in the majority of urban and rural areas. Studies conducted in Tucson, Arizona, a city ringed by copper mines and smelters, revealed an As(III):As(V) ratio of about 0.31 +/- 0.29 (i.e., 24% As(III)) indicating that As(V) may be the species present in the atmosphere at up to three times the concentration of As(III), [Solomon, 1984]. Furthermore the ratio of 0.31 represents the mean of the highest total arsenic measured in 15 of 60 samples taken over a one year period [Solomon, 1988]. These samples were collected about 500 meters from an electric powerplant. Comparing the ratio of As(III) reported by Andreae to the ratios of As(III) reported by Solomon suggest that there is 1.8 (88/50) to 3.7 (88/24) times as much As(III) in Tacoma air as in powerplant or California smelter air. Failing to incorporate the difference in speciation of arsenic in air overestimates risk by a factor of two to four.

III. The risk assessment should be revised and modified based on an evaluation of physical state and should incorporate the differences in physical state that exist between the arsenic compounds measured in the epidemiologic studies and those measured in the ambient exposures for the development of unit risk estimates. [Main comments by Dean Carter, Ph.D., some comments by Steven Pike, M.D.]

CAPTURE:

The size of the particles should be considered in the exposure extrapolation. The deposition of particles of different sizes has been well studied in the human lung. The particle size distribution of the arsenic oxide particles at the Tacoma Washington smelter has been studied. A brief description can be found in Piver (1983). It appears that about 55% of the arsenic particles were smaller than 2.5 um. Although it is not possible to directly compare this with the findings described in the California DHS report (page A-78), it appears that the California environmental samples are considerably smaller than smelter samples with regard to their arsenic distribution. Smaller particles do go deeper into the lung but their deposition decreases to the point that most very small particles are exhaled with the breath without deposition. Data suggests that only approximately 30% to 50% of particles between 0.1 um and 1.0 um are retained by the lung parenchyma [Task Force Group on Lung Dynamics,

1966]. The arguments made in the California DHS report (page 10-7) suggest that the bronchioles are the target site in the lung and not the lower alveolar region. This would be consistent with the deposition of larger particles. Thus, a risk assessment should include an evaluation of the particle size distribution of the environmental samples as compared with the smelter samples and an assessment of deposition rate and site differences.

RETENTION:

There are several considerations for an evaluation of toxicity based on physical state. First, assuming that the lung is the target organ in the DHS evaluation, the soluble compounds of arsenic described in this evaluation would be rapidly dissolved and absorbed from the lung (Marafante and Vahter, 1987). Arsenic is not retained in the body but is rapidly excreted into the urine (Cal DHS 2-6,7). Yet, smelter workers have been found to have high concentrations of arsenic remaining in their lungs several years after exposure ceased (Vahter, 1983). This suggests that the workers may have been exposed to insoluble forms of arsenic (i.e., sulfides, arsenite salts of calcium, lead, zinc, etc.) and the retention of these compounds may have been significant in the development of lung cancer.

BIOAVAILABILITY:

The hazard assessment discussion has ignored an evaluation of the physical state of the arsenic. The review does briefly distinguish between arsenic compounds in the vapor phase and in the solid (particle) phase (Cal DHS A2-A3, A72-A79). However, there are many arsenic compounds that are of environmental importance which have different water solubilities (NRC, 1977). These compounds of different solubilities have different bioavailabilities (Marafante and Vahter, 1987; Webb et al., 1984) and different forms of toxicity (Webb et al., 1986).

Insoluble arsenic (As(III)) salts are probably more hazardous than the soluble salts because they are retained in the target organ (the lung) whereas the soluble forms can readily enter the bloodstream where they can be taken up by the liver to undergo detoxification by methylation. This concept is supported by the animal work by Pershagen and coworkers which is cited in the California DHS report on page 8-3 as supportive of arsenic being a lung carcinogen in animals after intratracheal instillation of arsenic. All animal groups in this study received the arsenic in a carrier dust of charcoal carbon to increase the lung retention of arsenic as well as a solution of sulfuric acid. This supports both the concept that arsenicals retained in the lung may have had an effect on the development of lung cancer and that sulfur oxides may have a contributory effect on arsenic carcinogenicity. These critical experimental details were ignored in the California DHS report. Thus, a risk assessment should include an evaluation of the physical form and solubility of the arsenic with special emphasis on how much can be retained.

IV. The DHS Risk Assessment should consider the possibility of a threshold below which there are no significant adverse effects. The use of a zero threshold may actually create significant adverse effects if arsenic is an essential element in humans and is regulated to a level which would create a deficiency state. Thus a zero threshold would not be biologically plausible. DHS is arbitrarily dismissing the possibility of a threshold; a conclusion contrary to the opinions of other scientists. Furthermore, if evidence for arsenic as an essential element in humans becomes compelling, some scientists would argue that there is a teleologically sound basis for the existence of a threshold below which no significant adverse effects would result. [Main comments by Dean Carter, Ph.D., some comments by Steven Pike, M.D.]

The California DHS report discounts the possibility of a threshold dose. There are several workers in the field who would have come to the opposite conclusion. There is one point on page 10-5 of the report which shows a lack of understanding of arsenic binding. The report states "A single instance of sulfhydryl group binding to an enzyme might result in misrepair or breakage of DNA." This type of argument has been used with alkylating agents of DNA which form a covalent bond after an irreversible reaction with the DNA. In that case, one molecule forming one bond may indeed result in breakage of DNA. However, arsenic binding to sulfhydryl groups is an equilibrium process in which the bonds are continually being formed and broken. The number of molecules which have bound to arsenic depends on the free arsenic concentration and the actual sulfhydryl groups which are bound change constantly. The dose-response relationships for such equilibrium processes have been well described in basic pharmacology texts and support the concept of a threshold.

The argument that DHS raises in Section 10.5.2 that a single instance of sulfhydryl group binding to an enzyme might result in misrepair or breakage of DNA is biologically not plausible. Enzymes have great reserve capacity for function in human physiology. This is most dramatically evident when one considers the ability of heterozygous genotypes for enzyme deficiency in persons with inborn errors of metabolism to be phenotypically normal. It is extremely unlikely that one altered enzyme molecule would bind to DNA and cause misrepair or breakage in the midst of overwhelming numbers of "normal" enzyme molecules.

The staff at DHS cite the possibility that "a single instance of arsenolysis might result in DNA damage." However the hypothesis that inorganic arsenic (As(V)) competes with phosphorus to form unstable arsenate DNA and RNA esters has never been proven in vivo. All experimental results have been based on isolated enzyme or single cell studies and there is no evidence that this mechanism is biologically plausible in mammalian systems. DHS has not shown that a threshold model fails to fit the data as well or better than a linear no threshold model and evidence suggests that the converse is true.

BIBLIOGRAPHY

Andreae, M.O. 1980. Arsenic in Rain and the Atmospheric Mass Balance of Arsenic. J. Geophys. Res. 85: 4512-4518.

Marafante, E. and M. Vahter. 1987. Solubility, retention and metabolism of intratracheally and orally administered inorganic arsenic compounds in the hamster. Environ. Res. 42: 72-82.

National Research Council. 1977. Arsenic. National Academy of Sciences, Washington, DC. p. 4-15.

Piver, W.T. 1983. Mobilization of arsenic by natural and industrial processes. In "Biological and environmental effects of arsenic" edited by B.A. Fowler. Elsevier, Amsterdam, p. 40.

Solomon, P.A., Rabano, E.S., Castillo, N.T. and Torre, K.J. Speciation of Arsenic in Ambient Aerosols Collected in Los Angeles. Final Report 1182R/0214A submitted to California Air Resources Board, May 19, 1987.

Solomon, P.A. Collection and Analysis Techniques for Studies of Atmospheric Arsenic Species, Ph.D. Thesis, Dept. of Chemistry, University of Arizona, Tucson, Arizona (1984).

Solomon, P.A. Personal communication, May 3, 1988.

Task Force Group on Lung Dynamics, Committee II IRCP, Deposition and retention models for internal dosimetry of the human respiratory tract. Health Phys., 12, 173, 1966.

Vahter, M. 1983. Metabolism of arsenic. In "Biological and environmental effects of arsenic" edited by B.A. Fowler. Elsevier, Amsterdam. p. 172.

Webb, D.R., I.G. Sipes and D.E. Carter. 1984. In vitro solubility and in vivo toxicity of gallium arsenide. Toxicol. Appl. Pharmacol. 76: 96-104.

Webb, D.R., S.E. Wilson and D.E. Carter. 1986. Comparative pulmonary toxicity of gallium arsenide, gallium oxide or arsenic oxide intratracheally instilled into rats. Toxicol. Appl. Pharmacol. 82: 405-416.

Comments on

Health Effects of Arsenic Compounds
Prepared by
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Overview of DHS's risk assessment

DHS's risk assessment was based upon lung cancer data from three studies. A recent study by Lee-Feldstein (1986) was not used. The risk assessment relies heavily upon the EPA review of the epidemiological studies, which was prepared before any of these four studies were published. DHS should review these these studies in more depth. It is possible that the Lee-Feldstein study should not be rejected out of hand, since all of the studies involve defficiencies of some sort.

DHS's model of smoking and arsenic interaction is unsound and their explanation of this feature of their model in Appendix E is not understandable. Further, their basic assumptions with regard to smoking and arsenic interaction are not well supported by the data. DHS should

abandon the current model of smoking and arsenic interaction and replace it with a simpler approach or, in view of the disparity of the data, develop a range of estimates that are more or less equally consistent with the data available.

DHS's justification of use of a linear dose-response is primarily theoretical. DHS should evaluate this crucial assumption in light of the dose-response data, and examine what level of departure from this assumption is consistent with the data. In particular, DHS should discuss whether the evidence from the epidemiological studies is consistent with no risk from environmental exposures of concern.

DHS's reliance upon a single risk assessment model is unfortunate, particularly since it appears to have methodological defects. DHS should develop a range of estimates for different assumptions that are all more or less consistent with the data and with current scientific understanding. For example, since DHS utilized new data from the Tacoma smelter that were not available to EPA and have not heretofore been used in risk assessment, it would be useful to determine the risk estimates obtained by applying the EPA methodology to these data. The fact that the new study estimates a considerably higher air concentration for a given urine level suggests that the EPA procedure would produce lower risk estimates from the newer data.

Specific Comments

DHS relied heavily upon the review by EPA (1984) of the epidemiological studies. However, four studies, including all of those used by DHS for its risk assessment, appeared after EPA's review. The risk assessment would have profited from a more thorough review of these studies. In particular, the reason for not using the Lee-Feldstein (1986) study should have been more thoroughly described. Perhaps this study should be utilized since all of the studies have defficiencies of one sort of another. Also, the non-linear relation estimated by Enterline *et al.* between urinary arsenic and airborne arsenic could have important implications for risk assessment and should investigated more fully.

DHS's discussion of possible bias in estimates made for persons exposed as children is speculative and itself potentially biased. For example, it is not clear whether they are referring to dermal or inhalation exposures that are claimed to result from children playing in dirt. Dermal exposures are not considered to be related to lung cancer risk. One can also easily think of reasons why risk from early exposures could be overestimated: children breathe less than adults and children may have a stronger immune system than the elderly. Further, it is highly speculative to assume that a smoking and arsenic interaction would hold for arsenic exposures that precede the onset of smoking; consequently, it would be reasonable to consider a model in which any joint effect of

smoking and arsenic only applies to arsenic exposures that occur after the advent of smoking. DHS's discussion of these issues should be presented in a more balanced fashion.

The statement (page 11-11) that "short-term exposures are considered equivalent to long-term low exposures provided the cumulative dose is the same" is not quite correct. It is true that DHS's method of accumulating dose predicts that *at a given age* risk is determined only by cumulative dose to that age. However, with a high short-term exposure, cumulative exposure will be higher at intermediate ages than with an equivalent long-term exposure; consequently, lifetime risk will be estimated by DHS as being higher from a short-term high level exposure.

Kodell *et al* (1987) (page 11-11) refer to using total average exposure as a surrogate for taking the actual exposure pattern into account; since DHS is taking the exposure pattern into account in both the epidemiological populations and the posited exposures in the risk assessment, the situation discussed by Kodell *et al* is not comparable to that being evaluated by DHS. Comparing the results of having an early stage effected to DHS's use of cumulative exposure is problematic without carrying out a detailed analysis. Consequently, DHS's conclusion that their use of cumulative exposure may substantially underestimate risk from environmental exposures seems premature and

should be either buttressed by a more detailed analysis or be deleted.

DHS was perhaps premature (page 11-13) to dismiss an additive risk model for arsenic. DHS cited two factors in this decision: first, the assumption that risk is independent of age for a given cumulative dose is biologically implausible and, second, age-specific data were lacking. With regard to the first factor, DHS indicated that an absolute risk model would predict the same additional hazard for a five-year-old as for a fifty year old, given the same cumulative exposure and that this was biologically implausible. However, an absolute risk model would not predict the same risk in these two circumstances if latency was taken into account realistically. Beyond this, it is not clear that an additive risk model is implausible. Further, EPA found that additive risk models fit the available data better than relative risk models.

The reasons cited for using a linear dose-response (page 11-14) should include a discussion of the observed dose-responses in the epidemiological studies. Further, the range of departures from this assumption which are consistent with the epidemiological data should be explored.

The model used by DHS assumes that the joint effect of arsenic and smoking multiplies the background risk of lung cancer. Based upon their conclusion that the joint effects of arsenic and smoking are intermediate between multiplicative and additive, DHS develops a very

complicated model of interaction that involves inferring SMRs (standardized mortality ratios) and observed cancers in nonsmoking populations. As discussed below, this approach seems ill-advised.

First of all, the limited evidence on the interaction between smoking and arsenic exposure has been overinterpreted by DHS. Even if the basic model is one of a multiplicative effect upon age-specific background rates, this model will not predict that the expected RRs (relative risks) will be multiplicative, as assumed by DHS. This is because the expected number of cancers in a dose group is a sum of terms for each age- and calendar-year and even though a multiplicative relationship holds for each group, this will not in general result in a multiplicative relationship for the overall RRs. (It would be multiplicative if the multiplicative factors for both smoking and arsenic were constant; however, this will not be true in general because, for example, the relative risk associated with a worker's exposure to arsenic will increase with his exposure.) Moreover, even if the expected relationship was to be multiplicative, the observed relationship would be subject to random error. DHS, in deciding that a multiplicative relationship is not appropriate, did not investigate whether the disagreement could be explained by random error. It seems likely that some of the relative risks, for non-smokers in particular, were based on small numbers of cases; consequently, the disagreement with a multiplicative relation could well be due to random deviations.

DHS incorporated the effect of a non-multiplicative relationship between arsenic and smoking by including a parameter, ρ, that expresses the degree of departure from a multiplicative model. This parameter is assumed to decrease with increasing exposure to arsenic; the specific values used for this parameter are apparently not derived from data. A casual observation of the data in Appendix A did not support DHS's assumptions regarding this parameter. Values of ρ suggested by the Welch *et al* (1982) data vary from 0.4 to 3 depending upon how they are calculated and do not appear to vary with arsenic exposure in a consistent manner. Thus, DHS's selection of values for this parameter are not clearly supported by data.

DHS's dose-response modelling procedure is contorted and not well explained. There appear to be errors in the discussion of the implementation. The complications arise mainly from DHS's modelling of the joint effect of arsenic and smoking. To do this they calculate new "data" which they call "inferred nonsmokers data" and fit a linear dose-response model to this data by a least squares method (not explicitly defined).

I was not able to follow the mathematical explanation of the model contained in Appendix E. The basis for the derivation is overly simplistic; relative risks are actually calculated as ratios of sums

with each term in the sum being similar to the expressions used by DHS, but with different factors due to different background incidences, arsenic doses, and smoking categories. The formula for SMR on page E-3 must be incorrect (the SMR will be negative if ρ is less than one). Also, the mathematical derivation does not lead to this equation and I was unable to infer the formula used for the results in Table E-1.

The properties of statistical procedures applied to the "inferred data" are unknown. DHS warns at one point that the confidence limits calculated from the inferred data may not share the properties that would hold had they been applied to real, as opposed to inferred, data. However, the conclusion that "an excellent fit was obtained for both data sets" was not tempered by such a warning.

DHS indicates that the inferred observed deaths are treated as Poisson random variables. It is not clear what role this assumption plays in the sequel.

The data used in the risk assessment are not in Table 11-3 as stated on page 11-12. Presumably the data for Tacoma can be obtained by combining data from Tables 9-4 and 11-2, and the data for Anaconda by combining data from Tables 9-6 and 11-2. However, it is important that the actual data used be clearly designated.

The implication (pages 11-6 and 11-18) that Welch *et al.* (1982) and Higgins *et al.* (1985) were "incorrect" in their apportioning of person-years of exposure according to final exposure is too strong. "Less appropriate for the particular risk assessment approach applied by DHS" would be preferred.

ATTACHMENT D
COMMENTS BY TED HOLCOMBE
ON THE APRIL 1988 PRELIMINARY DRAFT
ARB/DHS ARSENIC RISK ASSESSMENT

COMMENTS ON PART A

1. THE PART A "INTRODUCTION AND SUMMARY" SHOULD BE CORRECTED TO CLEARLY STATE THAT DRINKING WATER EXPOSURES ARE TYPICALLY 100 TO 400 TIMES HIGHER THAN INHALATION EXPOSURES.

   The top paragraph on Page A-3 states that drinking water exposures "may result in greater intake". This is misleading and should at least be revised to read "almost always result in far greater intake". However to properly summarize the report, the following should be added to the Part A Introduction and Summary:

   > "The data contained in this report indicates that on average drinking water arsenic exposures are more than 100 to 400 times higher than inhalation arsenic exposures. In fact, the report indicates that even in the spot with the highest inhalation concentrations, drinking water exposures are still 1.4 to 16 times higher than inhalation exposures."

   For example, in Table 1.6 (page A-35) the ARB estimates that statewide drinking water exposures average about 5 ug/l or 10 ug/day. This is over 100 times higher than the maximum observed ambient average exposure inhalation exposure of 3.5 ng/m^3 or 0.07 ug/day. Similarly the maximum measured ground water arsenic concentration (averaged over the entire Sacramento and San Joaquin Valley region per Table 1.7 page A-38) of 232.8 ug/l or 465.6 ug/day is over 380 times greater than the maximum measured inhalation hot spot concentration of 61 ng/m^3 or 1.2 ug/day (see Table I-5 page A-31).

   Similarly, according to Table I-7 page A-38, average surface water arsenic exposures in the Los Angeles area are 9.9 ug/l or 19.8 ug/day. That is more than 16 times higher than the measured hot spot concentration of 1.2 ug/day in the same area. It is also more than 1.4 times the modeled impact of 700 ng/m^3 or 14 ug/day (see page A-30).

2. THE DISCUSSION OF DIETARY ARSENIC EXPOSURES IN PART A APPEARS TO CONTRADICT THE DISCUSSION IN PART B. THE PART A DISCUSSION SHOULD BE CORRECTED AND EXPANDED TO ADDRESS:

   a. THE LIKELIHOOD THAT SOME PORTION OF DIETARY EXPOSURES MIGHT BE INORGANIC;

   b. DATA INDICATING THAT ORGANIC ARSENIC COULD BE CONVERTED IN THE BODY TO CAUSE EXPOSURES SIMILAR TO THOSE CAUSED BY INORGANIC ARSENIC; AND

   c. THE FACT THAT EQUIVALENT INORGANIC EXPOSURES FROM DIETARY EXPOSURES ARE LIKELY TO BE AT LEAST 20 TO 100 TIMES HIGHER THAN TYPICAL INHALATION EXPOSURES.

At the end of the first paragraph on page A-3, the ARB summary dismisses dietary exposures with the comment that:

> "Diet is also a source of arsenic intake, but arsenic in food occurs primarily as complex organo-arsenicals which are of much less toxicological significance".

In item 3, page A-40, the ARB asserts that dietary arsenic

> "is not a significant source of inorganic arsenic exposures".

These statements appear to contradict statements in Part B on pages 2-2 through 2-3 which suggest that at least some common foodstuffs take up inorganic arsenic, and that diet provides a larger total exposure to elemental arsenic.

Given that "Ryegrass and spring wheat crops preferentially take up arsenic from flyash" (Part B page 2-2), it would appear reasonable to assume that they and probably other foodstuffs would take up arsenic from soils or surface and ground waters. Since surface and ground water arsenic concentrations throughout California, and particularly in the central valley with its extensive farmlands, are far higher than would be expected from fallout from ambient arsenic, either Part A or Part B should be revised to note that foodstuffs would be likely to pick up significant amounts of arsenic even if there were no airborne arsenic.

As summarized in Section A of the attached highlights of the Environmental Protection Agency's April 1988 draft "Quantitative Toxicological Evaluation of Ingested Arsenic", (a complete copy of which is also attached), work by Yamauchi and Yamamura in 1984 suggests 3 to 5% of organic arsenic exposures could convert in the body to forms similar to those resulting from inorganic arsenic exposures. Thus even if it were assumed that the average dietary exposures of 50 ug/day were entirely in the form of organic exposures, then that exposure could still be toxicologically equivalent to an inorganic exposure of 1.5 to 2.5 ug/day. Such an exposure would be more than 20 to 100 times higher than the 1.1 to 3.5 ng/m^3 (0.02 to 0.07 ug/day) average ambient inhalation exposures summarized on Table I-2 page A-12. The same result could be calculated by assuming as little as 3-5% of dietary exposures were in the form of soluble inorganic arsenic compounds.

3. THE SUMMARY SHOULD ACKNOWLEDGE THAT AMBIENT INHALATION EXPOSURES ON THE ORDER OF 2 NG/M^3 ARE PROBABLY INSIGNIFICANT, AND SHOULD NOT DWELL UPON SUCH EXPOSURES.

Part A estimates that ambient air in urban areas of California contains an average of 2.2 ng/m^3 arsenic (see page A-21). As detailed in comments 1 and 2, daily arsenic exposures from the inhalation of 2.2 ng/m^3 arsenic would be orders of magnitude lower than current average drinking water, dietary, or hot spot inhalation exposures.

Ambient concentrations of 2.2 ng/m^3 arsenic are also less than half of the 6 ng/m^3 average arsenic concentration currently calculated for the entire United States (page 5 of attached draft evaluation by Marcus, 1988; alternatively see page 3-10 of March 1984 final EPA arsenic risk assessment EPA 600/8-83-012F).

Finally, the Department of Health Services (DHS) is currently estimating that non-smokers inhaling the average ambient concentration of 2.2 ng/m^3 of inorganic arsenic would only be subjected to risks of roughly one in a million (Part B Table 11-5 page 11-33 estimates risks of 0.66 to 2.0 cases per million non-smokers exposed). While some may choose to subject themselves and their associates to higher risks by smoking, such higher exposures would be voluntary. Furthermore, if the DHS risk estimate were revised downward as suggested by other comments herein, 2.2 ng/m^3 exposures would be less than one in a million for even heavy smokers. Therefore risks could well be insignificant relative to the frequently cited one-in-a-million criteria.

In any event, risks are clearly insignificant relative to the February 1988, California's Health and Welfare Agency promulgated Health and Safety Code Title 22, Section 12703(b) criteria that "the risk level which represents no significant risk shall be one which is calculated to result in one excess case of cancer in an exposed population of 100,000".

In summary, 2.2 ng/m^3 arsenic concentrations are normal, pose additive risks of borderline or below borderline significance, and are clearly insignificant relative to total body burdens from other sources. We therefore recommend that the extensive and alarmist discussion of the 1.1 to 3.5 ng/m^3 exposures in pages A-3 to A-5 of the "Introduction and Summary" be shortened and placed into perspective. We particularly recommend deletion of the emphasis on the "millions of Californians" being exposed. A more reasonable summary might consist of the following:

> "Ambient air quality sampling in urban areas has indicated that inhaled arsenic concentrations average roughly 1.1 to 3.5 ng/m^3. Such exposures pose risks of borderline significance. Of far greater concern are measurements and modelling indicating that arsenic concentrations in a few isolated hot spots might be 20 to 320 times higher. Exposures from drinking water and foodstuffs generally exceed even such hot spot inhalation exposures. However, the inhalation of insoluble trivalent arsenic compounds may pose different risks than those resulting from ingestion of the same compounds."

4. THE REFERENCES IN THE "INTRODUCTION AND SUMMARY" TO "HOT SPOT EXPOSURES 100 TIMES HIGHER" AND OF "SEVERAL HUNDRED NANOGRAMS" SHOULD:

   a. NOT BE REPEATED;

   b. MORE CLEARLY IDENTIFY THE SOURCE TYPE;

   c. DISTINGUISH BETWEEN WHAT IS KNOWN AND CONJECTURED; AND

   d. BE PLACED INTO PERSPECTIVE.

As an operator of relatively large power plants, PG&E is concerned that describing such hot spots as due to "large sources" on page A-3 and then again on page A-5 might cause the public to associate such hot spots with our large fossil fueled power plants. The example detailed on pages A-29 through A-35 is a smelter, not an undefined "large source". Nowhere in the report is it alleged that large fossil fuel combustion sources would cause similarly high concentrations. The summary on page A-5 at least mentions smelters. We therefore recommend that the duplicative large source discussion on page A-3, which does not even mention smelters, be deleted.

The last sentence on page A-5 states that "studies determined that populations living near large sources, such as a secondary lead smelter, are being exposed to... several hundred nanograms per cubic meter". The report suggests that such studies were limited to one or more specific large smelter sources. Therefore the "studies" only "determined" that such exposures are occurring for those specific sources. The ARB should revise this sentence to correctly distinguish between what is known and what is conjectured.

If the ARB is conjecturing that large gas or oil fired power plants might cause similar average annual impacts in the 100 ng/m^3 range, then the basis for such a conjecture should be presented in the report, and PG&E should be afforded an opportunity to comment upon those assumptions.

The hot spot exposure discussion should clearly acknowledge that drinking water exposures would be even greater. The question of whether inhalation exposures are more risky should be addressed in Part B, and in the Combined A & B summary, not in Part A or in the Part A summary.

5. FOR THE HOT SPOT SOURCE, MODELED CONCENTRATIONS WERE TEN TIMES HIGHER THAN MEASURED CONCENTRATIONS. IT SHOULD BE ACKNOWLEDGED THAT OVERESTIMATION BY THE DISPERSION MODEL MIGHT SIGNIFICANTLY CONTRIBUTE TO THIS DIFFERENCE.

On page A-30 it is stated that dispersion modelling indicated a maximum smelter average ambient impact of 700 ng/m^3. However, the actual ambient monitoring results presented in Table I-5 on page A-31 averaged 61 ng/m^3. On page A-33 it is stated that meteorological variables and an offset from the predicted point of maximum impact might have caused this difference.

On page A-33, at the end of the top partial paragraph, it should be acknowledged that dispersion model or modelling assumptions might also contribute to differences between observed and modelled impacts — perhaps by adding:

> "It is also possible that the dispersion model may overestimate the ambient impact."

6. IN TABLE II-2 THE GEOTHERMAL STEAM UTILITIES EMISSION ESTIMATE WAS BASED UPON ARB RATHER THAN PG&E CALCULATIONS, AND THE REFERENCE SHOULD BE REPORT PAGES A-86 THROUGH A-87, NOT PG&E, 1982.

As summarized on page A-67, PG&E 1982 is the Geysers Unit 20 Application for Certification (AFC). Appendix A of that document (the Prevention of Significant Deterioration application) does contain an estimate of arsenic in incoming steam at Units 16, 17, 18 and 20. On page 3-4 of the AFC, there is also a summary of incoming steam arsenic and non-condensible gas concentrations from 61 producing wells in 1972-74, and an estimate of arsenic in Unit 20 steam on page 3-5. However, we are unable to locate any comprehensive estimate of arsenic emission from all geothermal sources in this AFC.

As summarized in our October 20, 1987 letter to Mr. Jim Guthrie, a copy of which is attached, PG&E's method of estimating Geysers arsenic emissions, and the amount of emissions estimated, differs considerably from the ARB method and estimate, and referencing the ARB emission estimates to PG&E is therefore inappropriate.

PG&E recommends that the "PG&E 1982" reference in Table II-2 on page A-49 be deleted. Appropriate references to specific data obtained from PG&E can be more properly made on pages A-50 through A-52 or pages A-86 through A-87.

7. THE STATEMENT THAT GEOTHERMAL STEAM CONTAINS ARSENIC AS SUSPENDED PARTICULATES, ARSENIC TRIOXIDE VAPOR AND ARSINE IS NOT DOCUMENTED, AND APPEARS TO BE CONJECTURE.

In the second sentence of item 1 on page A-50 it is stated that: "Arsenic is present in geothermal steam as suspended particulates, arsenic trioxide vapor and arsine." The basis for such a definitive conclusion should be provided.

Cobble, 1985 (see Part A page A-66) states that:

1. Arsine is thermodynamically unstable at all temperatures... and will not be considered further in any equilibrium calculations (page 2-7);

2. Obviously $As_4O_6(g)$ cannot be at any detectable concentration in equilibrium with dilute As(III) solutions. This comes about because it requires four $As(OH)_3$ molecules to make one As_4O_6 molecule, and the high power dependence in the equilibrium constant discriminates against the gaseous molecule (page 2-9);

3. As_2S_3 and As_2S_2 ... are <u>probably</u> the controlling factors in fixing arsenic concentrations (page 5-1, emphasis added); and

4. There is <u>probably</u> at least one volatile form of arsenic, arsenous acid gas, $As(OH)_3$, which can lead to gaseous arsenic concentrations in geothermal fluids (page 5-1, emphasis added).

8. THE 5TH LINE ON PAGE A-51 SHOULD BE CLARIFIED.

The 5th line from the top of page A-51 reads: "based upon the assumption that only the arsenic in the cooling tower drift is emitted". It would be more correct to say: "based on the assumption that arsenic vapor emissions are relatively insignificant, and only the arsenic in the cooling tower drift need be considered when estimating power plant emissions".

Lacking data confirming significant arsenic vapor emissions, PG&E has estimated arsenic emissions from its power plants based upon cooling tower drift (see the attached October 20, 1987 letter). However such estimates do not address emissions from geothermal steam suppliers.

9. THE FIRST TWO SENTENCES OF THE MIDDLE PARAGRAPH ON PAGE A-51 SHOULD BE CORRECTED.

The sentence reads: "Complete information on routes of arsenic in geothermal steam plants is lacking (PG&E 1987)". I never said that. It would be correct to attribute the first sentence to PG&E if the words "the mass balance" were substituted for "routes".

The second sentence states that "much of the arsenic present in geothermal steam may be released to the atmosphere" is an ARB, not PG&E, conclusion. If the reference to PG&E is retained in the first sentence, then the "However" in the second sentence should be replaced by the phrase "Therefore, the ARB has concluded".

10. THE TEMPERATURE AND PRESSURE CITED IN THE 9TH LINE OF THE MIDDLE PARAGRAPH ON PAGE A-51 ARE NOT UNIVERSALLY APPLICABLE.

Page A-51 states that "geothermal steam... is... condensed at around 125 degree F and 1.94 psia". That is based upon a hypothetical geothermal plant model, not some fixed plant criteria (see Cobble, 1985, page 4-4).

PG&E's surface condensers operate at slightly lower temperatures and higher pressures. For example the 100% guaranteed load heat balance diagram from the PG&E Geysers Unit 20 AFC, Figure 4.4-7, shows a surface condenser pressure of 2.84 inches Hg A and a non-condensible gas temperature of 103.8 degrees F. The comparable Unit 21 AFC values are 2.75 inches Hg A and 101.9 degrees F.

Of greater importance is the difference between direct contact condenser designs at Units 1-12, and the surface condenser designs at Units 13-21. In the direct contact condensers, the steam leaving the turbines mixes directly with the entire circulating water flow.

In the surface condenser units, only the steam condensate is mixed with the circulating water. However all of PG&E's surface condenser units pass the non-condensible gases through a Stretford solution designed to convert more than 99% of the gaseous hydrogen sulfide into oxidized, dissolved particles.

11. THE REFERENCE TO PG&E IN THE 11TH LINE OF THE MIDDLE PARAGRAPH OF PAGE A-51 SHOULD BE DELETED.

I never said "process specific data are not available". At least some information on how our power plants "process" geothermal steam is clearly available in the AFCs and plant data books.

12. THE OCCASIONAL HIGH CONCENTRATIONS MEASURED BY THE GEYSERS AIR MONITORING NETWORK SHOULD BE PLACED INTO PERSPECTIVE.

In 1983-4 and again in 1986-7, most of the Geysers Air Monitoring Program (GAMP) arsenic samples failed to show any detectable arsenic. Rather than quoting the single highest absolute high in 1986-7, and alluding to "higher concentrations... during previous periods" on page A-52, the average concentration, and the number of samples below the detectable concentration, should be clearly stated for both study periods.

Since the data was originally reported to the nearest nanogram, and the detection limit is so high, the ARB should also show how the average would differ when the effect of the originally assumed 1 ng/m^3 detection limit is compared with the subsequent 3 ng/m^3 limit. For example, the 1983-4 data, using the 1 and 2 ng/m^3 values reported, and assuming zeros to be 0.5, showed that concentrations averaged 1.4 ng/m^3 at Glen Brook, and 2.1 ng/m^3 in Anderson Springs. Assuming zeros to be zero would lower the Glen Brook average to 0.6 ng/m^3, and the Anderson Springs average to 1.4 ng/m^3.

Given that the occasional high concentrations are the exception rather than the rule, and power plant emissions are relatively constant, there should be some discussion of what factors may be causing the occasionally observed highs. Factors deserving consideration include variations in meteorology, levels of wind blown soil, and steam releases.

If, as PG&E currently estimates, only a small fraction of the arsenic in the incoming steam is emitted (as cooling tower drift), then arsenic emissions may be temporarily higher when steam suppliers are releasing steam directly to the atmosphere.

13. THE CERTIFICATION OF GEOTHERMAL WELLS DOES NOT NECESSARILY MEAN INCREASED STEAM USAGE OR HIGHER AMBIENT CONCENTRATIONS.

In the last paragraph of Section 1 on page A-52, it is suggested that higher arsenic emissions correlate directly with the drilling of additional wells. Some new wells are needed to merely maintain declining steam production from existing wells.

Although wells associated with new power plants will increase emissions, the highest average ambient concentrations in the area may not increase because of the distance between the existing and new wells.

It would be appropriate to expand the discussion on page A-52 to address such considerations.

14. THE 19 PPB ARSENIC AVERAGE IN PG&E 1982 ON PAGE A-86 IS DERIVED FROM PG&E 1974 AND REFERS TO CONCENTRATIONS IN CONDENSED STEAM FROM WELLS SERVICING DIRECT CONTACT CONDENSER UNITS, NOT CONCENTRATIONS IN SURFACE CONDENSER UNIT CONDENSATE.

    A copy of the complete 1974 report number 7485.16-74 is attached.

15. THE 3.98% NUMBER ON PAGE A-87 SHOULD BE 0.398% PER THE REFERENCE CITED.

    The effect of this change is to significantly lower the upper bound in the ARB estimated range of emissions.

16. THE STATEMENT THAT FUEL COMBUSTION RESULTS IN ARSENIC TRIOXIDE EMISSIONS IS AN INCORRECT SIMPLIFICATION OF THE DETAILED DISCUSSION IN THE REPORT.

    The sentence starting at the bottom of page A-48 and ending at the top of page A-50 implies that all fuel combustion is known for certain to be 100% arsenic trioxide. But the detailed discussion on pages A-74 and A-75 acknowledges that it is only high temperature combustion which can convert trivalent arsenic into pentavalent arsenic, and that compounds other than As_2O_3 may be present.

    Even if all arsenic were converted to the trivalent form in the combustion chamber, some or most of that arsenic might still revert to the more stable pentavalent form before being emitted, or before reaching receptors. For example, Paul Solomon's analysis of the highest 15 of 60 arsenic samples previously collected 500 meters downwind from an oil fired power plant in Tucson, Arizona, indicated that the trivalent to pentavalent ratio averaged 0.31. This means that only 24% of the arsenic, on average, was in the trivalent form [see Solomon, P.A "Collection and Analysis Techniques for Studies of Atmospheric Arsenic Species, Ph.D. Thesis, Dept. of Chemistry, University of Arizona, Tucson Arizona (1984)].

17. PG&E DATA IS CONSISTENT WITH SCE DATA.

    At the top of page A-55 it is noted the lower sulfur utility fuel data may contain lower arsenic concentrations than higher sulfur industrial or transportation fuel oils. PG&E believes that its limited data is consistent with that conclusion.

    In 1984, PG&E sampled arsenic in residual fuel oils in 11 power plant tanks. All but one of these samples indicated the arsenic concentration was less than the 0.5 ppm detection limit. The other sample indicated a concentration of 4.5 ppm Arsenic.

18. PART A SHOULD ACKNOWLEDGE THAT A SHORT TERM INCREASE IN RESIDUAL OIL USE MAY NOT SIGNIFICANTLY IMPACT AVERAGE LIFETIME EXPOSURES.

    On the bottom of page A-55, it is estimated that utility oil use may increase in the next decade, and then return to the very low 1984 levels. However, these statements do not acknowledge that 1984 oil use was exceptionally low, the equivalent of an 0.19% fuel oil use capacity factor.

Nor is any attempt made to estimate the effects of a temporary tripling of such low oil use on average population exposures. PG&E doubts that its fossil fuel combustion at three times its low 1984 rates would significantly contribute to total individual lifetime arsenic exposures. See also comments 1-3.

COMMENTS ON PART B

1. SEE PART A COMMENT #2.

2. THE ESSENTIAL ELEMENT DISCUSSION SHOULD ACKNOWLEDGE THAT COMMON DRINKING WATER AND DIETARY EXPOSURES ARE HIGH ENOUGH TO ELIMINATE THE NEED FOR A HOMEOSTATIC MECHANISM.

   On page 3-1 it is suggested that the absence of a process to maintain arsenic concentrations in the body may indicate that arsenic is not essential. However, the sheer magnitude and universality of the arsenic exposures summarized in Part A comments 1-3, and in the attached EPA evaluation by Dr. Marcus, suggests that the body may not have needed to develop such a mechanism for arsenic. This possibility should be acknowledged in the essential element discussion.

3. THE DISCUSSION OF POSSIBLE THRESHOLDS SHOULD BE EXPANDED TO RESPOND TO THE SPECIFIC THRESHOLD CONCEPT SUGGESTED BY DR. MARCUS AND SUMMARIZED IN SECTION D OF THE ATTACHED "SUMMARY OF HIGHLIGHTS OF 'QUANTITATIVE TOXICOLOGICAL EVALUATION OF INGESTED ARSENIC'".

   Dr. Marcus summarizes research indicating that there may be a threshold for a significant increase in ingested arsenic risks for exposures over 200 ug/day.

   Ingested arsenic threshold may very well meet the criteria of Health and Safety Code Title 26, Section 39662(c) in that adverse health effects from ingestion of less than 200 ug/day of arsenic may not in fact be significant. Certainly the possibility of a relatively high threshold is not contradicted by the absence of significant identifiable adverse effects in California's Central Valley (where it is estimated that exposures average over 80 ug/day)(see Part A pages A-37 through A-39).

4. SEPARATE UNIT RISK ESTIMATES SHOULD BE PROVIDED FOR THE INHALATION OF INSOLUBLE AS(III), SOLUBLE AS(III), SOLUBLE AS(V) AND INSOLUBLE AS(V).

   In view of:

   a. the relatively high levels of arsenic ingestion;

   b. the potential for a significant adverse effects threshold for arsenic ingestion; and

   c. data indicating that pentavalent arsenic in the lungs would significantly increase risks

i. only after it is converted to trivalent arsenic in the blood stream; and

ii. only to the extent that ingested arsenic increases risks;

the Department of Health Services should propose separate unit risks for pentavalent and trivalent arsenic compounds.

The data, as summarized by Doctors Pike, Carter, and Marcus, clearly support some differentiation in risks between the inhalation of trivalent and pentavalent arsenic. This data also appears to support a distinction between soluble and insoluble compounds. In this regard, insoluble As(III) compounds would appear to be the most hazardous [because they could remain available to react in the lung longer], while insoluble As(V) compounds would appear to be the least hazardous [because they would be unlikely to ever convert to the hazardous As(III) form].

SUGGESTIONS BY DR. PAUL A. SOLOMON FOR ENHANCING THE PRELIMINARY DRAFT DHS REPORT TO THE AIR RESOURCES BOARD ON INORGANIC ARSENIC

PART A - PUBLIC EXPOSURE TO AIRBORNE INORGANIC ARSENIC IN CALIFORNIA

COMMENTS OF MOST IMPORTANT SIGNIFICANCE

Comments suggested in this section address specifics in Part A which should be revised to reflect more recent or more accurate data presented in the published literature. In addition, suggestions for major editorial changes are also presented. Note, comments are listed in order as they would appear in the text of the report and not in order of importance.

Page A-2, paragraph 2, sentence 3;

Insert "a gas (As_4O_6) which condenses onto existing particles, primarily", after ... "predominantly as".

Page A-3, paragraph 3, sentence 2;

Delete the word "elemental". While elemental arsenic may be reported, it is not the species present in the atmosphere.

Page A-3, paragraph 3, sentence 4 and continued next page;

This sentence is not easily understood, perhaps it could be changed to the following;

However, available information suggests that most arsenic present on particulate matter in the atmosphere is in the inorganic forms (Johnson and Braman, 1975; Andreae, 1980). In addition, this accounts for a major portion of the inorganic arsenic in the air, since ambient measurements indicate that only a relatively small fraction of the atmospheric inorganic arsenic is present in the gas phase (Walsh et al., 1979; Walsh et al., 1977; Germani et al., 1981; Appel et al., 1984).

Page A-6, paragraph 2, sentence 3;

I suggest removing the parenthesis and inserting the word "analysis" before ... "method".

Comments by Dr. Paul A. Solomon (continued)

Page A-6, paragraph 2;

I suggest inserting the following statement after sentence 3;

It should be noted, that the use of glass fiber filters may over estimate particulate arsenic concentrations in the atmosphere since gas phase arsenic compounds, if present, may react with or be absorbed by the filter medium.

I am making this suggestion because the use of glass fiber filters for the collection of atmospheric particulate matter is known to over estimate atmospheric concentrations of other particulate oxyacids (e.g., particulate nitrate and sulfate). This problem results from the absorption of their gas phase counter parts, also oxyacids (e.g., NO_x, HNO_3, and SO_2, H_2SO_4), by the reactive glass fiber filter medium.

Page A-7, 5 lines from the top;

Add the following references to Johnson and Braman, 1975;

"Appel et al., 1984; Walsh et al., 1979, Walsh et al., 1977"

Page A-7, 12 lines from the top;

Add the following reference to Johnson and Braman, 1975;

"Andreae, 1980"

Page A-7, last 2 sentences on the page;

Much of this was mentioned above. Also, instead of stating your opinion I would like to suggest you reference Walsh et al., 1979 and change the sentence to the following;

Based on ambient measurements in marine and continental atmospheres (Walsh et al., 1979) it is believed that the fraction of solid phase organic arsenic compounds is likely to be much less than 20 percent. ... delete the last sentence on the page ...

Page A-8, paragraph 2, sentence 2;

Insert "collected in Tucson, Arizona" after ... "atmospheric particulate matter".

Comments by Dr. Paul A. Solomon (continued)

Page A-8, paragraph 2, sentence 4;

I suggest changing this sentence to the following; "A 16-day ARB study (see appendix C) at a site ... yielded As(III)-to-As(V) ratios from about 0.5 to 2.9 with an average ratio for total particle arsenic (sum of fine and coarse) equal to 1.2."

Page A-8, paragraph 3 and continued on the top of page A-9;

I think the last paragraph in section 1.A.1 is out of place and should be moved to after sentence 3 in the first paragraph of section 1.A.2. Paragraph 1.A.2 then becomes 3 paragraphs.

Page A-8, paragraph 3, sentence 1 (original text);

The two laboratories analyzed which particulate arsenic samples? Perhaps say "Two laboratories analyzed the particulate arsenic samples which were collected by the ARB air toxics monitoring network".

Page A-8, paragraph 3, sentence 2 (original text);

I suggest defining the limit of quantitation. Is it 1, 2, 5, or 10 times the blank and how was the blank determined, i.e., is the blank due to the instruments detection limit or to the amount of arsenic on an unexposed filter.

Page A-8, paragraph 3, sentence 4;

I suggest adding a statement about the relative error or precision of these measurements in this section of the report. This is in addition to your statement on page A-13 where you indicate the precision is $\pm$20 percent.

Page A-11, Table I-1, footnote**

The limit of quantitation usually refers to 10 times the instrument detection limit or 10 times the error of replicate blank measurements. If that is not what you mean, I suggest defining it within the footnote.

Comments by Dr. Paul A. Solomon (continued)

Page A-12, Table I-2, footnote*

How can all values be above 1 ng m^{-3}, yet some values at each site were below 0.4 ng m^{-3}. This footnote is not clear.

Page A-15, last paragraph;

The occurrence of high concentrations at a number of widely separated sites, within a short timeframe may also be due to nothing more than the meteorological conditions which occurred during that sampling period. The ARB should examine available meteorological data to determine if variations in the meteorological conditions could have significantly contributed to the observed high concentrations. I also recommend examining the concentration profile of other species such as particulate nitrate, sulfate, or lead to help understand the processes causing the high concentrations.

Page A-20, 6 lines from the top;

I suggest inserting "or unfavorable meteorology during April in the SFBAAB and April and August in the SoCAB" after the word ... "network".

Page A-22, Figure 1-7, caption;

Insert "Arsenic" after ... "Annual".

Page A-29, paragraph 1, line 8;

I suggest inserting "or unfavorable meteorology" after ... "intermittent sources".

Page A-29, paragraph 2;

What city in the SoCAB was the secondary lead smelter located in? Was the smelter located near the ARB air toxics monitoring site in the City of Industry, referred to in Appendix C of Part A of the DHS report to the ARB on inorganic arsenic?

Page A-35, Table I-6, line beginning with the word cigarettes;

I suggest changing "As(III)/As(V)**" to "arsenic oxides**".

Comments by Dr. Paul A. Solomon (continued)

Page A-35, Table I-6, Footnote **

Add the following reference, "USEPA, 1984".

Page A-40, paragraph 2;

I would like to see references added to support the data suggested in this section.

Page A-51, paragraph 2, line 3;

Results presented by Walsh et al., 1979, indicate that gas phase arsenic species, primarily As_4O_6, undergo rapid condensation onto airborne particles. I suggest that lines 3 and 4 of paragraph 3, page A-51 be changed to: "...gas phase emissions of arsenic may not. However, gas phase measurements 500m from the Tacoma copper smelter indicated rapid condensation of gas phase arsenic onto airborne particulate matter, and therefore, it would be collected by the aerosol sampler."

It should be noted, that this is significant since all Pacific Gas and Electric (PG&E) arsenic monitoring stations (i.e., the GAMP network) are more than 500 m from PG&E geothermal power plants. Therefore, if arsenic is emitted in the gas phase from the power plants it would have been detected by the GAMP monitoring network, and about 95% of the values reported by the GAMP network for arsenic are below 3 ng/m^3.

Page A-52, 12 lines from the top;

Insert the additional information to clearly indicate the meaning of the maximum values reported.

... for Glenbrook (ES&S ...). However, it should be noted that of the 62 data points reported during 1986-1987, at each site, only eight at Anderson Springs and one at Glenbrook were equal to or greater than the detection limit for the measurement of 3 ng As/m^3. Slightly higher ...

Page A-71, Table III-1;

The formula for arsenic acid is wrong. It should be "$H_3AsO_4 \cdot 1/2H_2O$" and not "$AsO_4 \cdot 1/2H_2O$". The latter formula has arsenic in the +8 oxidation state.

Page A-72, paragraph 1 in section B.1., sentence 2;

The word "elemental" should be deleted from the sentence. It misleading and implies that arsenic in the zero oxidation state is being measured.

Page A-72, paragraph 1, sentence 3;

Insert at the end of the sentence "or more likely as the oxyacid or salt of the oxyacid".

Page A-72, paragraph 2, sentence 1;

"A significant extent" should be changed to "some extent".

Based on the data of Walsh et. al. (1979) and Johnson and Braman (1975) the amount of arsenic in the gas phase is probably to low to be of significant effect.

Page A-72, section B.2., sentence 3;

I recommend the sentence read as follows; "Because of arsine's high acute toxicity, anthropogenic emissions of arsine are expected to be small since arsine emissions are strictly regulated and, therefore, should not significantly contribute to overall arsenic exposure."

Without this change the sentence relates acute toxicity directly with emissions.

Page A-73, paragraph 1, sentence 1;

I suggest the following changes; ... "is the primary form of inorganic arsenic expected to be emitted from high temperature industrial sources (Eatough et al., 1979; Germani et al., 1981; Davison et al., 1974)."

Page A-73, paragraph 1, sentence 3;

Insert "at 130C" after the word ... "effluent."

Comments by Dr. Paul A. Solomon (continued)

Page A-73, paragraph 1, sentence 4;

I suggest the following changes; "These results suggest that arsenic, probably As_4O_6 (Eatough et al., 1979; Germani et al., 1981; Davison et al. 1974) is present in the gas phase when emitted from a high temperature source. Calculations by Murray et al. (1974) also suggest an ambient arsenic concentration of about 600 ng/m^3 based on the vapor pressure of pure As_2O_3 at ambient temperatures. These results suggest that appreciable amounts of arsenic (probably As_4O_6; Eatough et. al., 1979) could be present in the gas phase under normal atmospheric conditions."

I think these changes and additions were necessary since you say "under normal atmospheric conditions" in reference to Germani"s work and his measurements were in-stack monitoring at 130C.

Page A-73, paragraph 2, insert before last sentence;

In addition, Walsh et al. (1979) have measured gas and particle phase arsenic in close proximity (500 m) to the Tacoma copper smelter. This source is probably the largest single source of arsenic in the country and most likely emits arsenic in the gas phase primarily as As_4O_6 (As III oxide). Walsh and co-workers observed that greater than 90 percent of the arsenic was in the particle phase and, therefore gas phase arsenic undoubtedly quickly condenses onto existing particles and will not be present to any great extent in the gas phase under normal atmospheric conditions.

Page A-74, last line on the page;

Insert references after the word processes (Germani et al., 1981; Eatough et al., 1979; Davison et al., 1974).

Page A-76, paragraph 2, sentence 5;

The statement (Solomon concluded ...) assumes only one source of arsenic (e.g. copper smelters), if other sources existed then the variation in the ratio may also be due to the different sources. Therefore, add to this sentence either a statement that, "if there is only one source," or "that there may be other sources contributing to the variations in the ratio."

Page A-77, 8 lines from the top;

Delete the phrase "graphite furnace ... (GFASS)." It does not define the entire method employed and is misleading.

Page A-77, paragraph 1, sentence 1;

I would like to suggest the sentence be changed to; "On the average, in both the fine and coarse particle size ranges, the concentrations of As(III) were approximately equal to those measured for As(V) (i.e., an As(III)/As(V) ratio of about 1)."

Page A-77, paragraph 1, sentence 2;

Insert "(sum of fine plus coarse)" after ... "As(III) concentration observed."

Page A-77, paragraph 1, sentence 3;

Insert "observed in the fine particles" after ... the "As(III) concentration."

Page A-77, paragraph 1, sentence 4;

Insert "(about 76 percent)" after ... "on the fine particles."

Also add a sentence at the end of paragraph 1;

These averages assumed that less than values were equal to the detection limit.

Page A-79, lines 5-7;

No measurements were obtained of the organic arsenic compounds, therefore, delete the following phase from the sentence; "most of the arsenic present on airborne particles at the monitoring site is inorganic, and".

Page A-79, paragraph 1, sentence 5;

Delete sentence 5. My method, (Solomon, 1984) would include organic arsenic compounds in the measurement but they would not be speciated except as to valance state. That is, they would have been included with either the As(III) or As(V) concentration measurements.

Comments by Dr. Paul A. Solomon (continued)

Page A-79, paragraph 1, sentence 6;

I would like to suggest the following changes; "Also, about one third of the arsenic +3 or +5 values observed on coarse particles were above the reagent blank ..."

Page A-80, paragraph 1, sentence 2;

Check the year of the Haywood reference, it can not be 1907.

Page A-80, paragraph 1, insert after sentence 3;

Results of Walsh et al., (1979) indicate this conversion occurs relatively quickly.

Page A-80, paragraph 2, sentence 3;

Insert "(USEPA, 1984)" at the end of the sentence.

Page A-82, paragraph 1, line 2;

Insert "(Wood, 1974)" after ... "Figure III-2"

Page A-82, paragraph 1, line 3;

Arsenate is "AsO_4^{3+}". As you have it written, arsenic is in the +8 oxidation state.

Page A-84, reference Haywood, J.K.;

Check the year, 1907 can not be correct.

Reference: The following are additional references which I would like to suggest for inclusion into the DHS draft report to the ARB on inorganic arsenic.

Appel, B. R., Y. Tokiwa, and E. R. Hoffer. 1984. "Efficiency of Filter Sampling for Arsenic in the Atmosphere", Atmospheric Environment, 18, p. 219.

Walsh, P. R., R. A. Duce, and J. L. Fasching. 1977. "Impregnated Filter Sampling for Collection of Volitile Arsenic in the Atmosphere", Environ. Sci. and Technol., 11, p. 163.

Walsh, P. R., R. A. Duce, and J. L. Fasching. 1979. Tropospheric Arsenic Over Marine and Continental Regions", J. of Geophys. Res. 84, p. 1710.

General Editorial Comments

A. I suggest converting all units to the metric system. It is standard practice and allows for an easy comparison between measurements.

B. I suggest being consistent on page usage, either use one side or both sides of the page through out the document, but not both.

LAKE COUNTY AIR QUALITY MANAGEMENT DISTRICT

— OFFICE AND LABORATORY —

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ROBERT L. REYNOLDS
Air Pollution Control Officer
Noise Control Officer

June 6, 1988

Mr. Robert Barham, Chief
Toxics Air Contaminant Identification Branch
Air Resources Board
Attn: Inorganic Arsenic
P.O. Box 2815
Sacramento, CA 95812

Dear Mr. Barham:

The District has reviewed the Preliminary Draft documents pertaining to the Public Exposure to Inorganic Arsenic and the Health Effects of Arsenic Compounds relative to our experience as an emission of geothermal steam at the Geysers Geothermal Development. Several observations and questions should be addressed in the Final Document relative to this source.

1) The Geysers complex consists of 25 operating power plants with two currently under construction and several more under permit consideration or recently permitted (not wells). Each power plant is connected to a steamfield consisting of ten (10) to twenty (20) individual wells and up to sixty (60) as the steam field ages. The difference between power plants and wells as sources needs significant attention.

2) Perhaps the largest source of arsenic is released with unabated steam vented at steam transmission line facilities or at the individual well sites during power plant outages, well rework, cleanout, well construction and testing or during periods of well standby bleed. Steam and particulate is normally vented largely uncontrolled during these operations. As geothermal development has matured, less steam has been vented because of the availability of pipeline facilities to produce wells to existing and operating power plants. Steam exploration and production well drilling precedes power plant construction and is considered a significant source not addressed in the report. At times these can be very significant sources. Uncontrolled steam releases such as that of Thermal #4 (Wild Well) is also a concern as compared to power plant sources.

Steam emissions from well sources are typically at higher temperatures and pressures than those considered using the power plant as a model and thus have a higher potential for emission via the sublimation of arsenic into airborne particulate. Untreated steam venting has not been addressed but was estimated at 5% of total production in 1983. The use of turbine bypasses, improvements in geothermal field controls, automated pipeline supervision and ability to intertie several power plants and steamfields has significantly reduced the need to vent untreated steam from well and transmission line sources.

3) Page A-86. Drift fraction as a function of circulating water flow rate is typically .001% for power plant cooling tower facilities constructed in the past 10 years, but markedly less for older units that have not been upgraded. Arsenic and arsenic compounds are used as a preservative in the wood construction of the cooling towers. A portion of this material enters the circulating water and is removed with the cooling tower sludge.

4) Page A-87. Noncondensible gasses present in geothermal steam is more typically less than 0.5% of condensate mass flow except in several areas of the production field. The noncondensible gas fraction can dramatically change on some wells during standby bleed conditions and appears to increase with time in production. The use of the 0.5% figure appears more appropriate for the calculation (utilized 3.98%) and would be a more accurate estimate of noncondensibles emissions. The dated source of the 3.98% figure is suspect and may have included condenser inleakage. The reference to the tabulation at the bottom of the page should again refer to power plants and not wells.

5) The local Districts, ARB, CEC and the geothermal industry has cooperated in the Geysers Air Monitoring Program (GAMP) which has performed two years of ambient monitoring for arsenic at two populated locations downwind of geothermal development. The data collected by dichotomous sampler and XRF analysis shows impacts of 1-4 ng/M^3 on a monthly average and 1-2 ng/M^3 on a annual basis. The District has also performed limited ambient arsenic monitoring using a PIXIE sampler and analysis which yielded similar results.

Additional data (DWR Bottlerock Determination of Compliance, February 22, 1982) estimates arsenic emissions at 0.002 lb/hr. Source test data at another Lake County power plant established an

emission rate of 0.0022 lb/hr for a steam flow rate of 1.4 million lb/hr of which 97.6% was particulate collected on a 0.45 micron filter. This value is consistent with other power plant arsenic emissions estimates. Bechetel and SAI have performed engineering and test analysis for arsenic emissions from Geysers cooling towers and are a source for additional data.

We appreciate the opportunity to bring these points to your attention and apologize for the belated response in this matter. The District, with the assistance of the CEC, ARB, NSCAPCD and geothermal developers intend to perform additional arsenic ambient monitoring within the geysers area to add to the data collected by previous monitoring programs.

Should you have additional questions in this regard please give us a call at (707) 263-7000. Your attention to this matter is appreciated.

Sincerely,

Robert L. Reynolds

RLK/RLR

cc: M. Tolmasoff

May 5, 1988

Mr. Robert Barham, Chief
Toxic Air Contaminant Identification Branch
Air Resources Board
P.O. Box 2815
Sacramento, CA 95812

RE: INORGANIC ARSENIC

Dear Mr. Barham:

United States Borax & Chemical Corporation wishes to take this opportunity to submit our comments on the preliminary draft report to the Air Resources Board on inorganic arsenic. For convenience, our comments are referenced by page and paragraph wherever possible.

PART A - PUBLIC EXPOSURE TO AIRBORNE INORGANIC ARSENIC IN CALIFORNIA

Page 1, para. 2

While it is certainly true that arsenic has been known to be chronically toxic for many years, it is equally true that the medicinal benefits and use of arsenic has also been well known for an equally long period as can be attested to by its appearance in nearly all western pharmacopeias until very recently. This should be noted to put the discussion in proper perspective.

Page 3, para. 1

Although complex organo-arsenicals in food may be of less toxicological signficance than the inorganic forms, it is suggested that arsenic in the diet should not be so summarily dismissed since the basic forms of arsenic in foods is largely unknown.

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Page 11, Table 1-1

The source of this and the other tables and figures in the reports should be noted if they are adapted from other publications. Without a source there is no way to trace or verify the data.

Page 36, Section 1, Water

Somewhere in this section there needs to be an estimate of the number of people all over California that are exposed to water with levels of arsenic above 50ug/l and also above 100 ug/l and 200ug/l.

Additionally, since only data from wells in the San Joaquin Valley were utilized in this report, it is inappropriate to use these data for developing a general statewide level on the basis of an assumed unique geology.

Page 43, para. 1

This paragraph should be revised to correct the implication that the Tacoma smelter is still operating. It was shut down in 1985. In this light, the status of ASARCO's other plants noted here should also be verified.

Page 63, Section 11

It is stated that "several" industrial activities in California are using arsenic yet only two are apparently active, and at least one of them is a negligible contributor. If such is the case, the need for this section is not clear nor is the appropriateness of singling out a particular company by name.

PART B, HEALTH EFFECTS OF ARSENIC COMPOUNDS

Page 1-1, para. 3

Inasmuch as the occupational exposures were from a copper smelter, it cannot be assumed that the effects noted were caused by exposure to 50 - 500 ug of arsenic alone. The workers would have been exposed to other toxics (e.g. lead) that could cause such effects as well. Additionally, a 4-day exposure during pregnancy should be clarified to indicate which 4 days during the pregnancy that the exposure occurred.

Page 1-3, para. 3

It is suggested that the blanket statement conce smelters and insecticide manufacturers is incorrect. only three (3) copper smelters (Tacoma, Anaconda, Ronnskarverken) has arsenic been strongly linked with cancer. A high mortality risk from lung cancer workers at the El Paso and Canadian smelters has not shown.

Page 1-5, para. 3

The statement is made that DHS is treating the mechani arsenic's carcinogenicity as a non-threshold pro Inasmuch as even EPA has agreed that arsenic is an esse element, there must be a threshold value between essentiality level and the toxic level. The state should be clarified by noting these factors and indic that the only remaining question is how the threshold i quantified.

Page 1-12, Sect. II (A)(2)

The data presented by Enterline et al. (1987) clearly s linear response between urinary arsenic levels (bioavai arsenic) and respiratory cancer, but not between air arsenic levels and respiratory cancer (see pages 9-4 a 5). The report should explain why this impo distinction for risk assessment is not discussed and wh sets of similarly concave airborne arsenic data (Tacon Anaconda) are being "forced to fit" a linear model, r than considering using a "biological marker" model.

Page 1-12, Sect. II(D)

See comment to Page 1-5, para. 3.

Page 1-13, Sect. III (B)(2)

This section appears to be in conflict with page 36 o A which states only data from San Joaquin Valle available.

Page 2-3 et seq, Sects. 2.2 and 2.3

The differences in distribution and metabolism fo various species, particularly those for rats, shou

clearly identified. Lacking such identification, DHS sh note why it is unnecessary.

Page 2-5, para. 2

Why is saturation of the methylation pathway not likel occur at occupational exposure concentrations associ with lung cancer?

Page 2-5, para. 3

The statement; "In a well conducted study, Crece (1977)...". Inasmuch as only one test subject was used what basis does DHS consider this to be a well condu study?

Page 3-1, para. 3

Prior to the work of Liebscher and Smith (1968), Dr. Harding-Barlow showed in 1961 ("Studies on the Trace Ele Content of Human Tissues", PhD Thesis, University of Town, RSA, 1961) that essential elements, such as mangan could show both normal and lognormal distributions depen on a number of variables. This should be considered in conclusions of this paragraph.

Page 4-1, para. 2

The data supporting the statement; "Based on lethal humans are an order of magnitude more sensitive to a arsenic exposure than other animals.", should be prese or the source of the statement referenced.

Page 4-2, para. 2

The report should provide some estimate of the dose leve which the noted effects can occur. Likewise, in the t paragraph on this page, what is the dose range for "on two teaspoonfuls"?

Page 5-5, para. 2

Referring to our comment to Page 1-1, para. 3, other n conductivity studies, where the subjects were not expose probable confounding factors such as lead, should discussed or the paragraph qualified to indicate t factors. This same comment also applies to page 5-5, par and page 6-2, para. 2.

Page 5-6, para. 1

A number of other Taiwanese studies have shown that Blackfoot's disease is not correlated with well-water arsenic levels. An example is: Kuo, T.P. and Chen, M.H. "Follow-up Study of Surgical Treatment of Endemic Spontaneous Grangrene in Tropical Taiwan", Journal of Formosan Medical Association, Vol. 68, pp 275-290, 1969.

Page 5-7, para. 4

The report should state the exposure levels producing the 80% and 36.1% values; otherwise the numbers are meaningless. Likewise, in para. 5 on this page, exposure levels would be helpful.

Page 8-2, para. 2

It is not at all clear why this paragraph is included since it only concerns a study which DHS concludes is not informative. If it is necessary that it remain in the report, it should be clarified to note that the study would also not be informative if the results had been found to be high, which they also could have been, given the vagaries of an inadequate population size.

Page 9-2, para. 1

The negative results from the studies in Lassen County, Oregon and Idaho are mentioned, but no mention is made of the significance of these studies or the results. Why these results are being ignored should be thoroughly discussed since they would appear to lead to conclusions contrary to those implied in the report.

Page 9-10, et al, Sects. 9.2 and 9.3

The confounding factors and synergistic interactions should be considered more systematically. For example, if smoking is synergistic with arsenic exposure, are benzo(a)pyrene, SO2 and particulate matter also synergistic? The data still required to prove or disprove this should be noted. Further, it would appear that if, as stated, occupational exposure to arsenic is almost always accompanied by exposure to other potential carcinogens, there is the possibility that arsenic by itself may be a promoter or co-carcinogen rather than an initiator.

Page 10-3, para. 2

Rat data should not be applied to humans without confirmation in another species.

Page 10-4, Sect. 10.5

As noted previously, EPA has agreed that arsenic is an essential element and therefore must have a threshold level. The reasons for and against a threshold should be discussed.

Page 10-6, Sect. 10.6

The clarity of the report would be enhanced by a listing of the factors co-present with arsenic in studies which lead to tumors in animals. This would be especially helpful since these co-factors also appear to be present in the positive human studies.

Page 10-9, Sect. 10.7

There is no data presented in this section which indicates that arsenic is an initiator rather than a promoter or co-carcinogen. What then is the basis for assuming arsenic is an initiator?

Page 11-2, para. 3

As noted in an earlier comment, the data presented by Enterline at al. (1987) clearly show a linear response between urinary arsenic levels (bioavailable arsenic) and respiratory cancer, but not between airborne arsenic levels and respiratory cancer. The report should state why this important distinction for risk assessment is not discussed and why a "biological marker" model is not considered.

Page 11-4, Sect. 11.1.1

It should be noted that Higgins, et al (1986) states:

> "Arsenic exposures assigned to individual men are certainly tentative and should be considered as broad indicators of exposure. The actual concentration in the exposure estimates should be treated with reserve, as should the exposure/response relationships derived from them." (Higgins, I.T. et al, "Arsenic Exposure

and Respiratory Cancer in a Cohort of 8044 Anaconda Smelter Workers/A 43 Year Follow-up Study", Final report to Chemical Manufacturers Association and Smelter Environmental Research Association, April 1986.)

Page 11-10 et al, Sect. 11.2

As arsenic is an essential element, high (toxic) short term exposures cannot be assumed to be equivalent to low (necessary) long term exposures. Also, arsenic at normal concentrations, is not a cumulative poison since it is rapidly excreted. This section concludes; "The use of a linear extrapolation and cumulative lifetime dose is likely to entail the greatest uncertainty of any of the assumptions used in this risk assessment." If this is so, why is there no consideration given to use of other models; such as a "biological marker" model?

Thank you for the opportunity to review and comment on these documents. We look forward to receiving the final review document. If you require additional information on any of our comments, please call me at 213/251-5615.

Sincerely,

J. C. Paulsen/gw

J. C. Paulsen
Senior Environmental Engineer
Government & Public Affairs

JCP:gw

State of California

Memorandum

To : Mr. Robert Barham, Chief
Toxic Air Contaminant Identification
Branch
Air Resources Board
Attn: Inorganic Arsenic
P.O. Box 2815
Sacramento, CA 95812

Date : April 22, 1988

Place :

From : Department of Food and Agriculture - 1220 N Street, P.O.Box 942981
Sacramento, California 94271-0001

Subject : Draft Report on Inorganic Arsenic

Our staff has examined the report, "Preliminary Draft Report to the Air Resources Board on Inorganic Arsenic", with the following comment:

Arsenic, when used as a wood preservative, is a pesticide. Therefore, the Wood Preservative Section on page A-45 more appropriately fits into the Pesticide Section on page A-46. You may also wish to reference wood preservatives as pesticides on page A-61 in the section entitled "Wood Preservatives".

Thank you for the opportunity to comment on your document.

If you have any questions, please contact David Duncan at (916) 445-7985.

Kathy Brunetti
Ag. Program Supervisor
Environmental Monitoring and
Pest Management, Room A-149
(916) 32408916

cc: Ronald Oshima
Dave Duncan
Bill Lockett

SURNAME

State of California

Memorandum

To : Jim Guthrie
Air Resources Board
1102 Q Street
Sacramento, CA 95814

Date : May 3, 1988

Place :

From : Department of Food and Agriculture -1220 N Street, P. O. Box 942871
Sacramento, California 94271-0001

Subject: Wood Treatment Chemicals Registered As Pesticides

We recently discussed the use of inorganic arsenicals as wood preservatives and whether or not these compounds are registered in California as economic poisons (the legal term for pesticides). I have enclosed two memoranda prepared by our staff discussing pesticidal uses of inorganic arsenicals. As you can see, arsenic pentoxide and arsenic acid are registered by this Department for use as wood preservatives.

If you have any further questions concerning registration of these products in California, please contact, Jerry Campbell, Supervisor of Registration, (916) 322-5130.

Kathy Brunetti
Agricultural Program Supervisor
Environmental Monitoring and
Pest Management, Room A-149
(916) 324-8916

Enclosure

cc: Jerry Campbell

000067

CHRONAME

State of California

Memorandum

: Lyn Hawkins
Pest Management, Analysis &
Planning Program

Date : December 21, 1987

Place : Sacramento

Phone: 4-8916

From : Department of Food and Agriculture—Bill Fabre
Pest Management, Analysis & Planning Program

Subject : Pesticide Information on Inorganic Arsenic

In response to your November 17, 1987 memorandum titled "Pesticide Information for Risk Analysis", I have gathered the following information. I hope it is suitable for the purpose you have in mind.

There are four inorganic arsenical active ingredients registered in California. They are arsenic acid, arsenic pentoxide, arsenic trioxide and sodium arsenite. Tables 1-4 list the registered products which contain these active ingredients, their formulations and any additional active ingredients which are found in these products. There are no Special Local Needs (Section 24-C) registrations or Emergency Exemptions (Section 18 registrations) for products containing inorganic arsenicals. The inorganic arsenicals are regulated as restricted materials but no permit is required for industrial or home use. Therefore, the Pesticide Use Report does not provide any information on arsenic acid, arsenic pentoxide or arsenic trioxide.

Attached is a printout summarizing sodium arsenite use which is based on the 1985 pesticide use report tapes. This active ingredient is only registered for use on grapes.

Attachments

000085

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SO-106

Table 1 Arsenic Acid Products

Product Name	Formulation	Other Active Ingredients
Chemonite Part A	emulsifiable concentrates	----------
Arsenic Acid 75%	soluble powders	----------
Oxcel Wood Preservative	liquids	chromic acid cupric oxide

Table 2 Arsenic Pentoxide Products

Wolmanac Concentrate 50/	liquids	chromic acid cupric oxide
Wood Treating Chemicals CCA Type C Concentrate 50% Wood Preservative	granular (tablets)	chromic acid cupric oxide
Koppers CCA Type B Wood Preservative	liquids	chromic acid cupric oxide
Osmose K-33-C (72%)	gels, pastes	copper oxide chromic acid
Osmose Special K-33 Preservative	liquds	copper oxide chromic acid
Osmose K-33-C (50%)	liquids	copper oxide chromic acid

Table 3 Arsenic Trioxide Products

Grant's Ant Control	impregnated materials	----------
Ant-Jex Redwood Ant Stakes	granular (tablets)	----------

Table 4 Sodium Arsenite Products

Sodium Arsenite Solution No. 6	liquids	----------
Sodium Arsenite Solution No. 4	liqids	----------

1985 PESTICIDE USE SUMMARY

COUNTY	MONTH	COMMODITY	POUNDS A. I.	ACRES
FRESNO	01	2503 : grape	618.8736	58.00
FRESNO	02	2503	8202.0286	1122.00
FRESNO	03	2503	5044.9923	682.50
FRESNO	12	2503	19.5023	5.00
KERN	01	2503	1638.1958	140.00
KERN	02	2503	1508.1803	190.00
KERN	03	2503	1879.1576	292.00
MADERA	02	2503	6531.9806	1016.50
MADERA	03	2503	468.0559	100.00
MARIN	01	2503	156.0186	40.00
MARIN	03	2503	156.0200	40.00
MENDOCI	01	2503	331.5395	85.00
MENDOCI	02	2503	46.8055	12.00
MERCED	02	2503	6557.9843	841.00
SAN DIE	03	2503	36.4043	8.50
SAN JOA	01	2503	629.2749	198.00
SAN JOA	02	2503	18536.9615	3137.00
SAN JOA	03	2503	26970.4163	3793.50
SAN JOA	05	2503	234.0279	30.00
SAN JOA	11	2503	15.6018	4.00
SONOMA	01	2503	46.8055	12.00
SONOMA	02	2503	468.0559	60.00
SONOMA	03	2503	447.2534	115.00
STANISL	01	2503	169.0200	60.00
STANISL	02	2503	405.6482	77.00
STANISL	03	2503	260.0310	40.00
TRINITY	02	2503	234.0279	60.00
TULARE	02	2503	6823.2154	816.00
TULARE	03	2503	2108.8515	788.00
TULARE	05	2503	312.0373	40.00

NUMBER OF RECORDS IN FILE => 426
NUMBER OF COMBINATIONS SUMMED => 30
TOTAL POUNDS => 90856.9677
TOTAL ACRES => 13863.00

130000

Memorandum

To : Lyn Hakwins
Program Manager
Pest Management, Analysis &
Planning Program

Date : December 15, 1987

Place : Sacramento

From : Department of Food and Agriculture — Sewell Simmons, Pest Management Specialist
Pest Management, Analysis & Planning Prog.

Subject : Inorganic Arsenicals Use Characterization

Section 6356 Title 3, of the California Administrative Code (CAC) lists the only registered uses of inorganic arsenicals permitted in California:

1. Ant syrup or paste (packaged in applicator devices or bait containers that prevent easy pouring or squeezing of the contents from the container).
2. Industrial wood treatment.
3. Grapes (dead arm and measle control).

Arsenic trioxide is an active ingredient in two pesticide products. Both products are ant poisons which are packaged in ready-to-use bait containers for home use. All of the six currently registered pesticide products which contain arsenic pentoxide are used as preservatives in the manufacture of treated wood products. Arsenic acid is an active ingredient in two products which are used in the manufacture of treated wood products. When used as wood preservatives, the inorganic arsenicals are sometimes mixed with other metal salts and acids, and wood products are dipped or pressure treated with the mixture.

Sodium arsenite is an active ingredient in two pesticide products. Both are registered for use on grapes only and are normally applied by brush and ground spray once a year during dormancy. Maximum application rate is 9 lbs/acre.

Attached is exposure information for inorganic arsenicals from EPA's Position Document 4.

Attachment

000092

SURNAME					
SO-108	Simmons				

The Agency received new information on exposure to the three wood preservatives which convinced the Agency to alter the assumptions made in the PD 2/3. The bases for the changes in exposure assumptions are presented in detail below. The changes are summarized in Tables 4 & 5 (Inorganic Arsenicals) and in Table 6 (Pentachlorophenol and its sodium salt). There is no table for creosote, as there was only one change.

1. INORGANIC ARSENICALS

a. AWPI (#36:30000/28C) stated that the air level of arsenic level to which workers may be exposed over an 8 hour period in wood treatment plants would not be as high the 0.07 mg/m^3 level estimated by the Agency in the PD 2/3. The 0.07 mg/m^3 estimate represented a time weighed average (TWA) found by the California Health Department (1979) in a survey of an arsenical treatment plant. The AWPI comment demonstrated that 0.07 mg/m^3 was based on the air level near a mixing area therefore overestimated the worker exposure. The Agency agrees and, in addition, the Agency has concluded that this plant was atypical because (1) its operations involved the mixing of powder formulations which are not widely used today, and (2) the formulations were mixed in an open area, not a closed system. AWPI stated that the level of 0.01 mg/m^3, would be more appropriate to use for purposes of estimating exposure. AWPI also submitted data (#36C:30000/28C) on urine level/airborne arsenic correlations which have convinced the Agency that 0.01 mg/m^3 is a more reasonable estimate (Day, Feb. 28, 1984).

Because of the above considerations the Agency has adopted the estimate of 10 ug/m^3 of arsenic in the ambient air for calculating exposure to applicators at arsenic treatment plants. The exposure estimates in Appendix B reflect this decision.

b. In the PD 2/3, the Agency assumed that respirators would provide 90% protection against inhalation exposure to the inorganic arsenicals. OSHA has found that "high efficiency filter" respirators provide 99% protection (29 CFR 1910.1018, Table 1). Because the Agency will require this type respirator if arsenic levels are either unknown or exceed 10 ug/m^3 in inorganic arsenical pressure treatment plants (see Section VI.C.1.), it will be assumed, as OSHA states, that the inhalation exposure is reduced by 99% instead of 90%. The inhalation exposure and exposure estimates with applicators using respirators, as presented throughout this PD 4, reflect the 99% reduction.

c. In the PD 2/3, the Agency assumed 100% inhalation absorption of arsenic from arsenic-laden sawdust, because no data were available to indicate otherwise. The Agency has revised the estimated inhalation absorption rates for sawdust containing inorganic arsenicals from 100% (PD 2/3) to 27% for chromated copper arsenate (CCA) and from 100% (PD 2/3) to 65% for ammoniacal copper arsenate (ACA) (Zendzian, Rebuttal Analysis, 1982; Zendzian, January 25, 1984; and Rispin, April 18, 1984). The revisions are based on an unpublished study by Peoples (1979) (AWPI Rebuttal #36:30000/28C) in which two beagle dogs were fed 2.0 grams of CCA-treated wood or 2.0 grams of ACA-treated sawdust for eight days. Neither dog showed signs of arsenic toxicity.

Table 4

Summary of Exposure Assumptions for the Inorganic Arsenicals for the PD 2/3 and PD 4*

Exposure Situations	PD 2/3 Assumption	PD 4 Assumption
a. Ambient arsenic air levels at treatment plants	0.07 mg/m^3	0.01 mg/m^3
b. Percent protection by high efficiency filter respirators	90%	99%
c. Inhalation absorption rates for CCA-and for ACA-laden sawdust; arsenic-laden dust	100% 100% 100%	27% 65% 100%
d. Dermal absorption rate for arsenic from arsenic-laden sawdust (CCA or ACA)	0.01%	Negligible
e. Dermal absorption rate for inorganic arsenic for: -liquid formulation -dry arsenic-laden dust	 0.1% 0.01%	 0.1% 0.1%
f. Dermal exposure to FCAP when emptying bags of FCAP powder	up to 10 grams	0.0038 to 0.142 mg/hr.
g. Inhalation absorbtion for sawing arsenic treated wood	0.36 mg/m^3	0.024 mg/m^3
h. Arsenic air levels in homes constructed with arsenic treated wood	0.031 ug/m^3	0.004 ug/m^3

*See text for the bases of the exposure assumptions

indicated that in the CCA-treated dog, 97.6 percent of the dose was excreted, with 27% of that amount excreted in the urine. The gastrointestinal absorption was thus calculated to be approximately 27% (i.e., 27% of 97.6%). In the ACA-treated dog, 80.7% of the dose was excreted, with 82% of that excreted in the urine. The gastrointestinal absorption was calculated to be approximately 65% (82.% of 80.7%).

Lacking other data, the Agency assumes that absorption of arsenic from arsenic-laden sawdust from inhalation exposure is the equivalent to absorption by the oral route (Rispin, April 18, 1984). The Agency assumes that 10% of the arsenic-laden sawdust will be respirable and that the remaining non-respirable dust will enter the gastrointestinal tract (PD 2/3, p. 213). The material would be deposited in the bronchial passageways, brought up by ciliary action and swallowed; absorption would then follow from the digestive tract (Zendzian, Rebuttal Analysis, 1982). Based upon the results of the study, the Agency has lowered the estimate of inhalation absorption rates for arsenic from sawdust containing arsenic, accordingly. Even though only two dogs were studied, the Agency determined that these data would be used to calculate an estimate for inhalation absorption rates for arsenic-laden sawdust in the absence of other existing data.

The Agency continues to assume, as in the PD 2/3 (pp. 203 and 210), that the inhalation and gastrointestinal absorption rate of arsenic-laden dust found in the ambient air at arsenic treatment plants or in homes constructed with All-Weather-Wood-Foundations is 100%, since the Agency lacks data that indicate otherwise (Rispin, April 18, 1984).

d. The Agency assumed in the PD 2/3 that the dermal absorption of arsenic from arsenic-laden sawdust was 0.01% (PD 2/3, pp. 199 and 209). A dermal absorption study by Peoples (unpublished, July 1979) submitted by AWPI (#36:30000/28C) has convinced the Agency that the dermal absorption of arsenic from arsenic-laden sawdust or dry arsenic-treated wood is negligible (Zendzian, Rebuttal Analysis, 1982; and Zendzian, April 16, 1982).

An area of skin on the back of each of two dogs was closely clipped. Urine from each dog was collected daily during the control (2 days) and treatment periods and was analyzed for arsenate (As V), arsenite (As III), methyl arsenate (MA) and dimethyl arsenate (DMA).

After the two-day control period, one dog had 1.5 gm fine southern pine sawdust from wood treated with CCA-C spread on a pad which was applied for two days in intimate contact to the skin with a plastic bandage. The sawdust contained 3.0% pentavalent arsenic.

After the-two day control period the second dog had 1.5 gm of ACA treated Douglas fir sawdust containing 6.7% arsenate applied in the same manner for three days.

No evidence of arsenic absorption was seen with either dog. Therefore, the Agency assumes there is negligible dermal absorption of arsenic from arsenic-laden sawdust or dry treated wood. The exposure estimates presented in this PD 4 reflect this change.

e. The Agency assumed (PD 2/3, p. 195) that the dermal absorption of inorganic arsenic in aqueous solution was 0.1% and that the dermal absorption from skin contact with dry arsenic-laden dust was 0.01%.

The Agency has revised the assumption for dermal absorption of inorganic arsenic from arsenic-laden dust from 0.01% to 0.1% based on a study by Datkizwicz (1977) which showed the upper limit for dermal absorption of arsenic from aqueous solutions of sodium arsenate was 0.1% (Zendzian, 1980). The dry arsenic-laden dust could become wet with perspiration and thus have a dermal absorption equivalent to that of arsenic in an aqueous solution. The exposure estimates summarized in Appendix C of this document reflect the assumption that dry arsenic-laden dust found in such settings as treatment plants or homes has a dermal absorption rate of 0.1% (Zendzian, April 14, 1982). The dermal absorption for inorganic arsenic in aqueous solution remains 0.1% (Rispin, April 18, 1984), as assumed in the PD 2/3 and is also based on studies by Datkizwicz (1970).

f. Regarding the emptying of bags of powder Fluor Chrome Arsenic Phenol (FCAP), the Agency estimated in the PD 1 and PD 2/3 that applicators would be dermally exposed to up to 10.0 grams of the dust concentrate. This estimate was not based on any actual exposure data. There are, however, exposure studies in which dermal exposure was measured during formulation and bagging operations with pesticide powders and dusts. (Comer et al., 1975; Jegier, 1964; and Wolfe et al., 1978). In the absence of data on FCAP, the Agency believes that the data from the cited studies can be used to estimate potential dermal exposure (Table 5). Assuming a maximum dermal absorption of 0.1% and 9.59% arsenic in FCAP, the Agency estimates the dermal exposure for FCAP during bag emptying to range from 0.0038 to 0.142 mg/hr. The Agency assumes bag emptying occurs one hour per day during an 8-hour work shift (Rispin, April 18, 1984). The Agency continues to assume, as in the PD 2/3, that the inhalation and gastrointestinal rate of absorption for water soluble salts of inorganic arsenic is 100%; the Agency has no data to indicate otherwise (Rispin, April 18, 1984).

g. The Agency had estimated the air concentration of arsenic while sawing, nailing or fabricating with arsenic treated wood to be 0.36 mg/m^3, (PD 2/3, p. 199). Data from a study at the University of Minnesota submitted by AWPI (#36C:30000/28C) convinced the Agency that a more reasonable estimate is 0.024 mg/m^3, the highest value in a Time-Weighted -Average (TWA). The exposure and risk estimates for sawing arsenic-treated wood in this PD 4 reflect this modification. However, the Agency continues to assume as in the PD 2/3 (p. 208) that 10% of the arsenic-laden sawdust particides will be respirable and that 90% is non-respirable but is deposited in the gastro-intestinal tract (Rispin, April 18, 1984). As discussed above, 27% CCA-laden sawdust and 65% ACA-laden sawdust inhaled or swallowed will be absorbed by the body (Zendzian, Rebuttable Analysis, 1982).

h. The Agency had estimated (PD 2/3, p. 186) the air concentration of arsenic at 0.031 ug/m^3 in homes with All-Weather Wood Foundations. Data

[illegible] by Koppers (Nov. 19, 1985) has convinced the Agency that a more realistic estimate for homes constructed with arsenic pressure-treated wood is an upper limit of 0.004 ug/m^3. The highest net increase over "blank" controls was 0.002 ug/m^3. The oncogenic risk estimation for people living in such homes reflects this change in exposure estimation, i.e. 0.004 ug/m^3 instead of 0.031 ug/m^3.

TABLE 5

Dermal Exposure (mg/hr)[a] During Pesticide Formulation

	Mean	Range	Dermal Estimate for Arsenic in FCAP
Mixing and bagging of 4-5% carbaryl dust[c]:	73.9	0.8-1209	142
Formulating 25% Guthion wettable powder[d]:	10.1	4.9-20.9	3.8
Formulating disulfoton as 0.5% dry mix fertilizer[e]:	2.0	0.1-10.5	38

a. Assumes workers were wearing short-sleeved shirts, no gloves or hats, and that covered areas of the body were protected from exposure.

b. Assumes worker is handling bags of (FCAP) containing 9.59% arsenic as metal.

c. From Comer et al. (1975).

d. From Jegier (1964).

e. From Wolfe et al., (1978).

II.

Air Resources Board Staff Responses to Summarized Comments on the Preliminary Draft Part A

II.

Air Resources Board Staff Responses to Summarized Comments on the April 1988 Preliminary Draft Part A

A) Silicon Valley Toxic Coalition, April 7, 1988

1) **Comment:** The information regarding the semiconductor industry is out of date and inadequate. On page A-61 of the preliminary draft, Table II-3 relies upon a 1981 study done by CDIR using data from 1979 that pertains to only 23 companies.

Response: Information from the CDIR study was used in the general discussion about the semiconductor industry and was not used to make any emission estimates. No emission estimates were given in the report for this industry because there was insufficient information to quantify the estimate.

2) **Comment:** EPA conducted its Integrated Environmental Management Program (IEMP) in Santa Clara County in which it was discovered that many semiconductor companies do not bother to scrub for arsine or use emission controls because it is expensive and traditional controls are not very effective. Most of those firms that do have controls believe that they are only about 25% efficient.

Response: In 1984, the BAAQMD conducted source tests at several semiconductor facilities in its jurisdiction and did not detect any arsine in the stacks (with a detection limit of 117.7 ug/m^3). These results represent data collected at the exit of in-use scrubbers (BAAQMD, 1987). Because there are no data about the arsine at the inlet of these scrubbers, we cannot estimate their effectiveness. Also, there are no available data on the efficiency of the scrubbers used at semiconductor facilities.

B) CalMat Company, April 28, 1988

1) **Comment:** Data on actual As emissions from Portland cement kilns in California are not available to CalMat. It is impossible to separately measure kiln stack As emission from coal combustion and from the cement clinker raw materials. Cement kiln As emissions related to coal combustion should be treated in the same section as cement manufacturing. This would avoid double counting and would be technically valid.

Response: While it is possible to estimate arsenic emissions from the cement clinker raw material and from the coal combustion associated with the cement production process, in our revised draft report, arsenic emissions from coal combustion associated with the cement production process will be estimated in the cement production category instead of the fuel combustion category.

2) **Comment:** The preliminary report stated that in 1984 approximately 3,030 tons of PM were emitted from California cement manufacturing excluding emissions from fuels. It is difficult to understand how the emissions from fuels could have been distinguished and excluded from the total PM emissions.

Response: Please see our response to the previous comment.

3) **Comment:** There are three types of PM emitted from traditional cement manufacturing point sources with respect to potential trace metallic elements:

1. Raw material preparation (primarily crushing, grinding, and homogenizing),

2. Calcining and clinkering (rotary kiln emissions which include coal combustion), and

3. Cement preparation (clinker cooling, finish grinding, and distribution).

Each of these types of PM will have a significantly different average trace concentration of As and each production process will have a substantially different average PM emissions rate for each of the California cement plants. Average concentrations will change as the fuel and raw materials change, which is common. To make even the roughest estimate of As emissions from cement manufacturing, three emissions factors (corresponding to each type of PM) are required. The total PM emissions also would have to be allocated among the production processes according to the type of PM emitted.

Response: We agree with CalMat that there are three general types of PM emitted from cement manufacturing point sources and that each of the PM types will have a different average trace element concentration of arsenic. At this time, we only have data to estimate arsenic emissions from the kilning process. Data on individual arsenic emission factors for the other two types of PM emissions are not available. However, it is important to note that raw material preparation and cement preparation processes are sources of arsenic emissions. These sources may be significant because most of them are not equipped with any control devices.

4) **Comment:** With respect to the rotary kiln emissions alone (calcining and clinkering, which would include coal combustion), use of the average As concentration in kiln baghouse dust to determine an emissions factor may be technically valid. However, the average As concentration must be weighted according to 1984 clinker production by each California plant, not the arithmetic average of USBM analyses of California kiln dusts (ARB, 1986e).

Response: Regarding the weighted average arsenic concentration in cement kiln dust, we have access to the sample identification of California cement kiln dust, but not the individual clinker production associated with these samples. Therefore, we changed the report to include a range of arsenic concentrations in California cement kiln dust which was used to estimate arsenic emissions.

5) **Comment:** In previous CalMat comments on the potential cement manufacturing cadmium emissions (Part C, Technical Support Document, Report to the Air Resources Board on Cadmium, December 1986), it was calculated that the maximum 1981 total PM emissions from all California rotary kilns was 1,855 tons (1981 total cement production was 7.9 million tons). Using the 1984 cement production of 8.7 million tons, total California PM emissions would be 2,040 tons. Again, the total potential kiln As emissions, which includes coal combustion, would be based upon this 2,040 tons of PM and the weighted average As concentration in cement kiln dust.

Response: Regarding the amount of PM emitted from cement manufacturing processes, the ARB Emission Data System (EDS) shows the PM emissions from the eleven cement manufacturers in the State in 1985 as follows:

a. Raw material preparation (primary crushing, grinding, and homogenizing): 2,780 tons,

b. Calcining and clinkering (including fuel combustion): 1,490 tons, and

c. Cement preparation (clinker cooling, finish grinding, and distribution): 2,250 tons.

Note that the PM emissions from the 1985 inventory for calcining and clinkering processes (1,490 tons) is only 73% of CalMat's estimate (2,040 tons) for 1984. These estimates are different because the ARB data represent actual test data while CalMat's data were calculated based on the PM standard for rotary kilns and 1984 cement production. We use the ARB's PM emission estimate to calculate arsenic emissions for the cement production category in the revised report.

Of the three PM sources listed above for cement plants, we have an arsenic emission factor only for the calcining and clinkering process. Therefore, arsenic emissions from the other two major point sources, raw

material and cement preparations, have not been estimated. We'll estimate arsenic emissions for these sources when data become available.

C) Fox, Weinberg, and Bennett for Quemetco, May 14, 1988

1) **Comment:** A secondary lead smelter is a facility within Standard Industrial Classification (SIC) Code 3341. According to the United States Environmental Protection Agency (EPA), there are 28 facilities located throughout the United States properly included in SIC Code 3341. See "The Impacts of Lead Industry Economics and Hazardous Waste Regulations on Lead-Acid Battery Recycling: Revision and Update," USEPA (1987). According to this EPA report, there are three secondary lead smelters located in the western part of the United States, each of which is located in California. Two of these secondary lead smelters are located in the South Coast Air Basin. The facility located in the City of Industry, the only source monitored by ARB for purposes of the draft report, is the smaller of the two lead smelters.

Response: We agree that the secondary lead smelters are included in SIC 3341. The ARB staff has reviewed "The Impacts of Lead Industry Economics and Hazardous Waste Regulations on Lead-Acid Battery Recycling: Revision and Update" report. This report only considered lead-acid batteries as the primary source of secondary lead. Thus only secondary lead smelters in California which use lead-acid batteries as feed materials were included. Other sources of secondary lead were not documented in this report.

Based on the information from the California Air Pollution Control Districts and from the 1988 survey conducted by the ARB, four secondary lead smelters were operated in California during 1987: three of which are in the South Coast Air Basin (ARB, 1988). Also, there is no difference in the amount of material processed by the two largest secondary lead smelters including Quemetco in the City of Industry. Thus, Quemetco is not considered to be a small secondary lead smelter.

2) **Comment:** A fundamental problem underlying Part A of the draft report is ARB's failure to define the term "secondary lead smelting". On page A-2 the draft report correctly states that secondary lead smelting is one of four major sources of inorganic arsenic emissions in California. RSR believes ARB meant to say that industrial operations involving lead processing, including lead smelting, are a major source of inorganic arsenic emissions. ARB's failure to distinguish properly between secondary smelting activities and lead processing activities leads to the erroneous inference that secondary lead smelters alone are among the largest contributors of inorganic emissions in the State of California.

RSR requests that ARB correct the draft report to read, where appropriate, that there are three secondary lead facilities in

California, not 30 as stated repeatedly throughout the draft report, and not 18 as stated on page A-49, Table II-2.

Response: We agree that emissions from the lead processing activities other than lead smelting may be large in other parts of the United States; however, in California they are relatively small according to the ARB survey conducted in 1988. The staff believes that secondary lead smelting is one of the major sources of inorganic arsenic emissions in California. In the revised report (A-41), the staff clarify the distinctions between secondary lead smelting and other lead processing activities. Also, the staff revised the number of operating secondary lead smelters in 1987 based on data from the 1988 ARB survey. Please note that the original number reported in the draft report was for inventory year 1981 or 1984.

3) **Comment:** ARB has improperly excluded other sources of inorganic arsenic emissions from the analysis. According to the draft report, page A-29, there are six companies within a five-mile radius performing different types of lead processing activities which could be potential arsenic sources. Without knowing more about these other potential arsenic sources, RSR cannot determine whether they are small companies or small sources. If any is not a small source, its omission from the data base would be a serious flaw, and ARB's preliminary findings regarding lead processing facilities would be arbitrary. To correct this deficiency, RSR recommends that ARB do the following: (1) identify all potential sources of inorganic arsenic emissions in the South Coast Air Basin, (2) monitor emissions from these sources, and, (3) revise the draft report findings, where appropriate, by properly incorporating the new emissions data into the ARB analysis.

Response: In the revised draft report, staff incorporated updated information including the 1987 inorganic arsenic emission estimate for secondary lead smelters. These estimates were also used in our modeling study.

4) **Comment:** ARB's reliance on the Radian Study is misplaced. On page A-33 of the draft report the ARB states that emission rates obtained from a report prepared by Radian Corporation were used to estimate the annual average impacts of arsenic emissions from the smelter on public exposure. The Radian Study at issue is entitled "Control of Arsenic Emissions from the Secondary Lead Smelting Industry - Technical Document" (May 7, 1985). The Radian Study did not include actual emission data from the secondary lead smelter monitored. Indeed, no emission data from any secondary lead smelter located in California is included in the Radian Study.

The ARB's inappropriate use of Radian Study emission estimates to predict annual ambient arsenic concentrations (700 ng/m^3) is highlighted by the inconsistency of that prediction with actual results of two ambient air studies conducted by the ARB at the monitored facility in

1986 (approximately 60 ng/m^3 predicted annual average) and 1987 (approximately 20 ng/m^3 highest monthly average concentration). Further, the source emission inputs from the Radian Study used by ARB for modeling of the smelter facility (at least 138.6 lbs. per year) are inconsistent with results from an actual source test at the monitored facility conducted by the SAI Corporation in 1981 (8 - 32 lbs. per year). To address this problem RSR recommends that ARB seek to obtain actual emission data from all potential sources of inorganic arsenic emissions located in the South Coast Air Basin.

Response: The estimates from the SAI and the Radian studies, and the differences between these two studies, were discussed in the preliminary draft report. The ARB staff also expressed concern about the Radian estimates (page A-30 to A-33). However, the SAI report is very limited in terms of what was tested. Only one stack was tested and no process fugitive emissions were included. Therefore, to be conservative, the ARB staff used the Radian estimates to predict the ambient arsenic concentration in the vicinity of the smelter. We no longer use this report because we have more current data derived from a 1988/1989 study of the facility.

The ARB staff recognized that the Radian estimate may not represent the actual situations of the modeling facility, therefore, in the revised draft report, the ARB staff uses data from the 1988 source test conducted by the South Coast Air Quality Management District (SCAQMD). These data are considered to be reliable and represent up-to-date information from secondary lead smelters.

Emissions data for every facility emitting inorganic arsenic in the SoCAB is not available. This information is not necessary for the identification phase, but will become more important in the control (risk management) phase.

D) GEO Operator Corporation, May 9, 1988

1) **Comment:** On pages A-50 and A-51, the draft report bases upper bound arsenic emissions on the assumption that arsenic trioxide, extracted from condensers at its maximum equilibrium vapor pressure, plus arsenic from cooling-tower drift is emitted into the atmosphere. GEOOC's chemical measurements indicate that arsenic partitions into the steam condensate (liquid phase) at the power plant inlet and most probably into the condenser as well. Thus power plant emissions are most likely limited to cooling-tower drift. The small amount of arsenic which might remain volatile in the condenser is most likely removed from non-condensible gases by the Stretford system before the gases are emitted to the atmosphere.

Response: Attempts to perform a mass balance for arsenic have provided inconclusive results. Because of the lack of complete information on other routes of arsenic effluence at geothermal plants, the worst-case assumption that all arsenic contained in the geothermal steam is emitted into the atmosphere is used. We recognize that actual emissions may be lower; however, arsenic loading measured in the condensed steam may also under-represent the actual concentrations of arsenic in the steam due to incomplete condensation of the arsenic or escape of soluble gas-phase arsenic that the particulate matter sampling devices will not detect.

In addition to power plant emissions, the current version of the report identifies the steam emissions from steam exploration, development, management, and transport of steam to the power plants as sources of unmitigated arsenic emissions. These types of emissions are not routed through pollution control devices that may condense or capture arsenic before it is released to the atmosphere, and are estimated to be responsible for a large portion of the inorganic arsenic emissions.

E) Freeport-McMoRan Resource Partners, May 9, 1988

1) **Comment:** On page A-50, the reference to 27 wells in operation as of December 1985 appears to be in error. The total number of wells in the Geysers Steam Field is approximately 400.

Response: The revised report uses information received in February of 1989 which indicates that California has a total of 47 geothermal power plants. In the case of dry steam-driven power plants, each plant may require from as few as 5 to as many as 60 wells over the life of the plant to provide a constant supply of steam.

2) **Comment:** On page A-51, the statement that very little water is reinjected during the summer does not reflect the facts. FMRP/GCC experience indicates that about 25% less condensate is injected in the summer than in the winter.

Response: Conflicting information exists regarding the amount of water reinjected during the summer. ARB staff believe that very little condensate is reinjected in the summer because most is used for cooling water makeup.

3) **Comment:** On page A-52, there appears to be confusion between wells and power plants. Power plants are certified; wells are not certified.

Response: We have revised the document accordingly.

F) Pacific Gas and Electric, October 20, 1987

1) **Comment:** The ARB draft report calculates arsenic emissions from geothermal power plants as though all the arsenic in the incoming steam is emitted. PG&E does not believe that significant amounts of arsenic are emitted as vapor at the Geysers. Traditional drift calculations use the guaranteed maximum cooling tower drift rate, the average circulating water arsenic concentration, and the designed full load circulating water flow rate. These calculations conservatively estimate annual arsenic emissions. The maximum calculable drift emissions exceed the likely actual drift emissions by more than enough to cover any potential vapor emissions. This idea is supported by tests failing to detect arsenic in non-condensible gases at a 3 ppb detection level.

Response: The geothermal steam section of the preliminary draft has been revised so that it does not rely on drift calculations to demonstrate that inorganic arsenic is being emitted from the use of geothermal steam. Also, we have modified the document so that it does not identify power plant steam emissions as the only source of inorganic arsenic; we recognize that steam production and steam transport are unmitigated sources of gas and particle-phase inorganic arsenic emissions and are contributing to the arsenic concentrations detected by the Geothermal Air Monitoring Program (GAMP). Staff believe that geothermal steam contains uncondensed inorganic arsenic, and that this arsenic can be undetected during monitoring and analysis.

Data derived from the GAMP has demonstrated that The Geysers area is being impacted with arsenic from the steam field operations. We estimate that arsenic emissions from geothermal steam use in the KGRA (development, supply, use, and disposal) were 2.7 tons in 1988. We recognize a need to gain more information on the emission routes and forms of arsenic emitted during geothermal steam field operations since these have not all been identified or quantified. Additional information on inorganic arsenic emission rates will be necessary for the risk management phase but are not as important in the identification phase.

G) Ted Holcombe for Pacific Gas and Electric, October 20, 1987

1) **Comment:** The Part A "Introduction and Summary" should be corrected to clearly state that drinking water exposures are typically 100 to 400 times higher than inhalation exposures.

Response: The purpose of the Part A report on inorganic arsenic is to explain and document public exposure to airborne inorganic arsenic. The other routes of exposure are mentioned in the report to inform the reader that there are other ways that they may be exposed to inorganic arsenic.

2) **Comment:** The discussion of dietary arsenic exposures in Part A appears to contradict the discussion in Part B. The Part A discussion should be corrected and expanded to address the following:

a. The likelihood that some portion of dietary exposures might be inorganic.

b. Data indicating that organic arsenic could be converted in the body to cause exposures similar to those caused by inorganic arsenic.

c. The fact that equivalent inorganic exposures from dietary exposures are likely to be at least 20 to 100 times higher than typical inhalation exposures.

Response: a) The draft version of the report informs the reader that arsenic in foods is generally in the form of an organo-arsenical rather than an inorganic form. The amount of information regarding arsenic species in foods is limited at this time.

b) It is known that arsenic forms can be converted in the body. This is addressed in Part B's Section 2.3.1. Detoxification.

c) The diet and sources of the foods consumed by the "average" Californian varies to a high degree, so no attempt at dietary arsenic exposure estimates have been made by the staff of the ARB.

3) **Comment:** The summary should acknowledge that ambient inhalation exposures on the order of 2 ng/m^3 are probably insignificant, and should not dwell upon such exposures. The extensive and alarmist discussion of the 1.1 to 3.5 ng/m^3 exposures on pages A-3 through A-5 should be shortened and placed in perspective.

Response: The purpose of Part A is to present data that demonstrates public exposure to airborne inorganic arsenic. The DHS has estimated that a lifetime exposure to 2.2 ng arsenic/m^3 will result in 5 to 7 excess cancer deaths per million.

4) **Comment:** 1) The references to "hot spot" exposures should clearly identify the large sources so that the public will not confuse large fossil-fueled power plants with smelters. 2) The basis for ARB's conjecture that large gas or oil fired power plants cause average annual impacts in the 100 ng/cubic meter range should be presented in the report. 3) It should be made clear that results from exposure studies performed on one or more specific smelters do not necessarily reflect exposures from all smelters. 4) The hot spot exposure discussion should

acknowledge that drinking water exposures would be greater than hot spot exposures.

Response: 1) The "hot spot" discussion in the revised version of the report explains that stationary sources with airborne inorganic arsenic emissions are capable of creating high localized concentrations of inorganic arsenic. It is the quantity of arsenic emitted from a facility that may qualify it as a hot spot, not the physical size of the facility. Our hot spot discussion focuses on the ARB study of a secondary lead smelter.

2) The statement that large gas or oil fired power plants cause annual impacts in the 100 ng/m^3 range is not in the report.

3) The revised report clarifies this point.

4) Our definition of a hot spot does not include other routes of exposure. The purpose of Part A is to present public exposure to airborne emissions of inorganic arsenic.

5) **Comment:** Modeled concentrations for the hot spot source were ten times higher than measured concentrations. It should be acknowledged that overestimation by the dispersion model might significantly contribute to this difference.

Response: The preliminary draft version of the report has been modified as a result of recent source testing and modeling. The latest modeling (1989) was based on a 1988 source test of the facility. The data developed by the modeling study estimates concentrations below those demonstrated in the 1986 monitoring study.

6) **Comment:** In Table II-2, the geothermal steam utilities emission estimate should not be referenced to PG&E. Appropriate references to PG&E data can be made more properly on pages A-50 through A-52 or pages A-86 through A-87.

Response: We now reference the ARB and the Geothermal Air Monitoring Program (GAMP) in Table II-2. Additional references from other sources have been added to this section of the report.

7) **Comment:** On page A-50, a basis should be provided for the conclusion that arsenic is present in geothermal steam as suspended particulates, arsenic trioxide vapor, and arsine..

Response: ARB staff believe that arsenic in geothermal steam may be present as suspended particulate matter, arsenic trioxide vapor, arsenous acid gas, and arsine due to the geologic origin of the steam. The concentrations and forms may be highly dependent on the geology of the resource reservoir. This is in the revised report.

8) **Comment:** The fifth line from the top of page A-51 should read: ". based on the assumption that arsenic vapor emissions are relatively insignificant, and only the arsenic in the cooling tower drift need be considered when estimating power plant emissions."

Response: Since this language does not add to the information in the report, no change was made.

9) **Comment:** On page A-51, the sentence: "Complete information on routes of arsenic in geothermal steam plants is lacking (PG&E)." should not be attributed to PG&E unless "the mass balance" is substituted for "routes". It should be made clear that the subsequent sentence: "... much of the arsenic present in geothermal steam may be released to the atmosphere..." is an ARB, not a PG&E, conclusion.

Response: The document no longer attributes the statement to PG&E.

10) **Comment:** On page A-51 there is a statement that geothermal steam condensed at around 125 degrees F and 1.94 psia. PG&E's surface condensers operate at slightly lower temperatures and higher pressures. The difference between direct contact condensers and surface condensers should be presented. In direct contact condensers, steam leaving the turbines mixes directly with the entire circulating water flow. In surface condensers, only the condensate is mixed with the circulating water, however, non-condensible gases pass through a Stretford solution designed to convert more than 99% of the gaseous hydrogen sulfide into oxidized, dissolved particles.

Response: The section no longer discusses the condenser operation.

11) **Comment:** The statement on page A-51 that the process-specific data are not available should not be attributed to PG&E. At least some information on how geothermal plants process geothermal steam is clearly available in the AFC's and plant data books.

Response: This statement is no longer attributed to PG&E. Information on the geothermal plant process is explained with more accuracy and detail in the revised version of the report.

12) **Comment:** On page A-52 the report refers to "higher concentrations .... during previous periods." The average concentration, and the number of samples below the detectable level, should be clearly stated. ARB should also show how the average would differ when a 1 ng/m^3 detection limit is used instead of 3 ng/m^3. Factors that might cause the higher levels such as meteorology, wind-blown soil, and steam releases should be discussed.

Response: GAMP data values are discussed in the revised report in a way that gives perspective to the fluctuating values; the range of maximum six-day averages and the percentage of samples below the level of detection (95%) are stated. Large fluctuations in the GAMP data indicate the presence of intermittent sources of arsenic emissions (e.g., well rework, steam exploration, or other intermittent activities).

13) **Comment:** Some new wells are needed merely to maintain declining steam production from existing wells and do not necessarily cause increased steam production or higher ambient concentrations of arsenic as suggested by the draft report on page A-52.

Response: Steam exploration, well drilling, and well rework are all sources of inorganic arsenic and can contribute to the ambient concentrations of arsenic; steam is vented to the atmosphere during all of these operations. Each power plant may require from 5 to as many as 60 geothermal steam wells over the life of the power plant. These makeup wells will produce arsenic emissions that may result in monitoring data fluctuations. This is included in the revised report.

14) **Comment:** On page A-86, the reference to the 19 ppb average arsenic concentration in process condensate is for 1974 data , not 1982 data. It should be made clear that this value is for direct contact condensers and not surface condensers.

Response: This section has been removed.

15) **Comment:** The drift fraction value of 3.98% on page A-87 should be 0.398% according to the reference cited.

Response: This section has been removed.

16) **Comment:** The sentence beginning at the bottom of page A-48 implies that all fuel combustion results in arsenic trioxide. The ARB should acknowledge that other compounds may be present as they did in the discussion on pages A-74 and A-75.

Response: The text has been modified to read "primarily arsenic trioxide".

17) **Comment:** On page A-55 of Part A, because the 1984 oil use was so exceptionally low, it should be acknowledged that a two-to-three-fold, short-term increase in residual oil use over the level used in 1984 may not significantly impact average lifetime exposures.

Response: The projected oil use trends for residual oil is presented in the text to explain the ARB expectation that inorganic arsenic emissions from sources using residual oil will increase through 1997. Lifetime

exposure is difficult to estimate in an aggregate-age population; staff of the ARB consider fluctuations in concentration to be significant to each individual's exposure.

H) Dr. Paul A. Solomon for PG&E, October 20, 1988

1) **Comment:** On page A-8, paragraph 3, sentence 1, it is unclear which particulate arsenic samples the two labs analyzed.

Response: The current version of the report uses data derived only from ARB's Southern Laboratory Branch; an appropriate reference is included.

2) **Comment:** On page A-8, paragraph 3, sentence 2 and on page A-11, Table I-1, footnote**, the limit of quantitation should be defined with reference to the blank or to the instrument's detection limit.

Response: The level of detection (LOD) was erroneously reported as the limit of quantitation (LOQ) in the preliminary draft report.

LOD is the reported data detected by the instrument with 95 percent confidence that it is correct. LOQ is a statistical version of the data used during mathematical manipulation to determine the location (value) of the data points that are below the LOD. In the case of the arsenic data used for this report, less than 1 percent were below the LOD.

3) **Comment:** On page A-12, Table I-2, footnote*, how can all values be above 1 ng/m^3, when some values at each site were below 0.4 ng/m^3?

Response: This table is no longer in the report.

4) **Comment:** On page A-15, the last paragraph, the ARB should examine available meteorological data to determine if variations in the meteorological conditions significantly contributed to the observed high concentrations. Examining the concentration profile of other species such as particulate nitrate, sulfate, or lead might also help to understand the processes causing the high concentrations.

Response: The text refers to Table I-2 and Figures I-3 and I-4. They have been removed, along with the accompanying text.

5) **Comment:** On page A-20, six lines from the top, insert "or unfavorable meteorology during April in the SFBAAB and during April and August in the SoCAB" after the word "network".

Response: The text has been rewritten to include this language.

6) **Comment:** On page A-22, Figure I-7 caption, insert "Arsenic" after "Annual".

Response: This figure is no longer in the report.

7) **Comment:** On page A-51, paragraph 3, change lines three and four to: "... gas phase emissions of arsenic may not. However, gas phase measurements 500 meters from the Tacoma copper smelter indicated rapid condensation of gas phase arsenic onto airborne particulate matter, and therefore, it would be collected by the aerosol sampler." It should be noted that all PG&E arsenic monitoring stations are more than 500 meters from PG&E geothermal power plants. Therefore, if arsenic is emitted in the gas phase from the power plants, it would have been detected. About 95% of the values reported by the monitoring system for arsenic are below 3 ng/m^3.

Response: While studies of copper smelter emissions have indicated that most gas-phase arsenic undergoes rapid condensation onto airborne particulate matter, we do not know that the same conditions exist to make a parallel determination for geothermal cooling tower emissions. Therefore, no change was made.

8) **Comment:** On page A-52, 12 lines from the top, insert: "... for Glenbrook (ES&S ...)." However, it should be noted that of the 62 data points reported during 1986 through 1987, at each site, only eight at Anderson Springs and one at Glenbrook were equal to or greater than the detection limit for the measurements of 3 ng As/m^3. Slightly higher...".

Response: The GAMP information has been rewritten to include the six day average maximums, monthly concentrations, annual averages, and the percentage of values that were at or below 3 ng/m^3.

9) **Comment:** On page A-73, paragraph 1, sentence 4, Germani's results from in-stack monitoring at a high temperature source of 130 degrees Celsius are used to suggest that appreciable amounts of arsenic gas could be present under normal atmospheric conditions.

Response: The text has been modified to briefly discuss the differences between Germani's in-stack monitoring study at 130 degrees Celsius and the other studies of ambient arsenic concentrations.

10) **Comment:** On page A-73, paragraph 2, insert the following before the last sentence: "In addition, Walsh et al. (1979) have measured gas and particle phase arsenic in close proximity (500 meters) to the Tacoma copper smelter. This source is probably the largest single source of arsenic in the country and most likely emits arsenic in the gas phase

primarily as As_4O_6 (As III oxide). Walsh and co-workers observed that greater than 90% of the arsenic was in the particle phase and, therefore, gas phase arsenic undoubtedly quickly condenses onto existing particles and will not be present to any great extent in the gas phase under normal atmospheric conditions."

Response: This information has been added to the text. This study demonstrates that all arsenic from a copper smelter may not be in the particulate matter phase.

The following group of comments were considered and incorporated into the text where appropriate:

11) **Comment:** On page A-2, paragraph 2 , sentence 4, insert "a gas (As_4O_6) which condenses onto existing particles, primarily" after the words, "... predominantly as ...".

12) **Comment:** On page A-3, paragraph 3, sentence 2 and on page A-72, Section B.1, paragraph 1, sentence 2, delete the word "elemental". While elemental arsenic may be reported, it is not the species present in the atmosphere.

13) **Comment:** On page A-3, paragraph 3, the fourth sentence is not easily understood. It should be made clear that the monitoring method primarily detects inorganic arsenic associated with particulate matter and that this represents the major portion of inorganic arsenic in the atmosphere. Only a relatively small fraction of atmospheric inorganic arsenic is present in the gas phase.

14) **Comment:** On page A-6, paragraph 2, sentence 2, remove the parenthesis and insert the word "analysis" before the word "method".

15) **Comment:** On page A-6, paragraph 2, it should be noted that the use of glass fiber filters may overestimate particulate concentrations in the atmosphere since gas phase arsenic compounds, if present, may react with or be absorbed by the filter medium.

16) **Comment:** On page A-7, 5 lines from the top, add the following references: Appel et al., 1984; Walsh et al., 1979; Walsh et al., 1977.

17) **Comment:** On page A-7, 12 lines from the top, add the following reference: Andreae, 1980.

18) **Comment:** On page A-7, replace the last two sentences on the page with: "Based on ambient measurements in marine and continental

atmospheres (Walsh et al., 1979), it is believed that the fraction of solid phase organic arsenic compounds is likely to be much less than 20 percent."

19) **Comment:** On page A-8, paragraph 2, sentence 2, insert "collected in Tucson, Arizona" after the words, "... atmospheric particulate matter".

20) **Comment:** On page A-8, paragraph 2, change the fourth sentence to: "A 16-day ARB study (see appendix C) at a site ... yielded As(III) to As(V) ratios from about 0.5 to 2.9 with an average ratio for total particle arsenic (sum of fine and coarse) equal to 1.2."

21) **Comment:** On page A-8, paragraph 3, the last paragraph in Section I.A.1. should be moved to follow sentence 3 in the first paragraph of Section I.A.2.

22) **Comment:** On page A-8, paragraph 3, sentence 4, add a statement about the relative error or precision of these measurements.

23) **Comment:** On page A-29, paragraph 1, line 8, insert "or unfavorable meteorology" after the words, "intermittent sources".

24) **Comment:** On page A-29, paragraph 2, the city in which the smelter was located should be named.

25) **Comment:** On page A-35, Table I-6, on the line beginning with the word "cigarettes", change the chemical form from "As(III)/As(V)**" to "arsenic oxides".

26) **Comment:** On page A-35, Table I-6, footnote**, add the reference USEPA, 1984.

27) **Comment:** On page A-71, Table III-1, the formula for arsenic acid should be $H_3AsO_4 \cdot 1/2\ H_2O$.

28) **Comment:** On page A-72, paragraph 1, at the end of sentence 3 insert: "or more likely as the oxyacid or salt of the oxyacid.".

29) **Comment:** On page A-72, paragraph 2, sentence 1, "a significant extent" should be changed to "some extent".

30) **Comment:** On page A-72, Section B.2., sentence four should read: "Because of arsine's high acute toxicity, anthropogenic emissions of arsine are expected to be small since arsine emissions are strictly regulated and, therefore, should not significantly contribute to overall arsenic exposure."

31) **Comment:** On page A-73, paragraph 1, sentence 1 should read: " ... is the primary form of inorganic arsenic expected to be emitted from high temperature industrial sources (Eatough et al., 1979; Germani et al., 1981; Davison et al., 1974).".

32) **Comment:** On page A-73, paragraph 1, sentence 3, insert "at 130 degrees Celsius" after the word, "effluent".

33) **Comment:** Units should be converted to those of the metric system throughout the report.

34) **Comment:** Be consistent on page usage throughout the document. Use either one side or both sides of the page.

I) Lake County Air Quality Management District, June 6, 1988

1) **Comment:** The difference between power plants and wells as sources needs to be made clear in the draft report.

Response: Wells are no longer reported as power plants in the report.

2) **Comment:** Uncontrolled steam releases, steam exploration, and production well drilling should be considered significant sources of arsenic. They are not addressed in the draft report.

Response: They are addressed in the current version of the report.

3) **Comment:** On Page A-86, the draft report discusses drift fraction. Drift fraction as a function of circulating water flow is typically 0.001% for power plant cooling tower facilities constructed in the past 10 years. It is markedly less for older units that have not been upgraded.

Response: This section has been removed from the report.

4) **Comment:** On Page A-87, the figure 3.98% is used to represent non-condensible gas emissions in calculating arsenic extracted. This figure may include condenser inleakage. Non-condensible gases present in geothermal steam are more typically less than 0.5% of condensate mass flow except in several areas of the production field. The reference to the table at the bottom of Page A-87 should clearly refer to power plants and not wells.

Response: This section has been removed from the report.

5) **Comment:** Source testing at a Lake County power plant with a steam flow rate of 1.4 million lb/hr established an arsenic emissions rate of 0.0022 lb/hr. 97.6% of the arsenic emitted was collected as particulate on a 0.45 micron filter. Ambient monitoring at two locations downwind of geothermal development shows monthly average concentrations of arsenic to be 1-4 ng/cubic meter with yearly average concentrations of 1-2 ng/cubic meter. These averages might be included on Page A-52 with maximum recorded concentrations for Anderson Springs and Glenbrook.

Response: The information from the Geothermal Air Monitoring Program has been rewritten and included in the report.

J) U.S. Borax, May 5, 1988

1) **Comment:** On page A-1, the medicinal benefits of arsenic as well as its toxic effects should be mentioned in order to put the discussion of arsenic in proper perspective.

Response: The revised report mentions that arsenic has been used medicinally for centuries, although its more infamous reputation is as a poison.

2) **Comment:** On page A-3, although complex organo-arsenicals in food may be of less toxicological significance than the inorganic forms, arsenic in the diet should not be so summarily dismissed since the basic forms of arsenic in foods is largely unknown.

Response: We recognize that the forms of arsenic in food are largely unknown and acknowledge this in the revised report.

3) **Comment:** On page A-11, the source of Table I-1 and of all other tables and figures in the report, should be noted so that data may be traced and verified.

Response: This table has been replaced in the current version of the report. Monitoring data comes from the ARB's toxic monitoring network and is analyzed in the ARB laboratory. This is mentioned in the report.

4) **Comment:** On page A-36, estimates of the statewide number of people exposed to arsenic in water above 50, 100, and 200 ug/L should be included. Also, it is inappropriate to use only data from wells in the San Joaquin valley to develop a general statewide level.

Response: The draft version of the report briefly discusses the other routes of exposure in an effort to inform the reader of other ways they may be exposed to inorganic arsenic. The San Joaquin valley has high

levels of arsenic in the drinking water supply and is used in the report as an example of an area where arsenic exposure from another route can be much higher than airborne arsenic exposure.

5) **Comment:** On page A-43, the report implies that the Tacoma smelter, shut down in 1985, is still operating. The status of all ASARCO's plants should be verified.

Response: This has been removed from the text.

6) **Comment:** On page A-63 it is stated that several industrial activities in California are using arsenic yet only two are apparently active, and at least one of them is a negligible contributor. If such is the case, the need for this section is not clear nor is the appropriateness of singling out a particular company by name.

Response: This text has been rewritten and reorganized. The current version of the report no longer gives facility names.

K) Department of Food and Agriculture, May 3, 1988

1) **Comment:** The inorganic arsenicals used as pesticides are regulated as restricted materials, but no permit is required for industrial or home use.

Response: The text has been expanded and modified to inform the reader of the responsibilities of both the DFA and the ARB regarding the use of arsenicals as pesticides.

III.

Department of Health Services Staff Responses to Summarized Comments on the Preliminary Draft Part B

DEPARTMENT OF HEALTH SERVICES
STAFF RESPONSES TO PUBLIC COMMENTS
ON THE PRELIMINARY DRAFT REPORT TO THE AIR RESOURCES BOARD
ON INORGANIC ARSENIC:
PART B -- HEALTH EFFECTS OF ARSENIC COMPOUNDS

General Comments

Comment: It should be noted that since even EPA (the U.S. Environmental Protection Agency) has agreed that arsenic is an essential element, there must be a threshold value between the essentiality level and the toxic level. The reasons for and against a threshold should be discussed. The document should indicate that the only remaining question is how the threshold may be quantified. Since arsenic is an essential element, high (toxic) short-term exposures cannot be assumed, in the context of risk assessment, to be equivalent to low (necessary) long-term exposures (United States Borax & Chemical Corporation [Borax]).

Response: Although arsenic is a nutrient for certain animal species, and has been used for medicinal purposes in humans, it has not been convincingly shown to be essential in human nutrition. DHS (Department of Health Services) staff have made inquiries regarding EPA's position on arsenic and nutritional essentiality. It appears that EPA has not found that arsenic is an essential element. In developing a rule for arsenic in drinking water, EPA staff considered the possibility that arsenic is an essential element and discussed a regulatory option based on that possibility (Inside EPA, June 24, 1988, p. 3; August 12, 1988, p. 5; October 7, 1988, p. 5). This "essentiality option" has been dropped from consideration and the rule is scheduled for publication in December 1989 (personal communication, Maria Gomez-Taylor, EPA Office of Drinking Water, January 31, 1989). Whether arsenic-induced cancer is characterized by a threshold is discussed in Chapter 10 of the draft DHS health effects document.

Comment: The information regarding the semiconductor industry is out of date and inadequate. Arsine storage is more prevalent than indicated in Part A. Also, many firms in the industry do not use emission controls for arsine, and firms that do have controls believe them to be only about 25% effective. Information on the health effects of arsine should be incorporated into Part B of the report (Silicon Valley Toxics Coalition).

Response: According to staff of the Air Resources Board, arsine has not been detected either in ambient air in California or in stack tests conducted by the Bay Area Air Quality Management District at several semiconductor industry facilities. The stack tests were performed at the exit of functioning scrubbers and had a limit of detection of 37 parts per billion. Arsine presents a potential hazard mainly due to its acute toxicity after an accidental release. The toxic air contaminants program, for which the draft DHS health effects document was prepared, has not considered the regulation of accidental releases of toxic substances. If in the future the ARB wishes to evaluate health effects following possible accidental releases, arsine would be a good candidate for consideration. If ARB wishes to develop an emissions standard specific to arsine, DHS staff

will review the health effects of this compound and will prepare appropriate recommendations.

Comment: Either Part A or Part B should be revised to note that foodstuffs would be likely to pick up significant amounts of arsenic even if there were no airborne arsenic (Pacific Gas and Electric Company [PG&E]).

Response: Airborne arsenic is a naturally occurring phenomenon. The cycling of arsenic in the environment and the relative contribution of airborne arsenic to levels of arsenic in food have not been detailed in the revised Part B (health effects document).

TOPIC: Metabolism

Comment: Why is saturation of the methylation pathway not likely to occur at occupational exposure concentrations associated with lung cancer (Borax)?

Response: As mentioned in Section 2.3.1, Buchet and co-workers found in human subjects that this pathway was not saturated at moderate non-toxic doses of arsenic. Significantly elevated rates of lung cancer were associated with chronic inhalation of similar doses in occupational environments. Furthermore, as noted in Section 2.1.2, airborne arsenic cannot be methylated before it reaches lung tissue.

Comment: The differences in distribution and metabolism of arsenic among various species should be clearly identified (Borax).

Response: Inadequate quantitative comparative data are available for detailed interspecies comparisons of distribution and metabolism of arsenic. However, it is generally accepted that the rat is an atypical animal model for arsenic metabolism and toxicity. Blood concentrations are unusually high in the rat (this is noted in Section 2.2 of the document), and the time course of biliary excretion and elimination is unusual in this species (Section 2.4). Accordingly, caveats regarding the relevance of studies in rats are included in Sections 5.1.3 and 6.2.1.

Comment: Why is the study of Crecelius (1977) characterized as well conducted, on page 2-5 (Borax)?

Response: This study is characterized as well conducted because it utilized an analytical method which is more valid than those used in previous studies.

TOPIC: Essentiality

Comment: A 1961 Ph.D. thesis by I. Harding-Barlow should be considered in the discussion of arsenic and nutritional essentiality. This thesis showed that concentrations of essential elements can show both normal and lognormal interindividual distributions (Borax). The DHS report should acknowledge that common drinking water and dietary exposures are high enough to eliminate the need for a homeostatic mechanism (PG&E).

Response: To DHS staff's knowledge, Dr. Harding-Barlow's findings have not been published in the open literature. Findings such as described above would certainly contradict the conclusions of Liebscher and Smith (1968) cited in Chapter 3. Indeed, an essential element for which there is no homeostatic mechanism would likely show a log-normal interindividual distribution. For arsenic, the revised DHS report acknowledges that common exposures may be high enough to eliminate the need for a homeostatic mechanism.

TOPIC: General Toxicology

Comment: It cannot be assumed that the noncarcinogenic adverse health endpoints associated with occupational exposures to arsenic compounds ("arsenic") were caused by arsenic alone (Borax).

Response: This is true; the detailed discussion in the draft document clearly indicates that interpretation of the smelter data may be confounded by the presence of toxicants other than arsenic (see, e.g., page 6-2 and Section 9.2.1).

Comment: The statement on page 4-1 regarding lethality and the sensitivity of humans compared to other animals should be better supported in the text (Borax).

Response: By comparing the lethal oral dose range reported in Section 4.1 for humans (0.8 to 2.3 mg As/kg) to the range of oral LD_{50} values reported in Section 4.2 for animals other than rats (10 to 150 mg/kg for various arsenic compounds), it can be seen that humans are approximately an order of magnitude more sensitive to lethality from acute arsenic exposure than other animals. The document has been revised to include this comparison.

Comment: The report should provide better estimates of the dose levels at which the effects noted on page 4-2 occur (Borax).

Response: The effects in question resulted from poisoning and accidental ingestion. If more precise estimates of the doses required to produce the effects were available, they would have been reported.

Comment: Nerve conductivity studies with subjects who were not exposed to probable confounding factors should be discussed; otherwise, where nerve conductivity studies are discussed, the probable confounding factors should be indicated (Borax).

Response: Controlled studies of airborne arsenic exposure and nerve conductivity in humans are not available. Elsewhere, the document clearly indicates that interpretation of data from occupational exposure of humans may be confounded by the presence of toxicants other than arsenic. A similar caveat has been added in Section 5.2.

Comment: The exposure levels in Antofagasta, Chile, associated with the effects noted in Section 5.2.5 should be stated (Borax).

Response: These levels are discussed in Section 5.2.2, which is referred to in Section 5.2.5.

Comment: Some studies in Taiwan have shown that Blackfoot disease is not correlated with well-water arsenic levels (Borax).

Response: As noted in the document, Blackfoot disease has been shown to be caused by arsenic-contaminated groundwater, but other vasoactive substances in the water may have contributed to the disease. The commentor listed one report as an example (Kuo TP and Chen MH (1969) Follow-up study of surgical treatment of endemic spontaneous gangrene in tropical Taiwan. J Formosan Medical Assn 68:275-290). The authors of this report noted that the etiology of Blackfoot disease had not been established and that arsenic might still be the primary cause. They then presented data matching the prevalence of Blackfoot disease with the arsenic concentration of well water in several villages. No correlation is present in this dataset. Nevertheless, incomplete information is presented regarding the well-water consumption patterns in the villages (purer sources of water were available in some areas) and the number of cases upon which the prevalence rates were based. This report predates the widely-cited analysis of Tseng (1977) which links arsenic and Blackfoot disease.

TOPIC: Reproductive Toxicology

Comment: The Executive Summary should be clarified to indicate which four days during pregnancy mice were exposed to airborne trivalent arsenic (As(III)) as described on page 1-1 (Borax).

Response: Although this is an important detail, it need not be included in the Executive Summary. By reference to Chapter 6 and Appendix G, it can be seen that the result is from the study of Nagymajtenyi et al. (1985) and that the exposure was during days 9-12 of gestation. Section 6.2.3 has been modified to clarify this point.

TOPIC: Cancer

Comment: In Section 10.4, rat data should not be applied to humans without confirmation in another species.

Response: The rat does exhibit unusual pharmacokinetics with regard to arsenic. Nevertheless, the finding that arsenic induced the activity of a fetal enzyme in rats may be relevant to the mechanism of arsenic's carcinogenicity in humans. The rat information was not used to establish arsenic's carcinogenicity or to estimate risks of arsenic exposure.

Comment: It is not clear why the study of Glaser and co-workers (1986) is discussed, since DHS concludes that it is not informative. Due to its limited sample size, the study would not be informative even if it had produced a highly positive result (Borax).

Response: This study is discussed because few animal studies involving long-term inhalation of arsenic have been reported. Even negative results

can be informative. The sentence which suggests otherwise (the last sentence of Section 8.1) has been modified.

Comment: The blanket statement in the Executive Summary (page 1-3) concerning smelters and insecticide manufacturing is incorrect because arsenic has been strongly linked with lung cancer in only three copper smelters (Borax).

Response: Arsenic has been strongly linked to lung cancer in the five smelters located in Anaconda, Montana; Tacoma, Washington; Garfield, Utah; Ooita, Japan; Skelleftea, Sweden and in two pesticide manufacturing plants.

Comment: The DHS risk assessment relies heavily upon an EPA review of the epidemiological studies which was prepared before the studies were published. DHS should review these four studies in more depth (PG&E).

Response: The DHS risk assessment relies on the EPA review of epidemiologic studies only for those studies which were published before the EPA's document and which were adequately reviewed in that document. DHS staff reviewed the most recent analyses by Enterline et al. (1987), Higgins et al. (1985) and Lee-Feldstein (1986) in Section 9.1.1. The strengths and weaknesses of data from the two analyses by Lee-Feldstein (1983 and 1986) as well as the latest analyses by Enterline et al. (1987) and Higgins et al. (1985) are now discussed in more detail, from the point of view of risk assessment, in Chapter 11.

Comment: The data used in the risk assessment are not in Table 11-3 as stated on page 11-12 but appear to come from Tables 9-4, 9-6 and 11-2. It is important that the actual data used be clearly designated (PG&E).

Response: The comment is correct. All references to tables have been better designated.

Comment: The negative results from epidemiological studies in Oregon, Idaho and Lassen County would appear to lead to conclusions contrary to those being implied in the report. Why these results and their significance are being ignored should be discussed (Borax).

Response: These studies are not examined in detail because they relate to drinking water exposure rather than inhalation. Arsenic is recognized to be a carcinogen by ingestion. That these studies produced negative results does not necessarily imply otherwise. Factors such as sample size, amount of drinking water consumed, duration of exposure, and physiological and behavioral confounders may have contributed to the results. For the purposes of the document at issue here, it is sufficient to note the contamination levels and that the studies were conducted and were negative.

Comment: Part B should be revised to discuss more fully the implications of the Lee-Feldstein (1986) data. It is possible that the Lee-Feldstein study should not be rejected out of hand, since all of the studies involve deficiencies of some sort (PG&E).

Response: DHS staff agree that the Lee-Feldstein study should be considered, and have included a risk estimate derived from that study.

Comment: The word "incorrect" is too strong for characterizing the apportioning, by Welch et al. (1982) and Higgins et al. (1985), of person-years of exposure according to final exposure (PG&E). A phrase such as "less appropriate for the particular risk assessment approach applied by DHS" would be preferred.

Response: The assigning of a person-year to a high exposure level when the employee was known to have accumulated a low level of exposure as of that person-year is incorrect (regardless of whether the data are to be used in a risk assessment). This conclusion follows from the 1987 treatise by Breslow and Day (Breslow NE and Day NE (1987) Statistical Methods in Cancer Research, Vol II: The Design and Analysis of Cohort Studies. Lyon: International Agency for Research on Cancer). Text from the relevant discussion is included here as Appendix A.

Comment: It should be noted that I. Higgins has stated with regard to the Anaconda smelter worker studies that "the actual concentration in the exposure estimates should be treated with reserve, as should the exposure/response relationships derived from them." (Borax).

Response: DHS staff agree with the comment. Uncertainties related to exposures in the smelter are shown in Table 11-1. DHS staff have estimated the risks expected from low-level exposures using the best data and scientific methods available.

Comment: DHS's reliance on a single risk assessment model is unfortunate. The Department should develop a range of estimates for different assumptions that are all consistent with the data and with current scientific understanding (PG&E).

Response: DHS staff agree that a range of estimates would be desirable. Current scientific understanding of the mechanism associated with arsenic-induced carcinogenicity does not support use of an additive risk model for reasons stated in Section 11.3.1. More specifically, an additive risk model assumes that cancer risk due to arsenic would have a markedly different age-distribution from the age distribution of the background lung cancer risk. No experimental or epidemiologic data support such an assumption. As stated in the document, the best-fitting nonlinear model reported by Enterline et al. (1987) for the Tacoma data yielded implausibly high risks for environmental exposure. DHS staff have investigated the usefulness of nonlinear forms; the advantages of the linear assumption are described in Section 11.3.1.

Comment: The report should discuss more fully the nonlinear relationship estimated by Enterline and co-workers. DHS should evaluate the assumption of a linear dose-response relationship in light of the dose-response data and evaluate what level of departure from this assumption is consistent with the data (PG&E).

Response: The revised document includes a fuller discussion of the nonlinear relationship observed by Enterline et al. It also discusses the degree to which the assumption of linearity is consistent with the data.

Comment: Inasmuch as certain data indicate that there is a linear relationship between urinary arsenic levels and respiratory cancer, but not between airborne arsenic levels and respiratory cancer, the report should discuss this distinction and state why a "biological marker" model is not considered. This should be discussed in light of the conclusion of Section 11.2 (Borax).

Response: It would be impractical to use urinary arsenic to assess risks from low-level ambient airborne exposures. General population exposures are estimated using air measurements, not urinary levels. In the general population, urinary levels of arsenic are largely determined by oral (dietary) exposures to arsenic compounds. It is unlikely that fluctuations in urinary levels of arsenic due to fluctuations in ambient airborne levels could be detected in the general population. One should not conclude, however, that because fluctuations in airborne arsenic levels may not measurably affect urine concentrations, such fluctuations cannot affect risks of lung cancer.

Comment: The use of cumulative lifetime exposure as the measure of dose in the risk assessment is questionable because at normal (environmental) concentrations, arsenic is rapidly excreted (Borax).

Response: The risk assessment estimates the probability of cancer associated with exposure to certain amounts of arsenic. For arsenic, data associating human inhalation exposure levels with rates of lung cancer are available. The pharmacokinetic data are inadequate to allow consideration of such parameters as excretion, absorption, or metabolism in the risk assessment model. Note, in addition, that the tumor of concern occurs in the lung, where the toxicant contacts the body.

Comment: Part B should be revised to discuss whether evidence from the epidemiological studies is consistent with no risk (true risk = zero) from environmental exposures of concern. DHS has not shown that a threshold model fails to fit the data as well or better than a linear no-threshold model. The risk assessment should consider the possibility of a threshold below which there are no significant adverse effects. Research indicates a threshold for ingested arsenic. The use of a no-threshold model may cause harm if arsenic is an essential element in humans and is regulated (as a result of using the model) to a level which would create a deficiency state (PG&E).

Response: Because of inherent limitations in epidemiological studies, they cannot usually be used to establish or rule out a threshold mechanism of action. They can be used to establish an upper bound low dose risk. For arsenic, the shape of the dose-response data suggests greater increases in risk (per unit increase in exposure) at low levels of arsenic than at high levels. As discussed in Section 9.1.1, Lee-Feldstein found that even for those with the lowest occupational exposure, a significant increase in lung cancer mortality was observed. Therefore, no threshold for carcinogenicity is discernible in the epidemiologic data.

If arsenic were an essential nutrient, and if the nutritional requirement were known, then risk management decisions for low-level exposures could

consider the potential for arsenic deficiency. However, the data concerning nutritional essentiality are inconclusive.

Comment: Confounding and synergistic interactions should be considered more systematically. The data still required to prove or disprove such relationships should be noted. The clarity of the report would be enhanced by a listing of the factors present with arsenic in studies which lead to tumors in animals. Such co-factors appear to be present in the positive human studies (Borax).

Response: The possible role of confounding from smoking was discussed in Section 9.2.2. Potential synergistic effects were discussed in Section 9.3. The presence of other potential workplace carcinogens was discussed in Section 9.2.1. The fact that workers in the each of the different studies were exposed to different sets of chemicals in addition to arsenic adds to the weight of evidence implicating arsenic as a carcinogen.

Comment: DHS should reconsider the use of an additive risk model, as the arguments presented for using the relative risk model are weak. An absolute risk model would not predict risk to be independent of age if latency were taken into account realistically. EPA found that additive risk models fit the available data better than relative risk models. Part B should show the range of risk that would result from use of the EPA additive risk model assumptions and methodology (PG&E).

Response: The implausibility of additive risk models is evident from the arguments of Peto (1978). Even with the use of a latency, the additive risk model assumes a highly unusual age distribution of cancer. Consider, for instance, a ten-year-old exposed to arsenic at triple the concentration to which a thirty-year-old was exposed. The cumulative exposures of these two individuals would be identical. After 20-30 years latency, the additive model would predict the same excess risk for the ten-year-old now 30-40 years old as for the thirty-year-old now 50-60 years old. The choice of model must be based on a consideration of age distribution since the risk assessment from occupational data extrapolates results from adults to the general population and from high to low doses. There are neither experimental nor epidemiological data suggesting a mechanism that would produce an age distribution skewed to younger ages for arsenic-induced carcinogenicity. In the absence of such data, a relative risk model is the most plausible. EPA used data that are no longer current, as indicated in the draft DHS report (Section 11.5). Several of the studies have been updated and it is these updated reports that have provided the data for the DHS risk assessment. Finally, if the "best fit" were the primary criterion for choice of a risk assessment model, we would have adopted the model Enterline et al. (1987) fitted, which showed dose to the 1/3 power gave the best prediction. DHS staff believe that applying the data to more models would not further elucidate the carcinogenic risks of arsenic exposure.

Comment: The statement (page 11-11) that short-term high exposures were considered equivalent to long-term low exposures, provided the cumulative doses were the same, indicates that lifetime risk was overestimated by DHS. The conclusion that use of cumulative exposure may substantially underestimate risk from environmental exposures should either be buttressed by a more detailed analysis or be deleted (PG&E).

Response: If the workers' exposure had been at lower concentrations so that it had begun in childhood, and if arsenic functioned strongly at early stages in carcinogenesis, then a higher level of risk would have been expected. Since the exposure actually occurred during adult life, one is unable to observe the full potential impact of arsenic that could have occurred had the same cumulative exposure begun in childhood, because competing causes of death intervene. The potency may therefore have been underestimated. On the other hand, without consideration of age sensitivity, it is also possible that a high occupational exposure of short duration may be more potent than the same dose spread out over a longer period of time. However, neither hypothesis can be substantiated for arsenic at this time. A similar explanation has been included in the revised document in Section 11.2.

Comment: DHS's discussion of possible bias in estimates made for persons exposed as children is speculative and itself potentially biased (PG&E).

Response: All risk assessments require assumptions about phenomena we are unable to observe directly. The document cites published observations that provide evidence for potentially greater sensitivity among younger individuals.

Comment: The smoking interaction model is unsound and the explanation of this model is not understandable. DHS should replace this model or develop a range of estimates more consistent with the available data. Note that it is highly speculative to assume that a smoking and arsenic interaction would hold for arsenic exposures that precede the onset of smoking. Based upon the conclusion that the joint effects of arsenic and smoking are intermediate between multiplicative and additive, DHS developed a complicated model that involves inferring SMRs (standardized mortality ratios) and observed cancers in nonsmoking populations. This approach seems ill-advised. Note particularly that DHS, in deciding that a multiplicative relationship is not appropriate, did not investigate whether the disagreement could be explained by random error. Since the relative risks, particularly for nonsmokers, were based on small numbers of cases, the disagreement with a multiplicative relationship could well be due to random deviations (PG&E).

Response: DHS staff did investigate whether the deviations from a multiplicative relationship could be due to random error. The test for homogeneity showed a strong deviation from a multiplicative relationship to be statistically significant, and this, in part, motivated the development of smoking-habit-specific risks. DHS staff have included risk estimates from unadjusted data in the revised report. These are fully consistent with the smoking-habit-specific risks, the latter being an apportionment of the total risk for a mixed population.

Comment: DHS's selection of values for the parameter, ρ, that expresses the degree of departure from a multiplicative model, is not clearly supported by the data (PG&E).

Response: The precise values selected for ρ are less important than the overall pattern. A new table is included in Chapter 11 of the revised health effects document. Data in this table (Table 11-4) indicate a pattern

in which environmental (low) arsenic exposures are consistent with ρ=1 and occupational (high) arsenic exposures are consistent with overall values of ρ less than or equal to 0.6. This pattern implies smaller values for ρ for the highest occupational exposures.

Comment: The formula for SMR on page E-3 must be incorrect because the SMR will be negative if ρ is less than one (PG&E).

Response: The formula was incorrect as presented. The correct formula is presented in the revised document.

Comment: Although DHS warned at one point that the inferred data may not share the properties of real data, the conclusion on page 11-18 that "an excellent fit was obtained" for two data sets should have been tempered by such a warning (PG&E).

Response: The warning "the inferred data are not known to share the properties of the data with respect to statistical inference" appears in the same paragraph as the phrase "an excellent fit was obtained". The close juxtaposition (2 sentences apart) appears adequate.

Comment: It is not clear what role the assumption that inferred observed deaths are Poisson random variables plays in the analysis (PG&E).

Response: Observed events, in which the number of trials (opportunities for occurrence) is unknown and large, are generally assumed to follow the Poisson distribution. The Poisson distribution can be obtained theoretically as the limit of a binomial distribution in which n goes to infinity and p tends to zero. This distributional assumption is the basis of the regression analysis. Under the null hypothesis, the observed deaths are assumed to follow a Poisson distribution with the mean equal to the expected number of deaths. The inferred data are based on partitioning the actual data, and the sum of two or more Poisson random variables is again a Poisson random variable.

Comment: Part B should be revised to lower the risk estimate for total airborne arsenic by a factor of 20 to 40, because the types of arsenic compounds and particle size distributions historically found in occupational exposures differ from those in ambient air; otherwise, Part B should estimate risks from pentavalent arsenic (As(V)) separately from trivalent arsenic (As(III)) risks. DHS recognizes that assuming ambient air and occupational exposure involve similar As(III):As(V) ratios may overestimate risk. Arsenic trioxide (As(III)) is probably nearly the exclusive form of exposure of the Anaconda and Tacoma smelter workers. Certain sampling data indicate that failing to incorporate the difference in speciation of arsenic in ambient air overestimates risk by a factor of two to four. Existing data are sufficient to warrant a unit risk at least ten times lower for As(V) than for As(III). Note that As(V) was less active than As(III) in several of the assays discussed in Chapter 7. Considering as well the lack of evidence of ability of the lung to metabolize As(V) to As(III) or to detoxify As(III) by methylation, risk is overestimated by at least a factor of 20 to 40. Data indicate that As(V) deposited in the lungs would significantly increase risks only after it is converted to As(III) in the

blood stream and only to the extent that ingested arsenic increases risks (PG&E).

Response: Inadequate data exist to assess the risks from As(V) separately from As(III) risks. Sampling data do indicate that there is proportionately more As(V) in the ambient environment than in smelter work areas. As(V) is converted in the body to As(III), although it is unclear whether this occurs in the lung. Furthermore, insufficient data exist to demonstrate that inhaled As(V) only increases risk after it is converted to As(III) and only to the extent that ingested arsenic increases risks. In contrast to ingested arsenic, inhaled arsenic cannot be detoxified by the liver before it reaches the lung, a target organ for carcinogenesis.

Thus, it is not necessary to apply a potency-reducing factor as suggested by the commentor; nevertheless, the logic behind the proposed risk-lowering factor of 20 to 40 is unclear. Where the commentor calculates that differing species ratios in ambient versus workplace air indicate that the DHS risk estimates for ambient air should be lowered by a factor of two to four (1.8 to 3.7), it appears that As(V) has been assigned a carcinogenic potency of zero. To then assume that As(V) has one-tenth the carcinogenic potency of As(III) should not further decrease the risk estimates for total arsenic in ambient air (and result in a factor of 20 to 40); rather, it should add to those estimates (and decrease the factor below two to four).

Comment: The report should address the physiological implications of the physical chemical properties (e.g. particle size and solubility) of particles on such parameters as capture, retention, and bioavailability, in the calculation of the unit risk estimates. Insoluble arsenic salts are probably more hazardous than soluble salts because they are retained in the target organ (the lung) longer; the smelter workers may have been exposed to insoluble forms of arsenic. It also appears that with regard to the size distribution of arsenic particles, California environmental samples are considerably smaller (contain smaller particles in general) than smelter samples. The DHS report suggests that the bronchioles are the target site in the lung and not the lower alveolar region. This would be consistent with the deposition of larger particles (PG&E).

Response: Were there adequate relevant data on capture, retention, and bioavailability of arsenic compounds in human lung, they would be considered in the report. The data do not clearly establish that soluble salts of arsenic present less of a hazard than insoluble salts.

The data to which the commentor referred indicate that there may have been proportionally more particles larger than 2.5 μm in the smelter environments than in ambient air. It is possible that many large particles inhaled by smelter workers did not reach bronchioles but were trapped in the upper respiratory tract. If this were the case, extrapolation from the smelter worker data may underestimate the risk in ambient air where a greater proportion of inhaled arsenic will reach the lower respiratory tract. Note that "particles having an aerodynamic diameter of 5 to 30 μm are largely deposited in the nasopharyngeal region by impaction" and "particles having an aerodynamic diameter of 1 to 5 μm are deposited in the tracheobronchial regions by sedimentation" (Menzel DB and MO Amdur (1986) Toxic responses of the respiratory system. In: Casarett and Doull's Toxicology, 3rd ed., CD

Klassen, MO Amdur and J Doull, eds. New York: Macmillan Publishing Company, p. 343).

Comment: Arsenic binding to sulfhydryl groups is an equilibrium process in which the bonds are continually being formed and broken. The statement on page 10-5 that "a single instance of sulfhydryl group binding to an enzyme might result in misrepair or breakage of DNA" shows a lack of understanding of arsenic binding (PG&E).

Response: The binding of arsenic to an enzyme sulfhydryl group is reversible at the molecular level. However, arsenic can form quite stable complexes with enzymes containing sulfhydryls, particularly vicinal sulfhydryls. A DNA repair enzyme bearing an arsenic-sulfhydryl complex could cause misrepair, perhaps even breakage, of DNA. In this way, a single instance of sulfhydryl binding may be related to a genotoxic result.

Comment: The report cites the possibility that "a single instance of arsenolysis might result in DNA damage." However, the hypothesis that inorganic As(V) competes with phosphorus to form unstable arsenate DNA and RNA esters has never been proven in vivo. There is no evidence that this mechanism is biologically plausible in mammalian systems (PG&E).

Response: As noted in Section 10.1, this mechanism has been considered plausible in the literature. Much of our current understanding of molecular mutagenesis mechanisms comes from in vitro studies. Non-mammalian systems, such as bacteria and yeasts, provide particularly useful mechanistic information. While significant differences exist between lower and higher organisms in DNA organization, replication, repair, and expression, the basic chemical similarity of DNA among species is widely recognized.

Comment: There is the possibility that arsenic by itself may be a promoter or co-carcinogen rather than an initiator. There are no data presented in Section 10-7 that indicate that arsenic is an initiator. What then is the basis for assuming that arsenic is an initiator (Borax)?

Response: DHS staff are not assuming that arsenic is an initiator of carcinogenesis. The available data are consistent with arsenic being a promoter, an initiator, or both. Some mechanisms by which arsenic might act as an initiator are discussed in Section 10.7. As noted in that section, the risk assessment presented in the document makes no assumption regarding the timing of arsenic's carcinogenic activity. There is evidence that arsenic may act as an initiator of cancer. At the experimental level, arsenic compounds are known clastogens and are active in a number of assays of genotoxicity. At the epidemiological level, data suggest fairly long latencies, of around 10 to more than 30 years, which means that arsenic may act at an early stage in carcinogenesis (see Appendix B of Part B).

Comment: Part B should be revised as needed to incorporate the statements and references cited in submitted highlights of a recent draft toxicological evaluation of arsenic. The evaluation was prepared by William Marcus, of EPA's Office of Drinking Water. It suggests that no significant adverse health effects are anticipated from ingestion of less than 200 μg/day of arsenic, and therefore, for this route of exposure, there may be a threshold

exposure level which meets the criteria of Health and Safety Code Section 39662(c) for toxic air contaminants (PG&E).

Response: The toxicological evaluation in question is an undated preliminary draft which has been circulated for review of its technical merit. It would be inappropriate to consider this draft to represent the official position of a federal agency. Furthermore, whether there is a threshold to carcinogenesis from arsenic ingestion is not necessarily a central concern in addressing carcinogenesis from arsenic emitted into the ambient air. Oral exposure to arsenic is chiefly associated with skin cancer, whereas inhalation exposure is chiefly associated with cancer of the lung. The draft EPA report explicitly distinguishes between these two forms of cancer and recognizes a linear nonthreshold carcinogenic potency factor for lung cancer from inhaled arsenic (p. VIII-53). Thus, the threshold discussion in this draft EPA report is not applicable to respiratory cancer produced by inhalation of arsenic.

APPENDIX A

BRESLOW AND DAY (1987, p. 83) ON ASSIGNING PERSON-YEARS TO EXPOSURE CATEGORIES

WORLD HEALTH ORGANIZATION

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

STATISTICAL METHODS IN CANCER RESEARCH

VOLUME II - THE DESIGN AND ANALYSIS OF COHORT STUDIES

BY

N.E. BRESLOW & N.E. DAY

TECHNICAL EDITOR FOR IARC

E. HESELTINE

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LYON

1987

It is also of interest, however, to make comparisons among subgroups defined on the basis of variables that change values as the subject moves through the study. For example, subjects often continue to accumulate exposures of interest during the same period that they are being followed for evaluation of cause-specific mortality. Industrial workers may be entered on study while still relatively young and be followed through their working years and on into retirement. If the measured exposures are distributed continuously over the working lifetime, the subjects with the highest cumulative levels of exposure are frequently those who have lived the longest. This is even truer when a variable that reflects duration of exposure is being analysed for its relationship to the risk of disease. Special precautions are required to ensure that the allocation of person-years is made appropriately.

Several investigators have attempted to establish a dose-response trend in such circumstances by classifying each subject into a single subgroup on the basis of his total cumulative exposure or duration of employment at the end of the study. Mortality ratios computed separately for each subgroup are then compared. Unfortunately, results obtained in this manner are fallacious, since the early person-years of follow-up, when cumulative exposures are light, are being allocated to the same heavy exposure category as the later person-years. The death rates calculated in this fashion for the highest exposure categories are too low, since person-years during which no death could have occurred are included in the denominator. Rates for the lowest exposure categories are too high since it is only the individuals who die with short exposures who contribute to the denominator; the person-years of someone who might have died with short-term exposure, but in fact did not, are allocated elsewhere.

The correct assignment of each increment in person-years of follow-up is to that same exposure category to which a death would be assigned should it occur at that time. Subjects who change their exposure classification as they move through the study, as many in fact do, thus contribute to the person-years denominators of the rates for several exposure categories. Figure 3.1 illustrates schematically the proper, dynamic method of allocation as well as the improper, fixed method when duration of follow-up itself is used to define the subgroups being compared.

Table 3.1 presents an example of the magnitude of this dose-response fallacy in actual practice. In the original report of an early study of vinyl chloride workers (Duck *et al.*, 1975), the authors observed that the all-causes SMR declined from 110 for those employed for less than 15 years to 61 for those employed for 15 or more years and stated that no significant excess of mortality had occurred. However, the apparent decline in the SMRs was due entirely to the use of an improper methodology. After correcting the fixed person-years allocation used in the original analysis to an appropriate, dynamic one, the statistically significant negative trend in the SMRs disappeared. There was even an indication of a positive trend in the SMR for digestive cancer with duration of exposure (Duck & Carter, 1976; Wagoner *et al.*, 1976). Enterline (1976) discusses a similar error in the report of Mancuso and El-Attar (1967), who failed to detect a trend in respiratory cancer SMRs among asbestos workers who had been employed for increasing lengths of time.

We describe two algorithms for the correct assignment of person-years observation in the presence of time-dependent exposures categories, the use of which enables one

PART C ADDENDUM

PUBLIC COMMENTS AND RESPONSES TO THE DRAFT INORGANIC ARSENIC REPORT

Prepared by the Staffs of the Air Resources Board
and the Department of Health Services

March 1990

Part C Addendum contains the comments received from the public during the October 31, 1989 to December 1, 1989 public review period for the Draft Report on Inorganic Arsenic. The responses of the Air Resources Board and the Department of Health Services to those comments are also contained in this Addendum.

CONTENTS OF THE ADDENDUM TO PART C

I.

Comment Letters Received from the Public on the Draft Inorganic Arsenic Report

CalMat Co

P.O. BOX 2950. LOS ANGELES, CALIFORNIA 90051 (213) 258-2777
3200 SAN FERNANDO ROAD. LOS ANGELES. CALIFORNIA 90065

November 28, 1989

Mr. Robert Barham, Chief
Toxic Air Contaminant Identification Branch
Air Resources Board
Atten: Inorganic Arsenic
P. O. Box 2815
Sacramento, CA 95812

Dear Mr. Barham:

With one exception, I concur with your staff's responses to my April 28, 1988 comments (October 1989 Draft, Part C, Section II). This exception is to the statement that arsenic emissions from sources related to raw material preparation and cement preparation "may be significant because most of them are not equipped with any control devices". (Response to Comment #3). Indeed, dust emissions from virtually all such sources (crushers, screens, grinding mills, storage silos, clinker coolers, conveyor belt transfer points, air slide alleviators, etc) are controlled by high efficiency baghouses.

ARB staff has calculated that "arsenic emissions from cement kilns (including coal combustion) range from negligible amounts to 0.76 ton in 1985". (October 1989 Draft, Part A, Appendix D, #5). The lower limit of this emission range is 0.0042 ton (1490 tons x 2.8 ppmw x 10^{-6}). So that cement production emissions remain in perspective with other sources, I request that the range, "0.004-0.76", be shown on Table II-2 (October 1989 Draft, Part A, P. A-33) as combined coal combustion and cement production emissions, rather than the fixed 0.56 tons and 0.2 tons, respectively, presently listed. This would be consistent with the use of emission ranges for the other four fuel combustion sources listed.

Less than a year from now the actual AB2588 emissions data for arsenic and the other trace metals should be available for all operating California cement plants. As staff has observed, these data should provide far more accurate estimates than those from the

estimating techniques which previously have been employed by necessity.

Thank you for the opportunity to comment again on the inorganic arsenic report.

Sincerely,

David S. Cahn
Vice President, Regulatory Matters

CHEMICAL MANUFACTURERS ASSOCIATION

Geraldine V. Cox, Ph.D.
Vice President-Technical Director

January 18, 1990

Mr. Kelly Hughes
Toxic Air Contaminant Identification Branch
California Air Resources Board
Attn: Inorganic Arsenic
1219 K Street
Sacramento, CA 95814

Dear Mr. Hughes:

On behalf of the Arsenic Acid Task Force of the Biocides Panel of the Chemical Manufacturers Association, I am pleased to submit the enclosed comments on the California Air Resources Board Draft Report on Inorganic Arsenic.

These brief comments seek to clarify some areas of concern in the draft report issued by your office.

If you have any questions, please feel free to call Dr. Has Shah of my staff at 202/887-1192.

Sincerely yours,

Geraldine V. Cox

Enclosure

VIA FEDERAL EXPRESS

CHEMICAL MANUFACTURERS ASSOCIATION

BIOCIDES PANEL ARSENIC ACID TASK FORCE

COMMENTS ON

THE CALIFORNIA AIR RESOURCES BOARD

DRAFT REPORT ON INORGANIC ARSENIC, OCTOBER 1989

PART A

Public Exposure to Airborne Inorganic Arsenic in California

Section II, Sources of Atmospheric Inorganic Arsenic, Part C, Emissions, Subsection 9, Wood Preservatives, page A-42.

This section of the report addresses air emissions of arsenic from use as a wood preservative and states that the emissions from this use are negligible. The Task Force agrees with the Board in this assessment. The Task Force provides below additional data to further support this conclusion. These data were generated as a result of EPA-mandated air monitoring for arsenic at wood treatment plants. The study included 412 personal air monitoring samples gathered from employees in 141 treatment plants across the country. The results indicate that:

- In only one of the 412 samples was the airborne level of arsenic above 10 micrograms/cubic meter of air averaged over an eight-hour period;
- In only seven instances did the airborne concentration of arsenic reach 5 micrograms/cubic meter of air; and,
- In 98.3% of all measured air concentrations of arsenic were found to be less than 5 micrograms/cubic meter of air.

The Task Force feels that this information supports the assertion of the Board regarding the negligible contribution of wood preservatives to the atmospheric burden of arsenic. We welcome the use of this information by the Board in the final document and in the executive summary of the document.

PART B

Health Effects of Arsenic Compounds

Section 2.0, Uptake, Distribution, and Metabolism, Part 2.1, Absorption, page 2-1.

Unsupported statements in this section assert that approximately 80% of an ingested dose of arsenic is absorbed. According to Vahter, a recognized expert in the area of arsenic pharmacokinetics, the amount of arsenic absorbed following ingestion is dependent upon the solubility and valence state of the arsenical as well as the species of animal (Vahter, 1983, 1981, 1980). Apparently, soluble arsenicals are well absorbed from the gut of humans and several laboratory species except hamsters. Approximately 90% of the ingested soluble arsenic, trivalent or pentavalent, is reported to be absorbed. However, suspensions of insoluble arsenic trioxide are reported to be only 30-40% absorbed in rodents and not appreciably absorbed in humans.

Section 5.0, Chronic and Subchronic Toxicity, Part 5.1.2, Cardiovascular System, page 5-2.

The evidence for direct myocardial toxicity from arsenic overexposure is, in general, weak. In the report prepared by the Board, only two studies are presented to support an association between arsenic overexposure and myocardial effects. The cardiac effects observed in the 1983 Carmingnani study disappeared spontaneously during the chronic exposure of the test animals. The second study, a 1954 German investigation, is reported as a secondary source from an EPA review. Details of the cardiac changes (incidence, dose-response relationship, type of EKG change, statistical significance, etc.) are not provided.

Section 5.2.2 describes human data for myocardial toxicity, but these data are limited to a single reference (Weinberg, 1960). These effects have not been documented for arsenic in subsequent literature, despite the many descriptions of acute arsenic intoxication episodes published since 1960. Myocardial effects were also notably absent in eleven of the major epidemiology studies of arsenic exposure. If there were a strong association, it would have been revealed in those cancer epidemiology studies.

Peripheral vascular disease conditions are, however, consistently reported for arsenic overexposure. Descriptions of such conditions occur in anecdotal accounts of acute arsenic poisonings and in the findings of epidemiology studies. The finding is most prominently featured in the Tseng study (Tseng 1977, 1968), however, it is not without controversy. In any case, the peripheral vascular changes that are reported for arsenic overexposure are separate and distinct from myocardial toxicity and should not be taken as evidence for cardiotoxicity.

Section 5.0, Chronic and Subchronic Toxicity, Part 5.2.5 Skin, page 5-7.

Skin irritation and the development of abnormal skin pigmentation are regarded by clinicians (Hine, 1975) as a hallmark of arsenic intoxication. The lesions are characterized by hyperkeratinization and hyperpigmentation. Whether or not such lesions are "precancerous" is not scientifically established.

Section 6.0, Reproductive Toxicity, Part 6.2, Animal Studies, page 6-3.

Developmental toxicity studies on arsenic acid have recently been completed by the Pennwalt Corporation in mice and rabbits. The studies are unpublished, but the sponsor of the studies will make the results of the work available to the Board for consideration. In summary, the studies showed that in mice receiving 10, 32, or 64 mg/kg/day, the no effect level for maternal toxicity, embryolethality, and fetotoxicity was 10 mg/kg/day. In rabbits receiving .25, 1.0, or 40 mg/kg/day, the no effect level for maternal toxicity, terata, and embryotoxicity was 1.0 mg/kg/day.

Section 9.0, Carcinogenicity -- Human Data, page 9-1.

The peer-reviewed basis for considering inorganic arsenic to be a human carcinogen, as outlined in Table 1.1 on page 1-11 of the report, is based on considerations of both inhalation and ingestion data. The Board, however, bases its cancer potency estimates for arsenic on inhalation data only. If only inhalation data are to be considered as a basis for supporting arsenic as a human carcinogen, then only arsenic trioxide can reliably be considered a carcinogen.

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ATOCHEM NORTH AMERICA, INC.
Three Parkway - Philadelphia - Pennsylvania 19102 - (215) 587-7000

January 25, 1990

Mr. Robert Barham, Chief
Toxic Air Contaminant Identification Branch
Air Resources Board
Attn: Inorganic Arsenic
P.O. Box 2815
Sacramento, CA 95812

Re: Draft Report on Inorganic Arsenic

Dear Mr. Barham:

In late December 1989 the Chemical Manufacturer's Association (CMA) sent you its comments on your draft report on inorganic arsenic. In that letter three studies were referred to which required verification by their sponsor. At this time Atochem North America (formerly Pennwalt Corporation) is providing copies of summaries of the studies for your information: Teratology in Mice, Teratology in Rabbits, and Dermal Sensitization in Guinea Pigs, all performed with arsenic acid 75%. These are unpublished studies which have been submitted to EPA to support data requirements.

The information in these reports is proprietary and any use beyond reference in your report is not allowed. Please contact me if you have any questions about the studies or their results.

Very truly yours,

ATOCHEM NORTH AMERICA
AGRICHEMICAL DIVISION

Rebecca A. Clemmer

Rebecca A. Clemmer
Registration Specialist
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RAC/rvd

cc: Has Shah, CMA
Pazianos, Pazianos Association

file: arsenic-studies corr.

EnviroMD

[redacted] E. FORT LOWELL ROAD • TUCSON, AZ 85716 • 602 881-1000 • FAX 602 [redacted]

November 30, 1989

Mr. Robert Barham, Chief
Toxic Air Contaminant Identification Branch
Air Resources Board
Attn: Inorganic Arsenic
P.O. Box 2815
Sacramento, CA 95812

Dear Mr. Barham:

We wish to clarify our comments presented to the Air Resources Board (ARB) on May 9, 1988 by Dr. Furtado for PG&E. We agree with the ARB staff that our comment suggesting that the risk estimate for total airborne arsenic should be lowered by a factor of 20-40 is in error. The sentence should have read that the risk is overestimated by at least a factor of 2-4 (not 20-40). The corrected comment is included as Attachment A to this letter. While risk is overestimated by at least a factor of 2-4 it may be overestimated by as much as a factor of 10 when As(V) is the sole species present in air.

Speciation is still an important consideration in performing a risk assessment for inorganic arsenic due to the following considerations:

1) in-vitro As(V) is less toxic than As(III) based on experimental results, cited by the ARB staff in Part B of their October 1989 draft, with end points ranging from genotoxicity to lethality.[1 2 3 4]

2) mechanisms of action of As(III) and As(V) appear to differ:

   As(V) is believed to substitute for inorganic phosphate in vivo thus affecting ATP synthesis.

   As(III) binds to sulfhydryl and inactivates sensitive enzymes such as pyruvate dehydrogenase.

3) There is still no evidence of the lung's ability to convert As(V) to As(III). If the lung were to convert As(V) to As(III), we would expect the metabolic excretion profile for each species should be identical after administration of each

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species to the lung. The data in Attachment B, presented by Rosner and Carter (1987), demonstrate marked differences in metabolic excretion profiles for As(III) compared to As(V), thus the bioavailability for As(V) is not the same as As(III) in the lung.

4) Rosner and Carter demonstrate that intratracheal deposition of arsenate (As(V)) results in a markedly different metabolic excretion profile compared to intratracheally administered arsenite (As(III)).[5] They show that intratracheal As(V) is eliminated more rapidly than As(III), attained significantly lower blood levels than As(III) at 24h post dosing, as well as significantly lower levels in the liver than As(III), and is excreted predominantly as inorganic arsenic and more rapidly than As(III). It is also significant to note that As(V) was cleared more completely from the lung than As(III) at 24, 48, and 96 hours post dosing by an average factor of 1.56 +/- 0.26 (see Table 1 in Attachment B).

We do recognize that there is no epidemiologic evidence that As(V) is less carcinogenic to humans than As(III) but, likewise there is no direct evidence that As(V) is carcinogenic. Furthermore, the epidemiologic studies linking As(III) to respiratory tract cancer in humans have not been conclusively confirmed in animal experiments without the use of confounding factors. Lacking evidence to the contrary, it is a prudent and reasonable assumption, based on the available scientific evidence, that the toxicity and carcinogenic potency of As(III) is greater than that of As(V) and should be factored into the risk assessment.

Very truly yours,

Steven Pike, M.D.

Dean E Carter
Dean Carter, Ph.D.

Enclosure

NOTES

1. Amacher DE and Paillet SC. Induction of trifluorothymidine-resistant mutants by metal ions in L5178Y/TK$^{+/-}$ cells. Mutation Research 78:279-288 (1980).

2. Okada S, Yamanaka K, Ohba H and Kawazoe Y. Effect of inorganic arsenics on cytotoxicity and mutagenicity of ultraviolet light on Escherichia coli and the mechanism involved. J Pharm Dyn 6:496-504 (1983).

3. Rossman TG. Enhancement of UV-mutagenesis by low concentrations of arsenite in E. coli. Mutation Res 91:207-211 (1981).

4. Nordenson I and Beckman L. Chromosome aberrations in cultured human lymphocytes exposed to trivalent and pentavalent arsenic. Scand J Work Environ Health 7:277-281 (1981).

5. Rosner MH and Carter DE. Metabolism and excretion of gallium arsenide and arsenic oxides by hamsters following intratracheal installation. Fundamental and Applied Toxicology 9:730-737 (1987).

Review of California DHS Draft Report on Inorganic Arsenic

I. The risk assessment should incorporate the difference in potency of Arsenic III compared to Arsenic V in developing the unit risk estimate. Existing data are sufficient to warrant a unit risk at least ten times lower for Arsenic V than for Arsenic III. [Comments by Dean Carter, Ph.D. and Steven Pike, M.D.]

In Section 2.1.2 DHS suggests that inhalation of ambient arsenic may be more toxic than ingestion of an equivalent amount of dietary arsenic. DHS reasons that lack of methylation (detoxification) in the lung may be responsible. It is important to note that it is the trivalent arsenic that is taken up by hepatocytes for methylation and not the pentavalent. Speciation of arsenic plays an important role in metabolism, As(V) requiring reduction to As(III) to undergo methylation. Since the target for this risk assessment is the effect of arsenic on cells of the lung, a closer look at the effects of As(III) and As(V) on cells is warranted.

Section 7.1.1 cites reports in which arsenite As(III) inhibited DNA repair of damage caused by UV radiation in bacteria, while arsenate As(V) at five times the concentration had no effect on DNA repair.

In Section 7.3 concentrations of arsenate (As(V)) ten times greater than arsenite (As(III)) were required to inhibit mitogenesis. Furthermore, mutation of frequencies were negative in the mouse cell thymidine kinase (TK) locus assay when treated with As(V). Section 7.3 also reports positive responses for chromosomal abnormalities in mammalian cells exposed to As(III); As(V) was not tested.

In Section 7.3.1 DHS cites work reported on human lymphocytes exposed in vitro to sodium arsenite (As(III)) which resulted in chromatid breaks and gaps, but was negative when tested with sodium arsenate (As(V)).

It is apparent that there is at least a ten-fold difference in the potency of As(III) compared to As(V). When considering the lack of evidence of the lung's ability to metabolize As(V) to As(III) and detoxify As(III) by methylation, failing to factor in speciation of arsenic in considering toxicity combined with failing to consider ratios of As(III):As(V) in ambient air, risk is overestimated by at least a factor of 2 to 4.

II. The risk assessment should factor the relative contributions and potencies for the development of cancer that vary with particle size, solubility, and the proportion of As(III):As(V) in ambient air. The magnitude of such effects should be estimated and incorporated into the calculation of the unit risk for arsenic. Consideration of these factors will lower the resultant risk estimates. [Main comments by Steven Pike, M.D., some comments by Dean Carter, Ph.D.]

In Section 11.4.2C DHS recognizes that assuming ambient air and occupational exposure involve similar As(III):As(V) ratios may overestimate risk. Arsenic trioxide (As(III)) is probably nearly the exclusive form of exposure to the Anaconda and Tacoma smelter workers. Andreae, 1980 reports that nearly all the arsenic emitted from the Tacoma smelter is arsenic trioxide (As(III)) and that rainfall samples from the Anacortes, Washington site were 88% arsenite (As(III)) strongly supporting the argument that the Tacoma smelter is the dominant source of arsenic at this site. This result should be contrasted with the environmental ratio of As(III):As(V) reported in Appendix C of Part A [Solomon, 1987] to be close to 1 (i.e., equal mixture of both species, approx. 50% As(III)). However, this ratio was determined from samples collected in the City of Industry and thus may not truly reflect the ratio in the majority of urban and rural areas. Studies conducted in Tucson, Arizona, a city ringed by copper mines and smelters, revealed an As(III):As(V) ratio of about 0.31 +/- 0.29 (i.e., 24% As(III)) indicating that As(V) may be the species present in the atmosphere at up to three times the concentration of As(III), [Solomon, 1984]. Furthermore the ratio of 0.31 represents the mean of the highest total arsenic measured in 15 of 60 samples taken over a one year period [Solomon, 1988]. These samples were collected about 500 meters from an electric powerplant. Comparing the ratio of As(III) reported by Andreae to the ratios of As(III) reported by Solomon suggest that there is 1.8 (88/50) to 3.7 (88/24) times as much As(III) in Tacoma air as in powerplant or California smelter air. Failing to incorporate the difference in speciation of arsenic in air overestimates risk by a factor of two to four.

III. The risk assessment should be revised and modified based on an evaluation of physical state and should incorporate the differences in physical state that exist between the arsenic compounds measured in the epidemiologic studies and those measured in the ambient exposures for the development of unit risk estimates. [Main comments by Dean Carter, Ph.D., some comments by Steven Pike, M.D.]

CAPTURE:

The size of the particles should be considered in the exposure extrapolation. The deposition of particles of different sizes has been well studied in the human lung. The particle size distribution of the arsenic oxide particles at the Tacoma Washington smelter has been studied. A brief description can be found in Piver (1983). It appears that about 55% of the arsenic particles were smaller than 2.5 um. Although it is not possible to directly compare this with the findings described in the California DHS report (page A-78), it appears that the California environmental samples are considerably smaller than smelter samples with regard to their arsenic distribution. Smaller particles do go deeper into the lung but their deposition decreases to the point that most very small particles are exhaled with the breath without deposition. Data suggests that only approximately 30% to 50% of particles between 0.1 um and 1.0 um are retained by the lung parenchyma [Task Force Group on Lung Dynamics,

1966]. The arguments made in the California DHS report (page 10-7) suggest that the bronchioles are the target site in the lung and not the lower alveolar region. This would be consistent with the deposition of larger particles. Thus, a risk assessment should include an evaluation of the particle size distribution of the environmental samples as compared with the smelter samples and an assessment of deposition rate and site differences.

RETENTION:

There are several considerations for an evaluation of toxicity based on physical state. First, assuming that the lung is the target organ in the DHS evaluation, the soluble compounds of arsenic described in this evaluation would be rapidly dissolved and absorbed from the lung (Marafante and Vahter, 1987). Arsenic is not retained in the body but is rapidly excreted into the urine (Cal DHS 2-6,7). Yet, smelter workers have been found to have high concentrations of arsenic remaining in their lungs several years after exposure ceased (Vahter, 1983). This suggests that the workers may have been exposed to insoluble forms of arsenic (i.e., sulfides, arsenite salts of calcium, lead, zinc, etc.) and the retention of these compounds may have been significant in the development of lung cancer.

BIOAVAILABILITY:

The hazard assessment discussion has ignored an evaluation of the physical state of the arsenic. The review does briefly distinguish between arsenic compounds in the vapor phase and in the solid (particle) phase (Cal DHS A2-A3, A72-A79). However, there are many arsenic compounds that are of environmental importance which have different water solubilities (NRC, 1977). These compounds of different solubilities have different bioavailabilities (Marafante and Vahter, 1987; Webb et al., 1984) and different forms of toxicity (Webb et al., 1986).

Insoluble arsenic (As(III)) salts are probably more hazardous than the soluble salts because they are retained in the target organ (the lung) whereas the soluble forms can readily enter the bloodstream where they can be taken up by the liver to undergo detoxification by methylation. This concept is supported by the animal work by Pershagen and coworkers which is cited in the California DHS report on page 8-3 as supportive of arsenic being a lung carcinogen in animals after intratracheal instillation of arsenic. All animal groups in this study received the arsenic in a carrier dust of charcoal carbon to increase the lung retention of arsenic as well as a solution of sulfuric acid. This supports both the concept that arsenicals retained in the lung may have had an effect on the development of lung cancer and that sulfur oxides may have a contributory effect on arsenic carcinogenicity. These critical experimental details were ignored in the California DHS report. Thus, a risk assessment should include an evaluation of the physical form and solubility of the arsenic with special emphasis on how much can be retained.

IV. The DHS Risk Assessment should consider the possibility of a threshold below which there are no significant adverse effects. The use of a zero threshold may actually create significant adverse effects if arsenic is an essential element in humans and is regulated to a level which would create a deficiency state. Thus a zero threshold would not be biologically plausible. DHS is arbitrarily dismissing the possibility of a threshold; a conclusion contrary to the opinions of other scientists. Furthermore, if evidence for arsenic as an essential element in humans becomes compelling, some scientists would argue that there is a teleologically sound basis for the existence of a threshold below which no significant adverse effects would result. [Main comments by Dean Carter, Ph.D., some comments by Steven Pike, M.D.]

The California DHS report discounts the possibility of a threshold dose. There are several workers in the field who would have come to the opposite conclusion. There is one point on page 10-5 of the report which shows a lack of understanding of arsenic binding. The report states "A single instance of sulfhydryl group binding to an enzyme might result in misrepair or breakage of DNA." This type of argument has been used with alkylating agents of DNA which form a covalent bond after an irreversible reaction with the DNA. In that case, one molecule forming one bond may indeed result in breakage of DNA. However, arsenic binding to sulfhydryl groups is an equilibrium process in which the bonds are continually being formed and broken. The number of molecules which have bound to arsenic depends on the free arsenic concentration and the actual sulfhydryl groups which are bound change constantly. The dose-response relationships for such equilibrium processes have been well described in basic pharmacology texts and support the concept of a threshold.

The argument that DHS raises in Section 10.5.2 that a single instance of sulfhydryl group binding to an enzyme might result in misrepair or breakage of DNA is biologically not plausible. Enzymes have great reserve capacity for function in human physiology. This is most dramatically evident when one considers the ability of heterozygous genotypes for enzyme deficiency in persons with inborn errors of metabolism to be phenotypically normal. It is extremely unlikely that one altered enzyme molecule would bind to DNA and cause misrepair or breakage in the midst of overwhelming numbers of "normal" enzyme molecules.

The staff at DHS cite the possibility that "a single instance of arsenolysis might result in DNA damage." However the hypothesis that inorganic arsenic (As(V)) competes with phosphorus to form unstable arsenate DNA and RNA esters has never been proven in vivo. All experimental results have been based on isolated enzyme or single cell studies and there is no evidence that this mechanism is biologically plausible in mammalian systems. DHS has not shown that a threshold model fails to fit the data as well or better than a linear no threshold model and evidence suggests that the converse is true.

BIBLIOGRAPHY

Andreae, M.O. 1980. Arsenic in Rain and the Atmospheric Mass Balance of Arsenic. J. Geophys. Res. 85: 4512-4518.

Marafante, E. and M. Vahter. 1987. Solubility, retention and metabolism of intratracheally and orally administered inorganic arsenic compounds in the hamster. Environ. Res. 42: 72-82.

National Research Council. 1977. Arsenic. National Academy of Sciences, Washington, DC. p. 4-15.

Piver, W.T. 1983. Mobilization of arsenic by natural and industrial processes. In "Biological and environmental effects of arsenic" edited by B.A. Fowler. Elsevier, Amsterdam, p. 40.

Solomon, P.A., Rabano, E.S., Castillo, N.T. and Torre, K.J. Speciation of Arsenic in Ambient Aerosols Collected in Los Angeles. Final Report 1182R/0214A submitted to California Air Resources Board, May 19, 1987.

Solomon, P.A. Collection and Analysis Techniques for Studies of Atmospheric Arsenic Species, Ph.D. Thesis, Dept. of Chemistry, University of Arizona, Tucson, Arizona (1984).

Solomon, P.A. Personal communication, May 3, 1988.

Task Force Group on Lung Dynamics, Committee II IRCP, Deposition and retention models for internal dosimetry of the human respiratory tract. Health Phys., 12, 173, 1966.

Vahter, M. 1983. Metabolism of arsenic. In "Biological and environmental effects of arsenic" edited by B.A. Fowler. Elsevier, Amsterdam. p. 172.

Webb, D.R., I.G. Sipes and D.E. Carter. 1984. In vitro solubility and in vivo toxicity of gallium arsenide. Toxicol. Appl. Pharmacol. 76: 96-104.

Webb, D.R., S.E. Wilson and D.E. Carter. 1986. Comparative pulmonary toxicity of gallium arsenide, gallium oxide or arsenic oxide intratracheally instilled into rats. Toxicol. Appl. Pharmacol. 82: 405-416.

FUNDAMENTAL AND APPLIED TOXICOLOGY 9, 730–737 (1987)

Metabolism and Excretion of Gallium Arsenide and Arsenic Oxides by Hamsters following Intratracheal Instillation[1]

MITCHELL H. ROSNER AND DEAN E. CARTER

Department of Pharmacology and Toxicology, College of Pharmacy, University of Arizona, Tucson, Arizona 85721

Metabolism and Excretion of Gallium Arsenide and Arsenic Oxides by Hamsters following Intratracheal Instillation. ROSNER, M. H., AND CARTER, D. E. (1987). *Fundam. Appl. Toxicol.* 9, 730–737. The increasing use of gallium arsenide (GaAs) in the electronics industry has produced the need for pharmacokinetic and toxicologic data on GaAs. The disposition in male Syrian golden hamsters ($n = 4$) following intratracheal instillation of GaAs (mean volume diameter 5.8 μm), arsenic(III) oxide (arsenite), and arsenic(V) oxide (arsenate) at a dose of 5 mg/kg body weight was examined. Blood, kidney, liver, and lung samples were collected at 1, 2, and 4 days after administration. Excreta were collected daily. Urinary metabolite profiles were determined after separation on a mixed anion–cation-exchange column. Total As content was analyzed by direct hydride flame atomic absorption spectrophotometry after digestion. Arsenic blood levels after GaAs, arsenite, and arsenate administration were 0.185 ± 0.041, 0.596 ± 0.117, and 0.310 ± 0.045 ppm, respectively, after Day 1. Arsenic blood levels after GaAs administration increased to 0.279 ± 0.021 ppm on Day 2 indicating continued absorption while levels decreased for the arsenite and arsenate groups. At Day 1 the liver contained 0.565 ± 0.036, 2.62 ± 0.26, and 0.579 ± 0.144% of the arsenic dose of GaAs, arsenite, and arsenate, respectively. The arsenite and arsenate were rapidly excreted in the urine with almost half the dose appearing after 4 days; in contrast, only about 5% of the GaAs was found at the corresponding time. Total recoveries, as arsenic equivalents, for the three compounds were between 75 and 80%. Ratios of the two major urinary metabolites (dimethylarsinic acid/total inorganic As species) were 1.41, 1.71, and 0.983 for GaAs, arsenite, and arsenate, respectively. GaAs is metabolized to the same compounds as arsenite and arsenate, and shows a metabolic profile most similar to that observed for sodium arsenite.

Due to its unique physical characteristics, gallium arsenide (GaAs) has several applications in the electronics industry. The integral components of discrete microwave devices, lasers, light emitting diodes, photoelectric chemical cells, and semiconductor devices may be composed of GaAs (Robinson, 1983). Exposure to GaAs in the semiconductor industry is a possible occupational risk since cleaning and slicing GaAs ingots to yield the desired wafers can generate GaAs particles (Briggs and Owen, 1980). Current manufacturing processes use 5 to 10 tons of arsenic in GaAs devices, and it is thought that the production will increase 3- to 10-fold by 1990 (Willardson, 1983).

GaAs has been shown to be soluble in aqueous solutions and forms unidentified gallium and arsenic species upon dissolution (Webb *et al.*, 1984). The various species of arsenic which are formed following inhalation may lead to both pulmonary and systemic effects. This study was designed to compare the metabolism and excretion after intratracheal instillation of GaAs and the soluble arsenic oxides, sodium arsenate (As(V)) and sodium arsenite (As(III)). The hamster was chosen as the animal model since its urinary metabolic profile most closely resembles that of humans following inorganic arsenic exposure.

[1] This work was supported by NIH Grant OHO2076.

0272-0590/87 $3.00

METHODS

Preparation of particles. Particles of GaAs were prepared as described by Webb *et al.* (1984) except that the pulverized GaAs was ultimately sieved through a 10-μm precision microsieve (No. L3-M10, ATM Corp., Milwaukee, WI). This fraction was determined to have a mean count diameter of 1.63 μm and a mean volume diameter of 5.82 μm by an electrozone celloscope fitted with a 48-μm orifice probe. Particle shape was determined to be approximately spherical by scanning electron microscopy.

Analytical determination of arsenicals. The procedure of Webb and Carter (1984) was employed for quantification of total arsenic in all biological samples. Standards for dimethylarsinic acid (DMAA), monomethylarsonic acid (MMAA), arsenic(V), and arsenic(III) were prepared as described by Webb and Carter (1984). The chromatographic procedure of Maiorino and Aposhian (1985) was used for separation of the urinary metabolites. A modification of the spectrophotometric method of Lasko *et al.* (1979) was used as a confirmatory method for both the total arsenic and the metabolites. This was done on samples containing greater than 1 μg As, the detection limit of the method. The apparatus used to generate the various arsines was similar to the arsine generator used by Webb and Carter (1984). The exit line was fitted with a lead acetate trap and the nitrogen entrained flow (0.1 ml/min) was terminated in a 10 × 150-mm borosilicate tube fitted with a serum cap with an outlet for the nitrogen gas and filled with a 0.5% silver diethyldithiocarbamic acid in pyridine solution. The sodium borobydride ($NaBH_4$) was introduced into the reaction vessel dropwise via a 1-ml gas-tight syringe as a 10% (w/v) $NaBH_4$ in 1 N NaOH solution. A volume of 20 ml of pH 5.2 citrate–acetate buffer or 3 N HCl was used in the reaction vessel. The buffer was used to evolve dimethylarsine and arsine derived from arsenite.

Dose solution. The GaAs particles were continually mixed using a magnetic stirrer to yield a suspension of 5 mg As/ml (96.53 mg GaAs/10 ml) in a 0.05% Tween 80 (No. 1754, Sigma Chemical Co., St. Louis, MO) physiological saline solution. The dose solution was delivered immediately to the animals to ensure minimal particle dissolution. Sodium arsenite (No. S 225, Fisher Chemical Co., Fair Lawn, NY) and sodium arsenate (No. SO 4145, Pfaltz and Bauer, Stamford, CN) were used to prepare 10 ml of the dosing solutions by initially dissolving the powders (86.7 and 208.2 mg, respectively) in 0.1 N NaOH and subsequently adjusting the pH to 7.4 with HCl. The final volume was diluted with a 0.05% Tween 80 saline solution. These solutions were quantified by both analytical procedures to determine the purity and form of the arsenic dosed. All arsenate and arsenite dosing solutions were found to be at least 98% pentavalent and trivalent, respectively, as determined by the combined ion exchange–atomic absorption technique. The spectrophotometric technique showed greater than 95% purity. A solution of saline and Tween 80 was given as the vehicle to the control animals.

Treatment of animals. Male Syrian golden hamsters (130 ± 15 g) were obtained from Charles River Breeding Laboratories (Boston, MA) and allowed to acclimate for at least 1 week prior to dosing. Water and food (Wayne Lab Blox) were provided *ad libitum* throughout the studies. A 12-hr light cycle was maintained with artificial lighting. The hamsters were randomly divided into groups of four animals. Groups administered GaAs, arsenite, and arsenate were killed at 1, 2, and 4 days, and a control group was included at Day 1. The hamsters were dosed intratracheally with 5 mg/kg As of the appropriate solution by a modified method of Brain *et al.* (1976). A plastic speculum was placed into the trachea as a guide for the needle and to prevent expiration of the dose. After dosing, the hamsters were placed into individual polycarbonate metabolism cages (No. 1114-ALS, Thomas Scientific, Philadelphia, PA) for the daily collection of excreta. To aid in the collection of the viscous hamster urine, the cages were washed down with water and the washings were added to the urine. The urine and feces were stored frozen at −15°C until analysis.

The animals were sacrificed by carbon dioxide inhalation. A chest incision was made, the rib cage was removed, and 1 ml of blood was drawn by cardiac puncture and placed in 4 ml of a saturated EDTA solution. Only three major organs were collected for assessing the distribution of the three compounds: the lung (site of administration), the liver (major site of metabolism), and the kidney (major site of concentration for urinary elimination). The lungs were separated into the individual lobes and the liver and kidneys were trimmed of extraneous fat and connective tissues and weighed. All three organs were homogenized with a Ultra-Turrax Tissumizer (Tekmar Model SDT, Cincinnati, OH) in 15 ml of water and adjusted to a final volume of 20 ml. After thawing, the urine volume was adjusted to 10 ml. Feces were digested overnight in 20 ml of 1 N NaOH and mixed vigorously. Aliquots of the homogenates and the blood were analyzed for total As and expressed as percentage of As administered. Blood was analyzed for total arsenic similarly but reported as concentration (μg As/ml blood) for easier comparison to literature data. An aliquot of urine was analyzed for metabolites and expressed as percentage of the total urinary As metabolites.

Statistics. The results expressed as ratios and percentages were mathematically transformed to induce approximate normality since the distributions of these values are naturally skewed. The transformed values followed more closely a normal distribution. The blood concentration values were assumed to fit a normal distribution. Results expressed as percentage of dose administered were transformed by arc sin $(p)^{1/2}$, where p is the percentage divided by 100. The metabolite ratio results were transformed by taking the log of the ratio value. The

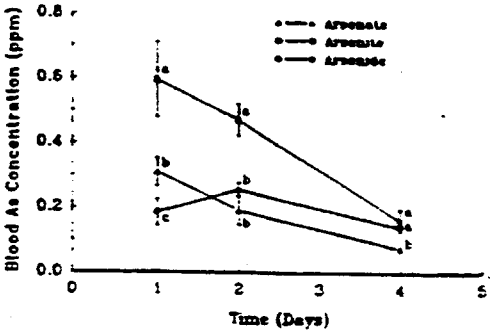

FIG. 1. Mean total arsenic blood concentrations expressed as As equivalents as determined by direct hydride FAAS. Animals were dosed intratracheally with 5 mg/kg As equivalents of the appropriate compound. Values are means ± SD ($n = 4$). [a,b,c]Values not sharing common letters are significantly different at corresponding times ($p \leq 0.05$). Only arsenic levels at the same time point were compared for significance.

transformed values were employed to establish statistically significant differences ($p < 0.05$) by two-way ANOVA and Newman–Keuls multiple means comparisons.

RESULTS

Controls. The control animals were tested for trace levels of arsenic in the tissues, blood, and excreta and yielded no significant amounts of arsenic. Although the urine had traces of arsenic, the levels present could not be quantified by the atomic absorption method employed.

Absorption and distribution. All three compounds were absorbed from the lung into the blood (Fig. 1). The blood concentrations at 24 hr corresponded to 0.418 ± 0.069 (arsenate), 0.827 ± 0.141 (arsenite), and 0.230 ± 0.056% (GaAs) of the dose administered. The peak concentration for GaAs at 48 hr was equivalent to 0.347 ± 0.026% of the GaAs given. Total arsenic blood values from arsenite were significantly higher than those after arsenate at the time points examined. Both compounds showed a continued decrease in blood level with time, suggesting the terminal elimination phase of both arsenicals was reached by 24 hr. The GaAs arsenic blood levels peaked at 2 days after dosing, suggesting that the absorption phase of GaAs was incomplete by Day 1. Even after 4 days the blood arsenic levels were not significantly lower than after 24 hr, suggesting a continuous absorption phase or steady-state conditions.

The absorbed arsenicals were distributed to various tissues (Table 1). The solubles of arsenite and arsenate were almost entirely cleared from the lung by the first day: less than 1% of the dose administered remained. Large amounts of arsenic were present in the lung after GaAs dosing: more than 40% of the dose still remained in the pulmonary region of the respiratory tract after 24 hr. Lung clearance of the particles continued until the end of the experiment. The liver concentrations at 24 hr were 3300 ± 350, 752 ± 189, and 731 ± 103 ppb for arsenite, arsenate, and GaAs, respectively. The arsenite-treated animals had significantly greater arsenic levels in the liver at Days 1 and 4 than did the arsenate-treated animals: arsenic levels in the liver following GaAs administration were significantly lower than either soluble arsenical after the 24-hr time point. The concentrations of arsenic in the kidneys at Day 1 were 3.82 ± 0.83 (arsenite), 3.42 ± 0.48 (arsenate), and 7.62 ± 1.33 ppm (GaAs). No significant differences were found in the kidney after arsenite or arsenate administration; a significantly higher amount of arsenic was found at Day 1 and a smaller amount was found in the kidney at Day 2 after GaAs administration.

Metabolism and excretion. The cumulative percentages of the dose excreted in the urine and feces are shown in Table 2. There is significantly more arsenic eliminated in urine at 24 and 48 hr after the arsenate than after the arsenite dose: after 4 days about 50% of both compounds had been eliminated in the urine. After the GaAs dose, only about 5% of the arsenic was excreted in the urine after 96 hr. Only 10% of the administered dose of soluble arsenic oxides was eliminated in the feces after Day 1; however, 27% of the GaAs-derived As was found in the feces. At

TABLE 1

PERCENTAGE DOSE OF ARSENIC EQUIVALENTS IN TISSUE[a]

Compound	Day	Liver	Kidney	Lung
Arsenate	1	0.579 ± 0.144[b]	0.520 ± 0.081[b]	0.185 ± 0.029[b]
	2	0.545 ± 0.153[b]	0.541 ± 0.058[b]	0.070 ± 0.025[b]
	4	0.266 ± 0.067[b]	0.334 ± 0.114[b]	0.040 ± 0.014[b]
Arsenite	1	2.62 ± 0.26[c]	0.589 ± 0.111[b]	0.329 ± 0.046[c]
	2	0.652 ± 0.136[b]	0.541 ± 0.051[b]	0.089 ± 0.020[b]
	4	0.464 ± 0.070[c]	0.251 ± 0.082[b,c]	0.065 ± 0.013[c]
Arsenide	1	0.565 ± 0.036[b]	1.207 ± 0.218[d]	41.78 ± 5.83[d]
	2	0.312 ± 0.040[d]	0.365 ± 0.056[d]	29.69 ± 1.91[d]
	4	0.144 ± 0.017[d]	0.152 ± 0.026[c]	23.58 ± 1.82[d]

[a] Tissue levels are expressed as percentage of administered dose (as As equivalents) as determined by direct hydride flame atomic absorption spectroscopy (FAAS). Animals were dosed intratracheally with 5 mg/kg As equivalents of the appropriate compound. Values are means ± SD ($n = 4$). Arsenide is GaAs.

[b,c,d] Values not sharing common letters for corresponding tissue and time are significantly different at $p \leq 0.05$. Only arsenic levels at the same time point were compared for significance.

tional 10% of the As was eliminated the next day and a total of almost half of the administered As was found in the feces 4 days after exposure to GaAs. Both arsenic oxide salts showed a large increase in the fecal elimination of arsenic after 48 hr; about 30% of each soluble arsenical was excreted in feces after 4 days.

Metabolite levels in urine after doses of the three inorganic arsenicals is showed in Table 3. A fraction of the arsenate administered was eliminated unchanged in the urine 17.4, 11.3, and 11.2% by 1, 2, and 4 days, respectively. A portion of the arsenite was also eliminated unchanged; 3.7, 9.2, and 9.8% of the arsenite was eliminated as the parent compound on

TABLE 2

CUMULATIVE PERCENTAGE DOSE EXCRETED AS ARSENIC EQUIVALENTS[a]

Compound	Day	Urine	Feces	Total
Arsenate	1	24.64 ± 2.07[b]	7.44 ± 0.49[b]	32.07 ± 1.69[b]
	2	43.43 ± 5.42[b]	20.34 ± 2.41[b]	63.77 ± 7.07[b]
	4	48.49 ± 2.91[b]	29.25 ± 5.49[b]	77.74 ± 7.84[b]
Arsenite	1	15.24 ± 1.49[c]	3.43 ± 0.81[c]	18.67 ± 0.81[c]
	2	32.07 ± 0.88[c]	18.48 ± 1.57[b]	50.55 ± 2.16[c]
	4	48.52 ± 2.60[b]	31.57 ± 3.30[b]	80.08 ± 4.99[b]
Arsenide	1	1.94 ± 0.37[d]	27.01 ± 4.35[d]	28.94 ± 4.48[b]
	2	4.15 ± 0.68[d]	36.74 ± 5.21[d]	40.89 ± 4.67[d]
	4	5.42 ± 0.26[d]	46.34 ± 3.15[d]	51.75 ± 3.00[d]

[a] Levels are expressed as percentage of administered dose (as As equivalents) excreted as determined by direct hydride FAAS. Hamsters were dosed intratracheally with 5 mg/kg As equivalents of the appropriate compound. Values are means ± SD ($n = 4$). Arsenide is GaAs.

[b,c,d] Values not sharing common letters for corresponding excreta and time are significantly different at $p \leq 0.05$. Only arsenic levels at the same time point were compared for significance.

TABLE 3

URINARY METABOLITES AS PERCENTAGE ARSENIC[a]

	As(III)	As(V)	MMAA	DMAA	UA
Arsenate					
Day 1	18.77 ± 1.59[d]	30.24 ± 5.50[b]	8.69 ± 0.59[c]	38.62 ± 0.59[c]	3.69 ± 0.39[b]
Day 2	23.94 ± 4.83[b]	26.01 ± 4.40[b]	10.51 ± 1.83[c]	35.67 ± 3.40[c]	3.86 ± 0.49[b]
Day 4	22.94 ± 4.83[c]	23.16 ± 0.94[b]	4.76 ± 1.52[a]	45.32 ± 1.22[b]	3.84 ± 0.35[c]
Arsenite					
Day 1	24.40 ± 2.98[c]	13.62 ± 1.08[c]	7.64 ± 0.74[b]	52.06 ± 2.89[c]	2.29 ± 0.31[a]
Day 2	30.27 ± 2.45[b]	8.79 ± 1.65[c]	8.17 ± 1.92[b,c]	48.91 ± 3.89[c]	3.86 ± 1.37[b,c]
Day 4	20.29 ± 1.90[b]	12.08 ± 1.05[c]	8.65 ± 2.00[c]	55.46 ± 1.96[c]	3.52 ± 0.62[b,c]
Arsenide					
Day 1	19.70 ± 3.76[b,c]	10.12 ± 1.41[d]	5.38 ± 1.04[a]	58.90 ± 4.29[c]	5.99 ± 0.83[c]
Day 2	13.54 ± 0.96[d]	23.01 ± 3.67[b]	7.48 ± 0.97[c]	51.92 ± 3.20[c]	4.04 ± 0.34[b,c]
Day 4	11.83 ± 1.62[d]	25.77 ± 1.49[d]	6.52 ± 0.91[b,c]	52.88 ± 2.76[c]	3.00 ± 0.52[a,c]

[a] Values are expressed as percentage of cumulative urinary arsenic values (from Table 2). Each metabolite was determined by mixed-bed strong anion- and cation-exchange column chromatography followed by direct hydride FAAS. Values are means ± SD ($n = 4$). MMAA, monomethylarsonic acid. DMAA, dimethylarsinic acid. UA, unknown arsenic containing metabolite. Arsenide, GaAs.

[a,b,c,d] Values not sharing letters for corresponding metabolite and time point are significantly different at $p < 0.05$. Comparisons were made only between treatment groups at a single time point.

Days 1, 2, and 4 respectively. In all cases, DMAA was the major metabolite. An unidentified arsenic metabolite accounted for between 2 and 6% of the total dose found in the urine. MMAA was another minor metabolite for the compounds, accounting for 5–10% of the total urinary arsenic. The variation of values found probably reflects the use of different animals for each time point for each compound in our experimental design.

The levels of As derived from GaAs were less than 5-μg As equivalents of trivalent arsenic, so significant oxidation may have occurred on the chromatographic column. This would only affect the relative amounts of As(III) and As(V). If the total inorganic arsenic (the sum of arsenite and arsenate) was used to compare the results, DMAA was the major metabolite after arsenite and GaAs exposure, but total inorganic arsenic was the major urinary form of As following arsenate administration. The ratio of these two major metabolite fractions (DMAA/total inorganic arsenic; DMAA/TIA) was used to compare the urinary metabolite profiles (Fig. 2). On Day 1, the DMAA/TIA ratio values from the studies were statistically different from each other. At 48 and 96 hr, the metabolite ratio after arsenate administration was significantly different from that of the arsenite and GaAs; ratios for the arsenite and GaAs doses

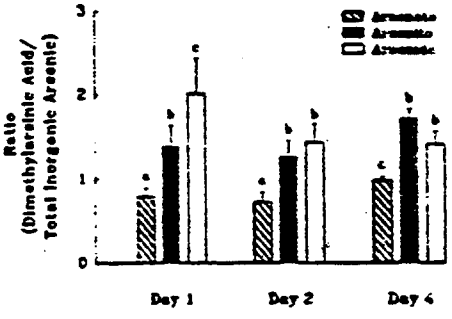

FIG. 2. Cumulative urinary metabolite profile analysis expressed as the ratio of dimethylarsinic acid to inorganic As species. As(III) + As(V), expressed as As equivalents as determined by chromatographic separation followed by direct hydride FAAS. Animals were dosed intratracheally with 5 mg/kg As equivalents of the appropriate compound. [a,b,c]Values not sharing common letters are significantly different at corresponding times ($p < 0.0$

were not statistically different from each other.

Total recoveries. The total recoveries of the administered dose for the three compounds were 78.49 ± 7.92, 81.05 ± 5.04, and 75.83 ± 4.59% for arsenate, arsenite, and GaAs at 96 hr, respectively. The recovery of As after the arsenate and arsenite doses increased with time. Arsenic recoveries of 33.78 ± 1.90 and 65.21 ± 6.87% of the arsenate dose were found in the tissue and excreta collected for 24 and 48 hr, respectively; recoveries of 23.04 ± 0.99 (Day 1) and 52.51 ± 2.74% (Day 2) of the administered arsenite were found.

DISCUSSION

The dissolution of GaAs in aqueous media and animals has been demonstrated from *in vitro* and *in vivo* experiments (Webb *et al.*, 1984); however, these studies did not attempt to characterize the dissolved species. Our results show that the arsenic in the GaAs zinc-blend crystal was biotransformed to arsenic metabolites like arsenic and arsenous acids once it was released from the solid. These results after intratracheal dosing support those found previously (Yamauchi *et al.*, 1986) for GaAs administered orally.

Webb and co-workers (1984) showed that the rat absorbed about 10% of the arsenic after intratracheal instillation of GaAs at doses ranging from 10 to 100 mg/kg. To determine absorption, we have compared the relative levels of arsenic in the urine and tissues for the different treatments. Insufficient time points were collected to determine absorption by area under the blood concentration–time curve calculations. (The individual hamster blood arsenic values are only an indicator of the amount of arsenic in the systemic circulation at the specified time.). About 5% of the As given in the form of GaAs was excreted in the urine by 96 hr. This represents about one-tenth as much urinary arsenic as was found after arsenite and arsenate administration. If the urinary excretion can be related to the cumulative arsenic absorbed, an absorption of about 5–10% of the As from GaAs could be estimated from the excretion data. The urinary excretion data of Yamauchi and co-workers (1986) showed that less than 1% of the total dose was excreted following oral administration of 10–1000 mg/kg GaAs.

The 27% fecal elimination of the GaAs dose after 24 hr was probably due to the lung clearance into the gastrointestinal tract since the completely absorbed soluble arsenicals had values of less than 10% at the same time point. Some gastrointestinal absorption may occur. Webb *et al.* (1984) reported that 56% of the GaAs-derived total arsenic was found in the feces of rats administered a 10 mg/kg oral dose. Yamauchi *et al.* (1986) found 87.5% of the total As from GaAs in the feces of hamsters after a 10 mg/kg oral dose. This expectoration and subsequent gastrointestinal absorption may explain the apparent continuous absorption phase observed with GaAs.

The data we obtained demonstrated a slower rate of arsenic elimination of arsenite when compared to arsenate. Regardless of the route of administration, this relationship held true for most mammals tested (Inamasu, 1983; Odanaka *et al.*, 1980; Vahter, 1981). Mice retained 12% of the dosed arsenite in the body compared to 7% of the administered arsenate at 48 hr when given 4 mg/kg orally (Vahter, 1981). By 96 hr the amount of total arsenic found in the excreta of both soluble arsenicals was about the same in our experiments. GaAs was eliminated more slowly than either arsenite or arsenate. A large amount of the dose of GaAs was still present in the lungs; this shows the much slower rate of absorption and pulmonary clearance when compared to the trivalent and pentavalent arsenic oxyacids. The GaAs retained in the lungs is a source for a prolonged pulmonary exposure as the particulate and has the potential for absorption into the systemic circulation during that time.

Due to the decreased pulmonary absorption and the relatively poor absorption from the gastrointestinal tract. GaAs had a much lower calculated bioavailability following equimolar doses of the three compounds. Distribution of the bioequivalent doses of arsenate and arsenite were compared to allow further evaluation of our results. Arsenite showed significantly greater levels in the blood (596 ppb) than arsenate (310 ppb) at 24 hr. One day after administration of arsenite. liver tissue levels (3300 ppb) were significantly greater than arsenate liver values (752 ppb). These trends agreed favorably with the literature results for hamsters (Lindgren *et al.*, 1982); 1 day following intravenous injection of arsenite and arsenate. arsenic blood levels were 3 times greater and liver levels were 3.5 times higher for arsenite as compared to arsenate. Absolute levels 24 hr after the intravenous dosing were substantially lower than those found after intratracheal dosing. Lindgren *et al.* (1982) also found the kidney concentration for both arsenicals to be 20 ppb at 24 hr. Our kidney concentrations for arsenite (3.82 ppm) and arsenate (3.42 ppm) were substantially higher but were not significantly different from each other either.

The urinary metabolite profile after arsenite exposure was different from that of arsenate at the time points tested. The values obtained compared favorably with hamster experiments by Inamasu (1983); DMAA, total inorganic arsenic, and MMAA were reported as 48.7, 38.4, and 12.8% of the arsenic excreted in the urine following a 10 mg/kg arsenite treatment. Although the absolute amounts of the arsenic metabolites were much lower in the urine of GaAs pretreated animals, the normalized values, expressed as percentage of total urinary arsenic, showed that the GaAs results were not statistically different from those for arsenite at 48 and 96 hr. Thus, the systemic arsenic released from GaAs appeared to be treated like trivalent arsenic by the body. The increased DMAA levels in the urine of the GaAs group may be related to the different amounts of arsenic in the circulation between the two groups. Methylation of inorganic arsenic is a saturable process at higher doses or following low-level chronic exposure (Bencko *et al.*, 1976). The lower amount of arsenic from GaAs at 24 hours may have been methylated more efficiently than the higher level of arsenic from arsenite. An unknown arsenic metabolite was measured at levels which agreed with the literature, between 2 and 3% of the total urinary arsenic (Charbonneau *et al.*, 1980). This compound is probably trimethylarsine oxide (Cullen *et al.*, 1984) or arsenobetaine (Yamauchi and Yamamura, 1984).

Trivalent arsenic has been shown to be relatively more toxic than pentavalent arsenic (NAS, 1977). However, arsenite has been shown to be oxidized to arsenate *in vivo* (Bencko *et al.*, 1976) and As(V) was reduced to As(III) in mice and rabbits (Vahter and Envall, 1983). Careful interpretation of results for comparing inorganic arsenic exposures must be made. Our metabolism results suggest that the systemic arsenic from GaAs is metabolized similar to As(III) and may be As(III). If so, it would be the more toxic arsenic species. Recall that the relative amount of GaAs absorbed over the 4 days was estimated to be one-tenth of the amount absorbed following sodium arsenite exposure. The actual species of arsenic in the lung was not determined so it is difficult to assess the effects of the soluble arsenic present. The GaAs particles still remaining in the lung have been reported to cause numerous pathological lesions consistent with the onset of an acute progressive fibrogenic response (Webb *et al.*, 1984).

In summary, lung arsenic was rapidly cleared after sodium arsenate and arsenite exposure, but GaAs was cleared more slowly following intratracheal instillation. Arsenic blood levels had peaked for arsenic(III) and arsenic(V) before Day 1 but GaAs levels peaked at Day 2. Absorption of GaAs after 4 days was estimated to be one-tenth of that found for arsenite or arsenate if calculations

were based on tissue and excretion data. Thus, the soluble arsenicals had a relative bioavailability at least one magnitude greater than GaAs. The greater fecal elimination of GaAs was probably due to a large lung clearance into the gastrointestinal tract. Arsenic absorbed from GaAs was metabolized to DMAA, MMAA, As(III), and As(V). The urinary metabolite profile of GaAs was similar to both inorganic arsenicals, but the ratio of the major metabolites was statistically different from arsenate only. The DMAA/total inorganic As ratio for GaAs was about twice the value calculated for arsenate. The *in vivo* solubility and large lung retention show that the particulate nature of GaAs must be considered in assessing the toxic effects of this semiconductor material in addition to the systemic toxicity of arsenic.

REFERENCES

BENCKO, V., BENES, B., AND CIKRT, M. (1976). Biotransformation of As (III) to As (V) and arsenic tolerance. *Arch. Toxicol.* 36, 159–162.

BRAIN, J. D., KNUDSON, D. E., SOROKIN, S. P., AND DAVIS, M. A. (1976). Pulmonary distribution of particles given by intratracheal instillation or by aerosol inhalation. *Environ. Res.* 11, 13–33.

BRIGGS, T. M., AND OWENS, T. W. (1980). *Industrial Hygiene Characterization of the Photovoltaic Solar Cell Industry.* NIOSH Technical Report, DHEW (NIOSH) Publication No. 80-112. U. S. Dept. of Health, Education, and Welfare, Cincinnati, OH.

CHARBONNEAU, S. M., HOLLINS, J. G., TAM, G. K. H., BRYCE, F., RIDEWAY, J. M., AND WILES, R. F. (1980). Whole-body retention, excretion and metabolism of (^{74}As) arsenic acid in the hamster. *Toxicol. Lett.* 5, 175–182.

CULLEN, W. R., MCBRIDE, B. C., AND REGLINSKI, J. (1984). The reduction of trimethylarsine oxide to trimethylarsine by thiols: A mechanistic model for the biological reduction of arsenicals. *J. Inorg. Biochem.* 21, 45–60.

INAMASU, T. (1983). Arsenic metabolites in urine and feces of hamsters pretreated with PCB. *Toxicol. Appl. Pharmacol.* 71, 142–152.

LASKO, J. U., ROSE, L. J., PEOPLES, S. A., AND SIRACHI, D. Y. (1979). A colorimetric method for the determination of arsenite, arsenate, monomethylarsonic acid, and dimethylarsinic acid in biological and environmental samples. *J. Agric. Food Chem.* 27(6), 1229–1233.

LINDGREN, A., VAHTER, M., AND DENCKER, L. (1982). Autoradiographic studies on the distribution of arsenic in mice and hamsters administered ^{74}As-arsenite or -arsenate. *Acta Pharmacol. Toxicol.* 51, 253–265.

MAIORINO, R. M., AND APOSHIAN, H. V. (1985). Dimercaptan metal-binding agents influence the biotransformation of arsenite in the rabbit. *Toxicol. Appl. Pharmacol.* 77, 240–250.

NAS (1977). *Medical and Biological Effects of Environmental Pollutants: Arsenic.* Natl. Acad. Sci., Washington, DC.

ODANAKA, Y., MATANO, O., AND GOTO, S. (1980). Biomethylation of inorganic arsenic by the rat and some laboratory animals. *Bull. Environ. Contam. Toxicol.* 24, 452–459.

ROBINSON, A. L. (1983). GaAs readied for high-speed microcircuits. *Science* 219, 275–277.

VAHTER, M. (1981). Biotransformation of trivalent and pentavalent inorganic arsenic in mice and rats. *Environ. Res.* 25, 286–293.

VAHTER, M., AND ENVALL, J. (1983). *In vivo* reduction of arsenate in mice and rabbits. *Environ. Res.* 32, 14–24.

WEBB, D. R., AND CARTER, D. E. (1984). An improved wet digestion procedure for the analysis of total arsenic in biological samples by direct hydride atomic absorption spectrophotometry. *J. Anal. Toxicol.* 8, 118–123.

WEBB, D. R., SIPES, I. G., AND CARTER, D. E. (1984). *In vitro* solubility and *in vivo* toxicity of gallium arsenide. *Toxicol. Appl. Pharmacol.* 76, 96–104.

WILLARDSON, R. K. (1983). Arsenic in electronics. In *Arsenic: Industrial, Biomedical, Environmental Perspectives* (W. H. Lerderer and R. J. Fensterheim, Eds.), pp. 72–88. Van Nostrand, New York.

YAMAUCHI, H., TAKAHASHI, K., AND YAMAMURA, Y. (1986). Metabolism and excretion of orally and intraperitoneally administered gallium arsenide in the hamster. *Toxicologist* 40, 237–246.

YAMAUCHI, H., AND YAMAMURA, Y. (1984). Metabolism and excretion of orally administered dimethylarsinic acid in the hamster. *Toxicol. Appl. Pharmacol.* 74, 134–140.

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November 30, 1989

Via Federal Express

Mr. Robert D. Barham
Chief, Toxic Air Contaminant
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Air Resources Board
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Sacramento, California 95812

Re: Inorganic Arsenic

Dear Mr. Barham:

We are pleased to submit the appended comments of RSR Corporation and its wholly-owned subsidiary, Quemetco, Inc. (hereinafter collectively "RSR") on the California Air Resources Board's ("ARB") draft report on inorganic arsenic ("Draft Report").

RSR appreciates the opportunity to submit these comments and looks forward to assisting the Board as it develops its analysis of the effects of inorganic arsenic.

Respectfully submitted,

Lynn L. Bergeson
Counsel for RSR Corporation

mjl
Attachment

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COMMENTS OF RSR CORPORATION ON THE CALIFORNIA AIR RESOURCES BOARD'S DRAFT REPORT ON INORGANIC ARSENIC

December 1, 1989

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COMMENTS OF RSR CORPORATION ON THE CALIFORNIA AIR RESOURCES BOARD'S DRAFT REPORT ON INORGANIC ARSENIC

RSR Corporation, on behalf of itself and its wholly-owned subsidiary, Quemetco, Inc. (hereinafter collectively "RSR"), submits these comments in response to the California Air Resources Board ("ARB") Draft Report on Inorganic Arsenic ("Draft Report") circulated for comment on October 31, 1989.

I. INTRODUCTION AND SUMMARY

The April 1988 preliminary Draft Report was factually and analytically flawed. Factually, the preliminary analysis was flawed in that it improperly defined secondary lead smelting operations to include virtually all metal processing operations. At the same time, the preliminary analysis referenced the existence of other potential sources of inorganic arsenic emissions, but the analysis neither identified nor quantified those emissions. These deficiencies resulted in the erroneous inference that secondary lead smelters are major sources of inorganic arsenic emissions.

The preliminary analysis was analytically flawed in that it relied upon speculative emissions estimates contained in a study of questionable validity that had little relevance to the facilities discussed in the ARB analysis. In addition, much of the

modelling on which the emission estimates in the preliminary analysis were derived was improperly based on the Industrial Source Complex Short-Term model rather than the Industrial Source Complex Long-Term model.

None of these deficiencies has been adequately addressed in the Draft Report. ARB acknowledges in the Draft Report that potentially significant sources of inorganic arsenic emissions remain unidentified. Still, however, no apparent effort has been made to identify or quantify these emissions. Moreover, recent actual emissions data on Quemetco were not included in the analysis. This is especially troubling since these data indicate emissions of inorganic arsenic from its operations are significantly less than those noted in the Draft Report. The analytical deficiencies arising from the use of the short-term model have also not been remedied.

Moreover, ARB's risk assessment with respect to secondary lead smelter emissions concludes that these emissions are responsible for "6 to 9 excess cancer deaths." This statement is incorrect. Based on ARB's own modelling data and recent stack test data from a secondary lead smelter, inorganic arsenic emissions account for less than one-half excess cancer deaths.

As more fully discussed below, ARB should correct the mortality data regarding secondary lead smelting emissions, distinguish secondary lead smelter and metal processing operations, identify all potential sources of inorganic arsenic emissions, incorporate recent actual emissions data on Quemetco into the

analysis, and revise as necessary Parts A and B of the Draft Report to reference these data.

II. RSR'S INTEREST IN THIS PROCEEDING

Quemetco operates a secondary lead smelter located in City of Industry, California. City of Industry is located in the South Coast Air Basin. ARB characterizes the Draft Report as a summary of ARB's investigation to determine whether, pursuant to California law, inorganic arsenic should be identified as a toxic air contaminant. Draft Report, p. A-1.

Secondary lead smelters may be a source of inorganic arsenic emissions. RSR believes ARB's findings could play a major role in setting future regulatory requirements applicable to the operations of RSR's California subsidiary. RSR thus has a significant interest in this proceeding and offers the following comments on the Draft Report.

RSR submitted comments on the April 1988 preliminary Draft Report. Many of those comments have not been adequately addressed in the Draft Report. Because RSR references these comments in this submission, we have appended, for your convenience, a copy of the comments as Attachment 1.

III. COMMENTS ON THE EXECUTIVE SUMMARY

A. The Risk Assessment for Exposure to Inorganic Arsenic from a Secondary Lead Smelter is Incorrect.

ARB states in the Executive Summary that

> ". . . a one-month monitoring study of a secondary lead smelter in the South Coast Air Basin's City of Industry demonstrated an average inorganic arsenic concentration of 61 ng/m^3. These concentrations were subsequently reduced as a result of the study. If these concentrations had continued unabated for a lifetime (75 years), as many as 6 to 9 excess cancer deaths might have occurred among the 725,000 persons residing nearby."

Executive Summary, p. 6.

This statement is wrong and misleading. As discussed below, it is wrong because the average inorganic arsenic concentration of 61 ng/m^3 is based on limited and outdated data; it is misleading because the factual predicate that makes the "6 to 9" figure meaningful -- 61 ng/m^3 -- is not a real number. The real number is 11.44 ng/m^3.

The 61 ng/m^3 figure was derived from very limited data generated in 1986. These data consist of monitoring results from one monitor over a one-month period. Even if these data were not

stale, their limited nature renders suspect any inferences or conclusions drawn from them.

These data are, however, stale. More recent data obtained over a three-month period in 1988 from not one but six monitors located around Quemetco demonstrate conclusively that ambient inorganic arsenic emissions are orders of magnitude below those noted in the Draft Report. A summary of these data are appended at Attachment 2. According to this comprehensive three-month monitoring study, the area minimum, mean and maximum are 1.43 ng/m^3, 11.44 ng/m^3, and 61.52 ng/m^3, respectively. The fact that the area maximum in the 1988 monitoring study is the same as the area mean in the 1986 monitoring study demonstrates conclusively that the 1986 study is inherently flawed and must be rejected.

The mortality analysis is substantially different using these more recent data. Based on these 1988 data, inorganic arsenic emissions from the secondary lead smelter analyzed in the Draft Report account for less than one-half excess cancer deaths over a 75-year period. A summary of the analysis is appended at Attachment 3.

Based on the foregoing, RSR recommends that the ARB's "hot spot" exposure analysis set out at p. 6 of the Executive Summary and at Appendix D in Part B be revised to include the more recent and comprehensive exposure data.

B. ARB Has Not Demonstrated Secondary Lead Smelting Operations Are a Major Source of Inorganic Arsenic Emissions.

ARB states on page 2 of the Executive Summary that secondary lead smelting operations are a "major" source of inorganic arsenic emissions in the State of California. ARB has not demonstrated this statement is accurate. For the reasons set out below, (pp. 6-7), it is entirely unclear whether inorganic arsenic emissions from secondary lead smelting operations (as opposed to metal processing operations generally) are a major or relatively insignificant source of such emissions.

RSR recommends that this statement be revised as necessary pending completion of a thorough analysis of inorganic arsenic emissions for all sources of inorganic arsenic emissions in California.

IV. COMMENTS ON PART A AND PART B OF THE DRAFT REPORT

A. The ARB Continues to Confuse Secondary Lead Smelters with Metal Processing Facilities.

In our comments on the preliminary Draft Report, RSR identified a fundamental problem underlying Part A of the analysis. In the Draft Report, the ARB confused secondary lead smelting operations with metal processing operations.

In response to this comment, ARB acknowledged that lead processing activities other than secondary lead smelting "may be large in other parts of the United States," but, according to ARB these activities are "relatively small" in California. ARB staff

thus apparently concluded that "secondary lead smelting is one of the major sources of inorganic arsenic emissions in California." See Part C -- Public Comments and Responses to the Preliminary Draft Part A and B, at II. C).

There are several problems with the Staff's findings. First, the ARB claims to have addressed the definitional problem RSR commented upon by "clarifying" the distinction between secondary lead smelting operations and other lead processing activities. Although the ARB made passing reference to some distinctions between these operations on page A-40, this clarification is wholly inadequate and in fact, misses the point completely.

RSR's comment was intended to disabuse the ARB of the mistaken notion that "secondary lead smelting" is a generic designation that includes all lead processing activities. RSR's comment also was intended to urge ARB to recognize that metal processing operations other than secondary lead smelting operations exist in California and emissions from these other sources may be potentially significant.

In response, ARB staff acknowledged that other lead processing facilities exist, but summarily concluded that these sources are "relatively small," and, without making any effort to quantify emissions from them, summarily concluded that secondary lead smelting is a "major" source of inorganic arsenic emissions. This reasoning is circular. It also begs the issue of why other sources of inorganic arsenic have not been identified, what

emissions are properly attributable to each, and how these emissions compare with those already quantified. Only after this analysis has been undertaken can the ARB properly assess whether secondary lead smelting is a "major" or relatively minor source of inorganic arsenic emissions in California.

Second, the ARB's 1988 survey findings referenced at A-40 are nowhere reported in the Draft Report. It is thus impossible to determine whether the Staff's subjective determination that "lead processing activities" -- however these activities are defined -- are "relatively small" has any basis in fact.

Third, the ARB's conclusion that secondary lead smelting is a major source of inorganic arsenic emissions is inconsistent with the Staff's own findings. According to the Draft Report, out of a total of thirteen potential sources of inorganic arsenic emissions on which data are available, "secondary lead smelting" ranked eighth. Moreover, RSR believes this ranking could be significantly lower if emissions data on other potential sources of inorganic arsenic were available, i.e., arsenic concentration in cement production feed materials, pesticide manufacturing, wood preservative manufacturing, and electronics manufacturing. See Draft Report, pp. A-33 and A-39; see also C., infra. Emissions data from these suspected arsenic emitters and other sources are not included in the analysis. These data gaps make it impossible to draw any reasonable inferences from the limited data available. These data gaps also render the statement that secondary lead

smelters are "major" sources of inorganic arsenic emissions a meaningless truism under these circumstances.

RSR reiterates that to correct these fundamental deficiencies, ARB properly distinguish between secondary lead smelters and metal processing facilities, identify all potential sources of inorganic arsenic emissions, monitor emissions from each of these sources, and revise the Draft Report findings, where appropriate, by properly incorporating the new emissions data into the analysis in Parts A and B of the Draft Report.

B. Recent Data on Quemetco Are Omitted in the Draft Report.

In our comments on the preliminary Draft Report, RSR commented that the ARB's reliance on a study by Radian Corporation entitled "Control of Arsenic Emissions from the Secondary Lead Smelting Industry -- Technical Document" (May 7, 1985) ("Radian Study") was misplaced. The Radian Study did not include actual emission data from Quemetco, the secondary lead smelter monitored in the Draft Report. In addition, the Radian Study has, to the best of our knowledge, never been subjected to peer review. RSR recommended that ARB obtain actual emission data from all potential sources of inorganic arsenic emissions located in the South Coast Air Basin. RSR also suggested that ARB validate the emission estimates contained in the Radian Study. If unable to do so, or if the estimates proved invalid, RSR recommended deleting the Radian Study.

In response, the ARB now claims that it is no longer using the Radian Study "because we have more current data derived from a 1988-1989 study of the facility." See Draft Report, Part C at Comments C). As noted above, however, these recent data are nowhere noted elsewhere in the Draft Report. Omission of these data is troubling for at least two reasons. First, to be valid, the ARB analysis must rely on the most recent data available. The 1988 data obtained by the South Coast Air Quality Management District clearly fits within this category. The omission of these data is inexplicable and inappropriate. Second, omission of these is prejudicial to Quemetco because these data indicate that emissions from Quemetco are significantly lower than those referenced in the Draft Report.

To correct these deficiencies, RSR believes ARB must include the most recent data in the Draft Report and modify, as necessary, the Draft Report in all pertinent respects. As noted above, we have appended a copy of these data at Attachment 2. In addition, assuming ARB no longer intends to rely upon the Radian Study as it represents, RSR recommends that ARB delete all reference to it in the Draft Report.

C. ARB Should Obtain Inorganic Arsenic Emissions Data From Feed Materials Used in the Manufacture of Cement.

ARB reportedly believes that arsenic is a trace contaminant of feed materials such as limestone, gypsum, clay, shale, and sandstone used in cement production. ARB also believes arsenic is emitted along with other particulate matter during the

manufacture of cement. See Draft Report, p. A-39. ARB also claims there are no data available on the arsenic concentration of these feed materials. According to ARB, "even at low concentrations in the feed materials, total emissions can be significant due to the large volume of feed materials processed . . . ." Id. (emphasis added). If ARB suspects these feed materials potentially emit significant quantities of inorganic arsenic, RSR believes ARB should undertake to quantify these emissions. ARB's failure to quantify these emissions and, as noted above, other potential sources of inorganic arsenic emissions necessarily cause the data base to be incomplete. Thus, no inferences may properly be drawn from this data base.

To remedy this problem, RSR urges ARB to complete the analysis by identifying all potential sources of inorganic arsenic emissions and quantify emissions for each.

COMMENTS OF RSR CORPORATION ON THE CALIFORNIA AIR RESOURCES BOARD DRAFT REPORT ON INORGANIC ARSENIC

RSR Corporation, on behalf of itself and its wholly-owned subsidiary, Quemetco, Inc. (hereinafter collectively "RSR"), submits these comments in response to the California Air Resources Board ("ARB") Draft Report on Inorganic Arsenic ("Draft Report") circulated for comment on April 7, 1988. For the most part, RSR's comments are limited to those portions of the Draft Report relating to lead processing facilities. RSR may expand upon its analysis, however, and submit supplemental comments at a later date.

I. INTRODUCTION AND SUMMARY

Overall, RSR believes Part A of the Draft Report is seriously flawed, and that the ARB's preliminary findings relating to so-called "secondary lead smelting" activities cannot be supported. Among other serious defects, the data on which the emission estimates are based are inaccurate, and use

of a short-term model to calculate maximum annual average concentrations of inorganic arsenic is inappropriate.

Moreover, the data base in Part A is incomplete. ARB failed to identify all potential sources of inorganic arsenic emissions from lead processing facilities. In addition, it improperly attributed all measured emissions to a single lead smelter.

Finally, the Draft Report misapplies the term "secondary lead smelter" to any industrial activity involving lead processing. Misuse of this phrase unavoidably leads to the erroneous inference that secondary lead smelters -- as distinct from lead processing facilities, a broader category -- are a major source of inorganic arsenic emissions.

The draft conclusions contained in Part B of the Draft Report are generally well presented. These conclusions appear to rely, however, upon preliminary findings contained in Part A of the Draft Report. RSR may wish to submit additional comments on Part B pending review of ARB's revisions to Part A responsive to RSR's comments, and reserves the opportunity to do so.

II. RSR'S INTEREST IN THIS PROCEEDING

Quemetco operates a secondary lead smelter located in City of Industry, California. City of Industry is located in the South Coast Air Basin. ARB characterizes the Draft

Report as a summary of ARB's investigation to determine whether, pursuant to California law, inorganic arsenic should be identified as a toxic air contaminant. Draft Report, p. A-1. Secondary lead smelters may be a source of inorganic arsenic emissions. RSR believes ARB's findings could play a major role in setting future regulatory requirements applicable to the operations of RSR's California subsidiary. Accordingly, RSR has a significant interest in this proceeding, and offers the following comments on the Draft Report.

III. SECONDARY LEAD SMELTERS

A secondary lead smelter is a facility included within Standard Industrial Classification ("SIC") Code 3341 (Secondary Smelting and Refining of Nonferrous Metals). This SIC code includes "[e]stablishments primarily engaged in recovering nonferrous metals and alloys from new and used scrap and dross." Office of Management and Budget, Standard Industrial Classification, p. 148 (1972). According to the United States Environmental Protection Agency ("EPA"), there are 28 facilities located throughout the United States properly included in SIC Code 3341. See "The Impacts of Lead Industry Economics and Hazardous Waste Regulations on Lead-Acid Battery Recycling: Revision and Update," USEPA (1987).

According to this EPA report, there are three secondary lead smelters located in the western part of the United States, each of which is located in California. Two of these secondary lead smelters are located in the South Coast Air Basin. The facility located in City of Industry -- the only source monitored by ARB for purposes of the Draft Report -- is the smaller of the two lead smelters.

IV. COMMENTS ON PART A OF THE DRAFT REPORT

A. The Draft Report Contains Factual Inaccuracies Regarding Lead Smelters

A fundamental problem underlying Part A of the Draft Report is ARB's failure to define properly "secondary lead smelting." The Draft Report states that "secondary lead smelting" is one of four "[m]ajor sources" of inorganic arsenic emissions in California. Draft Report, p. A-2. This is incorrect. RSR believes ARB meant to say that industrial operations involving lead processing -- including secondary lead smelting -- are a major source of inorganic arsenic emissions. ARB's failure to distinguish properly between secondary lead smelting activities and lead processing activities leads to the erroneous inference that secondary lead smelters alone are among the largest contributors of inorganic arsenic emissions in the State of California.

RSR requests that ARB correct the Draft Report to read, where appropriate, that there are three secondary lead facilities in California, not 30 as stated repeatedly throughout the Draft Report, and not 18 as stated on p. A-49, Table II-2.

RSR also recommends that ARB distinguish clearly in the Draft Report between secondary lead smelters and lead processing facilities. At a minimum, RSR urges ARB to replace the term "secondary lead smelter" with the term "lead processing facility," where appropriate, throughout the Draft Report. Section V of these Comments identifies specific references in the text that appear to be inaccurate, and suggests revised language to eliminate these inaccuracies.

B. ARB Has Improperly Excluded Other Sources of Inorganic Emissions From the Analysis

The definitional error discussed above is the probable basis for another serious flaw in the Draft Report. In referring to lead processing facilities as "secondary lead smelters," ARB has failed to include other potential sources of inorganic arsenic emissions in the analysis. ARB acknowledges that other sources of inorganic arsenic emissions exist, but makes no effort to identify those sources or quantify emissions from them. According to the Draft Report, for example, "there are six small companies within a five-mile radius performing different types of lead processing

activities which could be potential arsenic sources." Draft Report, p. A-29. Without knowing more about these other potential arsenic sources, RSR cannot determine whether they are either "small" companies or "small" sources. If any is in fact not a small "source," its omission from the data base would be a serious flaw, and ARB's preliminary findings regarding lead processing facilities would be arbitrary.

Moreover, in failing to identify other probable sources of arsenic emissions, all emissions were attributed improperly to the only facility monitored by ARB, a lead smelter. This is inappropriate.

To correct this deficiency, RSR recommends that (i) ARB identify all potential sources of inorganic arsenic emissions in the South Coast Air Basin; (ii) monitor emissions from these sources; and (iii) revise the Draft Report findings, where appropriate, by properly incorporating the new emissions data into the ARB analysis.

C. ARB's Reliance on the Radian Study Is Misplaced

ARB states in the Draft Report that emission rates obtained from a report prepared by the Radian Corporation were used "to estimate the annual average impacts of arsenic emissions from the smelter on public exposure." Draft Report, p. A-33. The Radian Study at issue is entitled "Control of

Arsenic Emissions from the Secondary Lead Smelting Industry - Technical Document" (May 7, 1985) ("Radian Study").

ARB's reliance on the Radian Study is misplaced. The Radian Study did not include actual emission data from the secondary lead smelter monitored in the Draft Report. Indeed, no emission data from any secondary lead smelter located in California is included in the Radian Study. Nonetheless, the emission rates used for dispersion modeling were taken by ARB from the Radian Study. At best, these rates are speculative estimates based on assumptions regarding, among other variables, process capacities that likely do not accurately reflect the monitored facility's capacities.

The inappropriateness of ARB's use of Radian Study emission estimates to predict annual ambient arsenic concentrations (700 ng/m^3) is highlighted by the inconsistency of that prediction with actual results of two ambient air studies conducted by ARB at the monitored facility in 1986 (approx. 60 ng/m^3 -- predicted annual average) and 1987 (approx. 20 ng/m^3 -- highest monthly average concentration). Further, the source emission inputs from the Radian Study used by ARB for modeling of the smelter facility (at least 138.6 lbs per year) are inconsistent with results from an actual source test at the monitored facility conducted by the SAI Corporation in 1981 (8 - 32 lbs per year).

To address this problem, RSR recommends that ARB seek to obtain actual emission data from all potential sources

of inorganic arsenic emissions located in the South Coast Air Basin.

D. The Radian Study Lacks Independent Scientific Verification

It is unclear whether the emission estimates reported in the Radian Study have ever been validated. The Radian Study was sponsored by EPA. The Study contains, however, a disclaimer from EPA providing that "[t]he opinions, findings, and conclusions expressed are those of the author and not necessarily those of the EPA." Radian Study, p. iii. Similarly, it is unclear whether the Radian Study has ever been subjected to peer review, and if so, whether it satisfies peer review standards.

RSR believes that ARB should determine in the first instance whether the emission estimates contained in the Radian Study are valid. If valid, ARB should so state in the Draft Report. If invalid, ARB's reliance upon the Radian Study to support any of its preliminary findings is arbitrary.

E. ARB's Use of the Industrial Source Complex Short-Term ("ISCST") Model is Inappropriate

ARB states in the Draft Report that it used the Industrial Source Complex Short-Term ("ISCST") model to calculate maximum annual average concentrations. The short-term model typically overpredicts annual averages and is more

appropriately used to predict maximum short-term, not lo term, concentrations. The use of the ISCST is thus inappropriate, and the Industrial Source Complex Long-Term ("ISCLT") model should be used instead.

In addition, the ISCST model requires extensive and accurate source-specific data to produce meaningful estimates. ARB's findings do not include such source-specific data. Since use of the model requires data inputs and assumptions of some sort, and ARB's Draft Report identifies no such data or assumptions, RSR is unable to determine whether those used are valid.

To correct these deficiencies, RSR recommends that: (i, the ISCLT, rather than the ISCST, be used to calculate maximum annual average concentrations; (ii) the model utilize source-specific data from all potential sources of arsenic emissions; and (iii) any assumptions factored into the model be clearly stated.

F. The Part A "Introduction and Summary" is Misleading

The Part A "Introduction and Summary" is misleading. As currently drafted, it can be read to conclude that any exposure to inorganic arsenic emissions, regardless of concentration, is harmful.

Part A of the Draft Report is entitled "Public Exposure to Airborne Inorganic Arsenic in California." Part B

of the Draft Report is entitled "Health Effects of Inorganic Arsenic." The caption on page A-1 of the Draft Report, entitled "Part A Introduction and Summary," would appear to suggest that pages A-1 through A-5 of the Draft Report summarize only the findings of Part A. This summary, however, also refers to health effects actually contained in Part B of the Draft Report.

The potential for misinterpretation or confusion posed by the existing language can be cured by eliminating any reference to adverse health effects in the Introduction and Summary to Part A. Alternatively, ARB may wish to consider revising the caption on page A-1 of the Draft Report to read "Introduction and Summary" and summarize both the exposure information contained in Part A and the DHS health effects evaluation contained in Part B of the Draft Report.

G. Emission Measurements Should be Reported in Micrograms Per Cubic Meter

Throughout the Draft Report, emission measurements are reported in nanograms per cubic meter (ng/m^3). The more commonly used measurement, however, for air emissions is micrograms per cubic meter (ug/m^3). RSR believes that the Draft Report should conform with the more commonly used micrograms measurement. At a minimum, RSR recommends that ARB define whatever measurements it utilizes to avoid potential

confusion to readers unfamiliar with the difference in magnitude of the units in these measurements.

H. The Draft Report is Based on Inadequate Monitoring Data

The source-impacted ambient arsenic monitoring samples for the South Coast Air Basin were measured intermittently between May 17, 1986 and June 15, 1986. RSR believes these measurements, taken over a period of less than thirty days, are inadequate for calculating annual average arsenic concentrations.

Further, no meteorological data regarding the monitoring samples are included in the Draft Report. These data are essential in determining the likely source or sources of emissions and their respective rates. In order to comment meaningfully on these data, more information is necessary. Accordingly, RSR recommends that ARB include these data in the next version of the Draft Report.

I. The Draft Report Improperly Relies on Obsolete Meteorological Data

The Draft Report relies on 1972 meteorological data. It is possible that meteorological conditions have changed over the past sixteen years. RSR recommends that ARB replace the 1972 data with more recent meteorological data, if these data are available.

RSR also recommends that ARB obtain meteorological data from stations closer to monitored sources. Data from closer stations will better account for meteorological conditions uniquely impacting monitored sources.

V. SPECIFIC COMMENTS

RSR believes that data transmitted to the Scientific Review Panel must consist of only unbiased and independently verifiable facts. RSR believes there are a number of references throughout the Draft Report that do not meet this criteria. RSR has identified a representative sample of such references below, and has proposed changes to the Draft Report to eliminate the potential for misinterpretation or ambiguity. No attempt here is made, however, to identify all such references.

- Page A-5, last full paragraph -- "such as a secondary lead smelter" should be deleted.

- Page A-29, second full paragraph -- this paragraph should be deleted. Suggested insert: An analysis of arsenic sources in California indicated that industrial lead processing operations have the potential to emit large amounts of arsenic. Of the 30 lead processing operations located in California, one secondary

lead smelter in the South Coast Air Basin was selected by ARB for monitoring. There are also at least six other companies within a five-mile radius of the selected facility performing different types of lead processing activities which could be potential sources of arsenic emissions.

- Page A-30, first line, first full paragraph -- "[l]arge" should be deleted.

- Page A-31, first full paragraph -- the sentence "This is approximately 13 times the South Coast urban average," should be deleted.

- Page A-32, second paragraph, second sentence -- this sentence should be changed to read "[t]he smelter is the only source of arsenic in this area which ARB monitored, but it is likely possible that other unidentified sources in the area are contributing to the arsenic concentrations which ARB obtained."

VI. COMMENTS ON PART B OF THE DRAFT REPORT

The draft conclusions contained in Part B of the Draft Report are generally well presented. These conclusions appear to rely, however, upon preliminary findings contained in Part A of the Draft Report. RSR may wish to submit additional comments on Part B pending review of ARB's revisions to Part A responsive to RSR's comments, and reserves the opportunity to do so.

VII. CONCLUSION

Part A of the Draft Report is seriously flawed and scientifically unsupported. Based on the foregoing, RSR recommends that ARB defer submitting to the Scientific Review Panel those portions of the Draft Report involving lead processing facilities, properly address each of the deficiencies noted above, and reissue a revised Draft Report for public comment and review.

Appended for ARB's review are comments submitted by RSR's technical consultant, Dames & Moore.

Attachment

DAMES & MOORE A PROFESSIONAL LIMITED PARTNERSHIP
1550 NORTHWEST HIGHWAY PARK RIDGE, ILLINOIS 60068 (312) 297-6121

May 11, 1988

Lynn L. Bergeson, Esquire
Fox, Weinberg & Bennett
1714 Massachusetts Avenue, N.W.
Washington, D.C. 20036

Dear Lynn:

Re: Comments on California Air Resources Board
Draft Report on Inorganic Arsenic

This responds to your request for our comments on the California Air Resources Board's ("CARB") draft Report on Inorganic Arsenic Emissions. Dames & Moore's preliminary review of this Report has revealed the following areas where further additional analysis is warranted with respect to developing a more technically supportable assessment of ambient levels of inorganic arsenic:

- The calculation of maximum annual average concentration from sources should be based upon modeling with the ISCLT, not ISCST, dispersion model. The latter generally overpredicts annual averages and is more appropriately used to predict maximum short-term concentrations. The guidelines on air quality models (USEPA, revised 1986) state that when modeling for sources for which long-term standards alone are applicable, long-term models should be used.

- The CARB report did not provide detailed information pertaining to the dispersion modeling analyses performed. The detailed information should include emission inventory, version number of model employed, model options selected, and general discussion of the modeling methodology.

- The 1972 Ontario, California meteorological data employed by CARB should be replaced by more recent meteorological data, if available, and from stations located closer to the monitored sources. Meteorological conditions vary with geography; the closer the meteorological station to the source, the better, assuming similarity in surrounding terrain and urbanization.

  Moreover, the meteorological data should be based on a 5-year period. The USEPA has recommended that 5 years of representative meteorological data should be used when estimating concentrations

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with an air quality dispersion model. If a shorter period of record is being used, the meteorological data should contain appropriate worst-case conditions.

- In assessing the impact on public health of facilities that emit carcinogens, the USEPA as well as many states calculate the maximum individual lifetime risk ("MILR") and compare with a threshold such as one in one million. The MILR is calculated by multiplying the maximum annual average predicted concentration off plant property resulting from the facility's emissions by the unit risk factor for the carcinogen. The unit risk factor for arsenic is 4.29×10^{-3}.

- The arsenic modeling performed by CARB incorporated emission factors derived by the Radian Corporation. These emission factors were based on a study by Radian of smelting operations in existence at the time the Report was prepared. The correlation, if any, between smelting operations investigated by Radian and the lead smelter included in the CARB draft Report should be examined.

  The validity of the emission factors derived by Radian should be reviewed for their acceptance by the USEPA. Similarly, it is unclear whether the validity of Radian's emission factors has been subjected to peer review, and, if so, whether they meet peer review standards.

- Fugitive arsenic emissions modeled by CARB were based upon a formula in the the Radian Corporation Report. It is questionable whether this formula is applicable to the monitored lead smelter. Because of the importance of the amounts of stack and fugitive arsenic emissions employed in the model, much more detail should have been provided in the CARB report with respect to assumptions used in applying the arsenic emissions from the Radian Corporation report to the monitored lead smelter (i.e., stacks versus fugitives). Further, the CARB report was unclear with respect to how the fugitive emissions were treated in the ISCST model. In the USEPA's report, "Estimating Releases and Waste Treatment Efficiency for the Toxic Chemical Release Inventory Form," it is stated in the section treating estimation of fugitive emissions that, whenever possible, fugitive emissions should be calculated by the use of direct measurement. Since fugitive emissions vary widely between different facilities, use of formulas developed from measurements taken at other facilities will result in estimates having considerable uncertainty.

- While the CARB report suggests that the ambient arsenic measurements may result from arsenic sources other than the monitored lead smelter, no other potential sources are specifically identified in the draft Report, nor are their respective emissions quantified. Other sources are believed to include a lead smelter and at least two lead acid battery manufacturing plants. At a minimum, estimates of arsenic emissions from these and all other potential sources of arsenic emissions should be included in the report.

- The South Coast Air Basin ambient arsenic samples, measured from May 17, 1986 to June 15, 1986, are inadequate for the purpose of estimating annual average arsenic concentrations. Variation of meteorological conditions throughout the year as well as operation of the monitored lead smelter should cause the concentrations in Table 1-5 of the CARB report to be used with great caution with respect to estimation of annual averages.

- In expressing ambient arsenic concentrations, the CARB report uses units of nanograms per cubic meter rather than the more common micrograms per cubic meter, thus giving the uninitiated reader an impression of higher levels than would otherwise be the case if micrograms per cubic meter were used.

If you have any questions or comments, please feel free to contact us directly.

Sincerely,

DAMES & MOORE
A Professional Limited Partnership

Perry W. Fisher, Ph.D.
Partner (Ltd.)
Certified Consulting Meteorologist

Steven A. Frey
Project Meteorologist

PWF/SAF:dak

SOUTH COAST AIR QUALITY MANAGEMENT DISTRICT MONITORING

1988 --- NANOGRAMS OF ARSENIC PER CUBIC METER OF AMBIENT AIR

DATE	1	2	3	4	5	6
6/22	4.06	3.70	5.65	32.18	61.52	3.80
6/23	3.60	8.61	3.30	2.25	2.51	1.43
6/27	6.22	10.69	8.00	6.86	8.17	5.00
6/29	52.00		7.00	13.40	15.90	10.90
7/01	10.30	32.00	7.20	8.10	7.80	3.80
7/06	9.27	8.48	11.17	13.62	8.54	6.03
7/08	14.00	11.20	14.70	18.60	50.00	8.90
7/11	17.60	15.50	14.30	11.80	12.10	7.70
7/13	5.49	6.69	4.86	5.68	3.62	1.52
7/15	3.38	5.53	6.83	6.57	6.00	3.25
7/18	17.39	8.32	6.34	25.33	18.44	3.18
7/19	6.19	13.10	9.44		11.17	3.46
7/20	9.18	6.23	5.51	36.69	24.84	5.44
7/21	10.24	6.53	5.40	18.97	54.65	3.23
7/23	3.00	3.60	4.41	17.04	27.14	2.33
7/25	4.72	5.34	7.71	15.87	21.74	5.23
7/26	3.77	6.16	8.17	14.06	11.66	3.00
7/27	11.07	8.24	5.53	5.23	7.35	3.71
7/28	5.93	4.73	5.96	14.90	11.11	1.83
7/31	7.98	8.68	12.00	14.61	7.84	2.62
8/01	7.81	20.78	14.49	11.74	6.12	2.77
8/02	5.33	3.52	12.26	5.41	8.63	2.10
8/03	3.71	3.65	5.99	10.60	14.73	3.38
8/04	2.62	3.86	3.83	10.93	10.30	2.63
8/06	6.68	6.98	4.91	3.42	3.02	1.46
8/08	14.13	8.68	15.63	17.41	15.03	12.37
8/09	9.70	18.80	24.67	19.86	20.08	8.55
8/10	6.19	16.42	9.10	30.85	28.20	8.83
8/11	3.72	3.92	6.46	42.58	16.23	3.25
8/14	11.49	7.91	8.42	19.23	23.78	6.77
8/15	21.33	19.78	20.75	19.33	20.98	17.07
8/16	8.73	20.60	16.36	25.37	21.10	11.30
8/17	4.71	5.52	13.43	7.98	12.59	2.76
8/18	8.93		13.29	14.73	15.14	7.23
8/20	3.58	3.98	8.82	12.35	7.27	3.26
8/22	4.23	6.05	9.42	18.51	16.65	4.07
8/23	13.59	10.82	15.78	36.05	37.66	9.92
8/26	12.14	13.08	15.82	17.60		11.72
8/30	4.60	6.83	5.98	10.48	32.81	5.02
8/31	7.50	9.30	8.65	21.55	21.73	9.04
9/01	14.75	12.52	13.89	14.77		14.12
9/06	3.60	4.74	9.13	11.76	14.95	5.32
9/07		32.04	6.64	3.47	3.55	2.63
9/08		53.09		6.44	20.35	2.60
MINIMUM	2.62	3.52	3.30	2.25	2.51	1.43
MEAN	9.16	11.10	9.70	15.68	17.69	5.56
MAXIMUM	52.00	53.09	24.67	42.58	61.52	17.07

AREA MINIMUM 1.43
AREA MEAN 11.44
AREA MAXIMUM 61.52

24 - HOUR SAMPLES
1,056 HOURS SAMPLED

MONITORING SITES:

1 Chemical plant in a westerly direction from the lead smelter.

2 Automobile parts warehouse in a southwesterly direction from the lead smelter.

3 U.S. mail processing center in a northeasterly direction from the lead smelter.

4 Battery parts manufacturer (lead processor) in an easterly direction from the lead smelter.

5 Battery parts manufacturer (lead processor) in an easterly direction from the lead smelter.

6 Lighting manufacturer/distributor in a southerly direction from the lead smelter.

1988 --- POUNDS OF ARSENIC PER HOUR FROM LEAD SMELTER STACK

DATE	STACK	LBS/HR
6/8	REFINERY *	0.06300000
6/13	REFINERY	0.00270000
6/15	OXIDE (1)	<0.00001320
6/21	SCRUBBER (2)	0.00000785
6/22	SCRUBBER (1)	0.02040000
6/22	SANITARY	0.00065000
7/8	OXIDE (2)	<0.00001130
	TOTAL	<0.02378235
	TOTAL *	<0.08408235

* During arsenic metal addition to produce customer specific alloy.

HYPOTHETICAL ESTIMATES OF LUNG CANCER MORTALITY FROM RESIDENTIAL EXPOSURE TO ARSENIC EMITTED FROM A SECONDARY LEAD SMELTER --- BASED ON 1988-89 SCAQMD MONITORING DATA

ANNUAL EXPOSURE		# PEOPLE	q		MORTALITY	
RANGE	AVERAGE	EXPOSED	BEST EST.	95% UCL	BEST EST.	95% UCL
0.0 - < 0.1	0.05	492,543	2.09	3.32	0.051	0.082
0.1 - < 0.5	0.30	240,662	2.09	3.32	0.151	0.240
0.5 - < 1.0	0.75	22,646	2.09	3.32	0.035	0 056
1.0 - < 1.4	1.20	3,282	2.09	3.32	0.008	0.013
1.4 - < 1.8	1 60	926	2.09	3.32	0.003	0.005
1.8 - < 3.0	2.40	1,231	2.09	3.32	0.006	0 010
3.0 - < 9.4	6.20	546	2.09	3.32	0.007	0.011
	TOTALS	761,836			0.262	0.417

The Permanente Medical Group, Inc.
DIVISION OF RESEARCH
3451 PIEDMONT AVENUE
OAKLAND, CALIFORNIA 94611-5463

ANTIOCH
FAIRFIELD
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SAN JOSE
SAN RAFAEL
SANTA CLARA
SANTA ROSA
S. SACRAMENTO
SAN FRANCISCO
STOCKTON
SUNNYVALE
VALLEJO
WALNUT CREEK

December 18, 1989

Dr. George Alexeeff
Air Toxics Unit, Health Evaluation Section
2151 Berkeley Way, Room 515
Berkeley, California 94704-9980

Dear Dr. Alexeeff,

Overall I believe that your group's Report to the Air Resources Board on Inorganic Arsenic is excellent and I expect to recommend that the Scientific Review Panel approve it.

I have the following questions and suggestions for minor changes:

Executive Summary

p.5, line 5 from bottom: Insert "among nonsmokers" after "excess cancer deaths" if this is what you mean to say here.

p.6, first full paragraph: If smoking trends in California differ from those in the U.S. -- presumably less smoking in California -- why is the California range merely wider, rather than having both the upper and lower bound shifted lower?

p.6, last full paragraph, line 5: Insert "as such" after "it."

Part A

p.A2, third full paragraph: In the list of non-atmospheric exposures in the first sentence, did you consider mentioning medicinal exposures? Nowadays I would expect that medicinal exposure would be rare or nonexistent in California, but I do not know for sure. Similarly, on p.A-23, should drugs be added to the list in the first sentence under Heading C. and discussed later in this section?

p.44, second last sentence: Mono Lake is salty and is not being drained to provide drinking and irrigation water. Rather, the city of Los Angeles is taking water from some of the streams that feed Mono Lake and as a result its level has fallen. Thus, delete "e.g., Mono Lake."

Part B

It is not clear to me what the upper bound of the 95% confidence interval represents, e.g., in Table 1-1. Does this reflect the uncertainty in the original epidemiological data from which your risk estimates are extrapolated?

Are there other sources of uncertainty that contribute? Perhaps I missed it, but if not, I think this should be explained.

p.7-5, sentence on lines 10-12: This sentence does not seem to belong here.

p.9-14, lines 1 and 2: It is not clear to me why, if other exposures alone cannot explain the excess cancers, this strengthens the evidence for arsenic's role in the etiology of cancer. You mention the possibility of interaction with other exposures.

p.9-17, text below small table: There is a problem here with your use of the term "factor," which implies multiplication. If I interpret this material correctly, "factor" should be changed to "difference" in the first line and "a difference of" should be inserted in the second line before "6.2." Also, "calculated" in the third line from the bottom should be changed to "observed," I think.

p.11-15, line 8 from bottom and adjacent text: It is not clear what you are saying here. Would a low p value show a lack of homogeneity? If so, what does a p value of 0.14 mean?

p.11-21, line 12: Insert "is fitted" after model.

p.11-29, lines 4-5: You state that not allowing for latency suggests an underestimation of risk. But if the mathematical model that you use also does not consider latency, wouldn't this bias be compensated for?

p.D1, Table: Make clear that "E-06" etc. is e^{-6} if that is really what it represents. Or is it 10^{-6}?

I hope that we can meet and discuss the Report and some of my questions about it before the Scientific Review Panel considers approving it. I have not yet seen the second round of public comments but expect to receive them soon.

Sincerely,

Gary D. Friedman

Gary D. Friedman, M.D.
Assistant Director for
Epidemiology & Biostatistics

GDF/lw

cc: Dr. Aldrich
Bruce Oulrey ✓

J. H. BAXTER & CO. · P.O. Box 5902 San Mateo, California 94402-0902 Phone 415 349 1201 FAX 415 570 6878

JBaxter

28-E-5

November 28, 1989

Mr. Robert Barham
Chief Toxic Air Contaminant
Identification Branch
Air Resources Board
Attn: Inorganic Arsenic
P.O. Box 2815
Sacramento, CA 95812

Dear Mr. Barham:

J.H. Baxter & Co. would like to thank you for this opportunity to comment on your draft report on inorganic arsenic. Specifically we would like to comment on the paragraph entitled "Are there 'hot spot' emissions in organic arsenic in the state?" in the draft Executive Summary. The comment is on the last sentence of the first paragraph that reads "The extremely high arsenic concentrations in this case were probably the result of burning vine support posts (pressure treated with copper arsenate to control rotting) with the vine cuttings."

First, while it is true that burning arsenically treated wood with the vine cuttings would contribute to the overall arsenic content of the smoke, there is another source which you do not mention. That source is the use of inorganic arsenic pesticides, namely sodium arsenite, in vineyards for the controlling of two diseases of grapevines, namely black measles and dead arm, which are routinely controlled with sodium arsenite. The description of these diseases and the use of sodium arsenate for the control of them is included as Attachment A to this letter.[1]

This use is confirmed in a memorandum to Glen Hawkins, Pest Management Analysis and Planning Program from Bill Fabre, Department of Food and Agriculture, which is included in Section K, Part C, Public Comments and Responses to the Preliminary Draft, Part A and B Inorganic Arsenic Report prepared by your staff. This section goes on to describe the various amounts of sodium arsenite applied California vineyards by county and by month.

I would also like to point out that burning of arsenically treated wood is not what our industry recommends. Our Consumer Information Sheet given to our customers for education in the proper uses and disposal practices to be used for treated wood specifically recommends against burning the treated wood but rather recommends burying it in a landfill. The prevention of the sublimation of the arsenic oxides into the air and/or the retention of soluble arsenic oxides in the ashes are of course the reasons that our industry recommends against burning of arsenically treated wood.

We hope our comments are helpfulto you. If we can provide any additional information please do not hesitate to have one of your staff members give me a call.

Sincerely yours,

Joe Morgan III
Vice President, Technical Services

JM:mc
Attachment

cc: W. L. Martinell
A. X. Baxter
S. W. Conklin
N. V. Poletika
V. Lindenheim
F. O. Omundson

1. "The Biological and Economic Assessment of Pentachlorophenol in Organic Arsenicals, Creosote, Volume 2 Non Wood Preservatives" published by the United States Department of Agriculture, Technical Bulletin #1658-11, Page 175-180

Fate in the Environment
(See Volume 1, Chapter 4)

Alternatives

Formulations of four materials--aldrin, dieldrin, chlordane, and heptachl currently registered for use in treating soils to control native subterrane mites. These chemicals, when applied according to the prescribed rates and m have provided complete protection for 17 to 21 years in Gulfport, Mississipp (Johnston, et al., 1972).

Sodium Arsenite—Grape Disease Control

California ranks first nationally in grape production, and in 1974 grap vided 6.0% of the total value of California agriculture (CCLRS, 1975). G et al. (1975) and Moulton (1979) provide comprehensive production and econo views of the grape industry to date. They point out the dynamic nature of gra duction and acreage over the post-war years. Acreage increased until recent a shift to wine varieties over table and raisin varieties. Currently, raisin ties are on the increase, but total acreage is stable. Table and raisin grape ties can also be used for wine, but wine varieties have no alternative use. the industry is less flexible than formerly. Three years are required before yard bears a marketable product, whick makes adjustment of acreage to market tions difficult and often leads to overproduction depending on weather (M 1979). There are two diseases, Black Measles and Dead-Arm, which can be con with sodium arsenite. Sodium arsenite treatment is used only when Black Mea also present. Alternate materials are used otherwise.

Black Measles, also known as "Spanish measles" or "Apoplexy," was fi scribed in France, where it is known as Esca (Moller and Soll, undated; B 1926; Nelson, et al., 1949; Hewitt, 1952; Chiarappa, 1959, and 1959a; and Hew Jensen, 1965). The Black Measles disease can occur on wine, table, and raisin in most areas of California, although it is most prevalent in the interior which have consistently high summer temperatures. The disease is most notice the white and light-colored varieties; table grape growers in the San Joaquin suffering the most serious losses (Hewitt and Jensen, 1965; and Moller an undated). Generally, vines that are 8 to 10 years or older are affected.

Either the fruit, vine, or both, may be affected. One or more shoots, entire vine, may be diseased. Symptoms often are present on a vine 1 year and the next. Some vines may show symptoms several years in succession, and be r distributed throughout the vineyard. Symptoms are always correlated with an sive wood rot in the vine. Black Measles appears to be caused by toxins oxidative enzymes) released by one or more fungus species which invade the wood (Chiarappa, 1959). Species of fungi in the genera Fomes, Cephalospori Stereum (Phellinus) are most frequently implicated in the literature (Chi 1959, and 1959a; and Moller and Soll, undated). Rotting trunks of vines likely site for production of the fungus fruiting bodies, whose spores inv live plants through unhealed wounds. As wood rot develops over the years, the are apparently transported to other portions of the vines. Estimated annual losses of fresh market grapes range from 1.5 to 5% with an average level of ab Individual vineyards may suffer up to 35% loss of table grapes and 25% loss and raisin grapes (Christensen, 1978). Control on fresh market grapes is eco when about 3 to 4% of the vines are diseased (Hewitt, 1978).

Dead-Arm, so-called because of the dead arms sometimes associated with this disease, is caused by the fungus Phomopsis viticola Sacc. (Leavitt, undated; and Hewitt, 1971). It also causes black necrotic spots on leaves, leaf petioles, canes, and flower cluster stems, blighting of shoots and canes, and poor fruit quality and storage life. It occurs in the San Joaquin Valley of California and is most serious on the table and raisin grapes. Hewitt (1971) estimated that, in 1971, about 350,000 acres of vineyards (about 70% of California's acreage) were infected and Dead Arm was a serious disease on about 120,000 acres. Most recent estimates (Kasimatis, 1979) are about 40,000 acres affected by Dead-Arm. It was particularly severe in 1978 (Kissler, 1979).

Black Measles appears in severe and mild forms. The severe form usually occurs early in the growing season (May-June) and is characterized by sudden apical dieback of shoots, accompanied by leaf dropping and shriveling, bronzing, and drying of fruit clusters. Leaves remaining on the vines show necrosis and bronzing. In extremely severe cases, diseased shoots may completely die. The more common mild form may occur on all California vineyards, with symptoms developing throughout the growing season. Leaf symptoms are highly variable and consist of chlorotic and bronzed areas. The fruit may have dark, purple spots scattered throughout the outside of the berry. Affected grapes of certain varieties such as Emperor, Red Malaga, and Thompson Seedless have a slightly pungent, aromatic, and characteristic flavor. Affected clusters are worthless as table fruit regardless of variety (Hewitt, 1971).

Methods of Application

Sodium arsenite solution (43.4% $NaAsO_2$ in 30-gallon drums) is diluted (usually 3 qt./100 gallons water or about 3 pounds As/100 gallons) in a closed-system apparatus. California law presently requires employees, but not owners, to use closed systems for transfer and dilution of chemicals that have a poison label (Yagi, 1979). From 100 to 300 gallons per acre are applied (3 to 9 pounds As per acre) depending on size of vines and number of vines per acre. Some growers use a standard wind machine sprayer (Yagi, 1979), which would present some drift hazard if the applicator were not protected by an enclosed cab and proper clothing and face mask. Most growers use high-pressure sprayers with no air blower. Many are specially built sprayers that use dual nozzles on an extension boom that minimizes drift problems.

Application is made during the dormant season to the entire head or under-branch part of the vines. Treatment of individual infected vines has proven ineffective, and therefore the entire vineyard must be treated.

Use Patterns and Efficacy

Table 72 gives the acreage, production, and value of grapes in 1977, 1978, and estimates for 1979. The alternative usage of table and raisin grapes for wine makes estimates of actual production and income per acre difficult. It would appear from evaluating production, yield, and acreage statistics that about 50% of the table and raisin varieties actually are crushed for wine.

Acreage figures by region and variety are not directly available; however, production data are available and can be used to verify wine variety acreage. Table 73 shows that the San Joaquin Valley, which has the highest incidence of Black Measles, has nearly all of the table and raisin grape acreage and 74.7% of the wine grape production. Wine variety grapes are rarely treated for measle control. A very small percentage of the Thompson Seedless grape acreage dried for raisins might be sprayed.

Only Thompson Seedless grapes for fresh table use are commonly sprayed. Thus, probably about half of the 60,000 acres of table grapes would be treated yearly.

Table 72.--Acres, production, and value of grapes, California, 1977-1979

Type of Grape	Bearing Acres[a]	Yield Per Acre	Production[b]	Value Per Ton	Value Per Acre	Value of Production[b]
		Tons	1,000 Tons	- - Dollars - - -		1,000 Dollars
Grapes, all:						
1977	621,730	6.41	3,986	190	1,218	757,909
1978	616,247	6.52	4,017[c]	232[d]	1,513	874,307[c]
1979	616,247[e]	7.29	4,493	226	1,648	1,016,261
1977-79	618,075	6.74[f]	4,165	216[e,f]	1,456	882,826
Raisin type:						
1977	242,220	7.99	1,935	182	1,454	353,112
1978	240,348	7.98	1,918[c]	229[f]	1,827	381,641[c]
1979	240,348[e]	9.57	2,300	232	2,220	533,342
1977-79	240,972	8.51[f]	2,051	215[f,g]	1,830	422,698
Table type:						
1977	64,330	7.59	488	269	2,042	131,272
1978	62,245	6.31	393	342	2,158	134,406
1979	62,245[e]	6.64	413	303	2,012	125,139
1977-79	62,940	6.85[f]	431	302[f]	2,069	130,272
Wine type:						
1977	315,180	4.96	1,563	175	868	273,525
1978	313,654	5.44	1,706	210	1,142	358,260
1979	313,654[e]	5.68	1,780	201	1,142	357,780
1977-79	314,163	5.36[f]	1,683	196[f]	1,051	329,855

[a] California Crop and Livestock Rep. Serv., "California Grapes, Raisins, and Wine," 1978, Table 2, page 2, October 1979 (CCLRS, 1978a and 1979b).

[b] Noncitrus Fruits and Nuts Annual Summary (USDA, 1980; and CCLRS, 1979).

[c] Raisin and all grape total production includes 248,000 fresh tons (55,000 dry tons) laid for raisins, but not harvested due to severe weather damage. Value of lost raisins is not included in value of production. Data presentation is identical to published data.

[d] Calculated using 1978 harvested production (see footnote c); i.e., $874,307,000 ' [4,017,000 - 248,000 = 3,769,000] = $231.97.

[e] Bearing acres in 1979 assumed to be same as bearing acres in 1978 because SRS estimate of bearing acres in 1979 will not be released until June 1980.

[f] Weighted average.

[g] Calculated using 1978 harvested production (see footnote c); i.e., $381,641,000 ' [1,918,000 - 248,000 = 1,670,000] = $228.53.

Table 73.--Regional California projected grape production[a]

Region	Year	Bearing Acres			Percent of production		
		Table	Raisin	Wine	Table	Raisin	Wine
North and South Coast	1975	0	--	47,000	0	0	19.3
	1979	--	--	107,875	--	--	--
San Joaquin Valley	1975	68,300	250,000	123,400	100	100	74.7
	1979	58,937	242,306	183,049	--	--	--
Other	1975	0	0	14,900	0	0	6.0
	1979	5,407	2,936	22,831	--	--	--

[a] Garoyan, et al., 1975; and Moulton, 1979.

Table 74 summarizes establishment, production, and harvest costs for grapes. Establishment costs are similar except for the North Coast area. Production and harvest costs vary widely, depending on use and yield.

Hewitt (1978) estimates that from 3 to 20% of the susceptible acreage is subject to sodium arsenite treatment yearly. Based on 1978 figures, this would be about 16,000 to 54,000 acres, utilizing (at an average application rate of 6 pounds per acre) from 100,000 to 324,000 pounds As_2O_3. In 1976-1977, Los Angeles Chemicals sold about 20,000 to 30,000 gallons of 43.5% sodium arsenite (80,000 to 120,000 pounds As_2O_3), but 1977-1978 has seen a sharp increase in use, estimated at 60,000 t 70,000 gallons (240,000 to 280,000 pounds As_2O_3) (Stephens, 1979). More sodium arsenite could have been sold in 1978-1979 if it had been available; the increased demand is apparently due to a much higher incidence of Dead-Arm and Black Measles because of repeated spring rains in 1978 (Christensen, 1978; and Stephens, 1979). This use is much greater than the total estimated agricultural use of sodium arsenite in PD-1 (Federal Register, 1978).

Treatment for Black Measles by spraying with sodium arsenite in the dormant season is generally considered an effective (>80%) control (Nelson, et al., 1949; Hewitt, 1970, 1971, and 1978; Christensen, 1978; and Hewitt and Jensen, 1965). Moller and Soll (undated), however, feel that control is erratic and Soll (1978) has reservations about the efficacy of sodium arsenite. These questions can only be resolved by future research. Nevertheless, the industry continues to use this material; thus economic benefits must be assumed to occur.

Early treatment with sodium arsenite can damage grapevines (Nelson, et al., 1949), particularly if leaf scars on varieties such as Thompson Seedless have not healed and are sprayed directly. Also, yield reductions have been noted from treating vineyards with sodium arsenite for more than 2 consecutive years (Hewitt and Jensen, 1965).

Exposure Analysis

The sodium arsenite solution (43.4% $NaAsO_2$, 3.4 pounds As/gal.) commonly i delivered in 30-gallon drums. Because it carries a poison label, California law

Table 74.--Sample 1978 costs of grape establishment production and harvest

Region and Type of Grape	Establishment	Production		Harvest
	Dollars/Acre, 3 yr	Yield, Tons	Dollars/ Ton	Dollars/ Ton
North Coast Wine[a]				
Cane-pruned	5,680	4	465	75
Head-trained	5,680	4	295	54
San Joaquin-Thompson Seedless[b]				
Raisins	2,533	2.2	381	176
Wine	2,533	7.8	108	4
Table	2,981	6.0	227	448
San Joaquin-Emperor Table[c]	3,117	5.25	210	435
San Joaquin-Wine[d]				
High yield varieties	2,754	11	79	18
Moderate yield varieties	2,754	8	108	13

[a] Bowers, et al., 1978.

[b] Christensen, et al., 1978, 1978a, 1978b; and Swanson, et al., 1978.

[c] Christensen, et al., 1978c; and 1978d.

[d] Christensen, et al., 1978e; and 1978f.

requires employees to use a closed system for transfer and dilution of the solution, eliminating the possibility of direct contact (Yagi, 1979). Vineyard owners do not need to follow this rule, but because most vineyards are relatively large operations, little direct human contact with the solution should occur. Further, many growers use tractors with enclosed cabs and enforce the use of proper clothing. Thus, applicator contact is probably minimal. In 1969, only 12 lead or As-related occupational diseases attributed to pesticides or other agricultural chemicals from a total of 1,493 cases reported (CDPH, 1970). All 12 of these cases occurred during spring-summer, when sodium arsenite would not have been used on grapevines.

Inasmuch as the actual rate of As applied is relatively low (4 to 9 pounds per acre per treatment), and treatment is required only once every 4 to 7 years, the risks of environmental exposure at harmful levels should be minimal. Interestingly, some wineries in California do not purchase grapes treated with sodium arsenite (Moller and Soll, undated).

Fate in the Environment

Sodium arsenite is applied to arable soils, and its fate is therefore essentially that of arsenate (see Volume I, Chapter 4). Transport through runoff of topsoil containing elevated levels of arsenate is unlikely because most California vineyards are on level ground. The possibility of changes in land use (e.g., suburbs on As-treated vineyard land) must be considered, but at the levels of As used environmental problems would seem unlikely.

Alternatives

No alternatives for control of Black Measles are registered or in
mental stage. Diseased vines could be removed by hand, but this is not
feasible (Hewitt, 1971). Dead Arm (Phomopsis) can be controlled with
this treatment does not seem to be effective in severe outbreaks (Hewit
EPA, 1976b), although continued treatment with captan for 2 to 3 years m
cient (Hewitt, 1971). Other alternatives for Phomopsis control include
Dithane M-45. These must be applied as foliar treatments in early sprin
1978; Leavitt, undated; and Kissler, 1979). The dinitro compoun
(Premerge®), is a registered alternative for dormant eradication of Phomops

When more is known about the organisms responsible for Black Measl
mechanisms leading to the symptomatic damage, alternate chemical and/or
strategies may be developed (Soll, 1978).

Summary of Biological Analysis—Sodium Arsenite

Non-Selective Herbicide and Tree Killer

Sodium arsenite is normally applied as diluted solutions by sprink
Applicator exposure is minimal because the concentrate is formulated as
which is further diluted with water. Little exposure to the enviro- ent
with soil semi-sterilization uses.

Sodium arsenite is an effective soil semi-sterilant for weed contro
tree-stump control. Numerous alternatives are available, however, which h
toxicity and have less potential environmental impact. No benefits over the
tives seem apparent.

Subterranean Termite Control

Sodium arsenite is applied in trenches as a water solution for the c
subterranean termites. Exposure is limited to the application, as the trea
is covered over.

Several long-lasting alternatives are available for control of subt
termites. There are no suitable substitutes to sodium arsenite, however, fo
specialty uses where organic vapors cannot be tolerated.

Grape Disease Control

Sodium arsenite is used to control Dead Arm and Black Measles in Ca
grapes. It is applied as a directed dormant spray on 3 to 20% of the sus
acreage yearly. Application is at a rate of 3 to 9 pounds As_2O_3/acre. The
trate is diluted in a closed system and exposure is limited to the appl
process. No exposure data are available, however. The low application -te
present little environmental problems, especially since any one field .l
treated once every 4 to 7 years.

A summary of testimonial letters solicited from growers in California i
in Table 75. The responses are from professional extension workers, associ
and private individuals.

Pacific Gas and Electric Company

One California Street, Room [illegible]
San Francisco, CA
[illegible]
Telex 97[illegible] 6688
Mailing Address
P.O. Box [illegible]
San Francisco, CA 9412[illegible]

November 27, 1989

Mr. Robert Barnum, Chief
Toxic Air Contaminant Identification Branch
Air Resources Board
Attention: Inorganic Arsenic
P.O. Box 2815
Sacramento, CA 95812

Dear Mr. Barnum:

PG&E COMMENTS ON DRAFT ARSENIC EXPOSURE AND RISK ASSESSMENT

PG&E has received the October 31, 1989 "DRAFT REPORT ON INORGANIC ARSENIC". Part C of this report ("Public Comments and Responses"), excludes PG&E's comments on Part B ("Health Effects") of the preliminary draft.

On May 9, 1988, PG&E submitted comments on the draft report including a cover letter summarizing main points, five major attachments, and several referenced documents. The five major attachments were:

A. Comments from Dr. Dean Carter and Dr. Steven Pike, EnviroMed, Arizona;

B. Comments from Dr. K. S. Crump, K. S. Krump & Company, Louisiana;

C. Comments from Dr. Paul Solomon, PG&E;

D. Comments from Ted Holcombe, PG&E; and

E. Highlights of an attached draft William L. Marcus report which addressed the apparent existence of a safe threshold for arsenic in drinking water.

The cover letter, and Attachments A, B and E were all omitted from the Part C "Public Comments and Responses". Please also note that Attachment D of our May 9, 1988 comments was incorrectly listed in Part C as dated October 20, 1987.

PG&E's cover letter and comment attachments A, B and E constituted a major portion of the public comments on the safe-threshold/no-safe-threshold and unit lung cancer risk issues being decided at this stage of the carcinogen identification process. While we believe that the omission of these comments from Part C was accidental, we urge the Air Resources Board (ARB) and Department of Health Services (DHS) to correct this oversight by issuing a Part C addendum containing our omitted material, and extending the comment period to allow adequate time for interested parties to consider our comments.

DHS addresses our Attachment A and B comments. However, reviewers should have access to the comments. Furthermore, DHS does not appear to address Attachment E. Finally, there are areas where DHS has not summarized our comments the way we believe they should be summarized.

For example, on page 11, DHS summarizes PG&E's position as "Insoluble arsenic salts are probably more hazardous than soluble salts". PG&E's Attachment A addressed numerous factors including the reduced hazards of As(V) versus As(III) in contact with lung cells, the reduced likelihood of As(V) to As(III) conversion in the lungs, and the rapid clearance of soluble As compounds from the lungs. PG&E's Attachment D summarized the data/comments as suggesting that lung cancer risks are highest from inhalation of insoluble As(III) in the lung, and lowest from inhalation of insoluble As(V). Soluble As(III) would pose the second greatest hazard. Soluble As(V) the next to lowest hazard. We believe that the manner in which DHS has attempted to simplify and separate our intertwined comments has not correctly represented them.

In all fairness the state should recognize that while it can take as long as it needs to do a good job (in this case 32 months to prepare the initial report, and another 16 months to respond to comments), the public is currently only given one month in which to comment. This time constraint severely limits the public's ability to comment at all, let alone to detail step by step how the proper consideration of our comments would alter proposed unit risks. While PG&E offered to respond to any questions on these comments, we were never asked to "explain the logic behind our risk lowering factor". We were therefore surprised by the DHS response on page 11 that our logic was unclear. We will include a summary of our risk reduction logic with our comments on this draft.

Omission of our comments precludes the public from reviewing and commenting upon the adequacy of the DHS response to those comments. We therefore request that our omitted cover letter and major attachments A, B and E be distributed to all Part C recipients, and that the time period for responses be extended to at least 30 days after that distribution.

Part C also omits a number of references enclosed with our comments (see the attached list). PG&E does not expect the ARB/DHS to distribute copies of each of these references to each of the Part C recipients. But if those references are not distributed, a reference list such as the one attached to this letter should be distributed with the Part C addendum. Furthermore, the availability of the final Marcus article should be duly noted.

If you have any questions about these comments, or if the Scientific Advisory Panel would like Drs. Carter, Crump, Pike or Solomon to present oral testimony, please call me at (415) 972-7746, or Ted Holcombe at (415) 972-6910.

Victor C. Fustado

Attachment (Reference list, May 9, 1988 Cover letter and
Attachments A, B & E)

cc with reference list only

Dr. Steven Pike
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College of Pharmacy
University of Arizona
Tucson, AZ 85721

Dr. K. S. Crump
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1201 Gaines Street
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Dr. William L. Marcus
12521 Deoudes Road
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Dr. Paul Solomon
PG&E
Technical & Ecological Services
3400 Crow Canyon Rd.
San Ramon CA 94583

PG&E REFERENCES ALSO OMITTED FROM PART C
OF THE OCTOBER 1989 ARSENIC RISK ASSESSMENT

Part C also excluded the following references:

ATTACHED TO OUR MAY 9, 1988 COMMENTS:

1. April 1988 draft "Quantitative Toxicological Evaluation of Ingested Arsenic", by William L. Marcus, U.S. Environmental Protection Agency, Office of Drinking Water;

2. "Arsenic in Rain and the Atmospheric Mass Balance of Arsenic", Meinrat O. Andreae, Journal of Geophysical Research, Vol. 85, No. C8, Pages 4512-4518, August 20, 1980;

3. "Tropospheric Arsenic Over Marine and Continental Regions", Paul R. Walsh, Robert A. Duce, and James L. Fasching, Journal of Geophysical Research, Vol. 84, No. C4, Pages 1710-1718, April 20, 1979;

4. "Efficiency of Filter Sampling for Arsenic in the Atmosphere", B. R. Appel, Y. Tokiwa, and E. M. Hoffer, Atmospheric Environment, Vol. 18, No. 1, Pages 219-222, 1984;

5. "Impregnated Filter Sampling System for Collection of Volatile Arsenic in the Atmosphere", Paul R. Walsh, Robert A. Duce and James L. Fasching, Environmental Science & Technology, Vol. 11, No. 2, February 1977;

6. "Emissions of Noncondensible Gases and Solid Materials from the Power Generating Units at the Geysers Power Plant", PG&E Department of Engineering Research Report 7485.16-74, July 30, 1974;

ATTACHED TO OUR OCTOBER 20, 1987 COMMENTS:

7. "Chemical Characterization of Gases and Volatile Heavy Metals in Geothermal Effluents", David E. Robertson, Jonathan S. Fruchter, J. Donald Ludwick, Connie L. Wilkerson, Eric A. Crecelius and John C. Evans, Geothermal Resources Council Transactions, , Vol. 2, pages 579-582, July 1978;

8. "A Theory on Trace Arsenic in Geothermal Fluids", James W. Cobble, Electric Power Research Institute Report AP-4214, Project 1525-6, August 1985;

9. "Geysers Unit 17 and 18 Cooling Tower Drift Test", PG&E Department of Engineering Research Report 009.4-85.28, August 29, 1985;

10. Letters to the California Energy Commission dated March 14, 1983, July 19, 1983, November 4, 1983, January 12, 1984, April 30, 1984, August 7, 1984, October 30, 1984, and January 7, 1985, addressing the mass balance of arsenic in Geysers Unit 17.

Subsequent to our May 9, 1988 comments, Dr. Marcus's work was printed as: "Threshold Carcinogenicity Using Arsenic as an Example", W. L. Marcus and A. S. Rispin, Advances in Modern Environmental Toxicology, Vol. XV, Pages 133-158, 1988.

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Victor C. Furtado, Ph.D.
Manager
Environmental Services

May 9, 1988

Mr. Robert Barnum, Chief
Toxic Air Contaminant Identification Branch
Air Resources Board
Attention: Inorganic Arsenic
P.O. Box 2815
Sacramento, CA 95812

Dear Mr. Barnum:

PG&E COMMENTS ON DRAFT ARSENIC EXPOSURE AND RISK ASSESSMENT

PG&E appreciates this opportunity to comment on the draft assessment. To assist you in finalizing this assessment, PG&E has assembled comments from a variety of sources.

Comments from Dr. Dean Carter and Dr. Steven Pike are presented in Attachment A. These comments focus on the need to revise Part B to either:

1. lower the current combined arsenic risk estimate by a factor of 20 to 40 to better account for the differences in the types of arsenic compounds and particle size distributions found in historical occupational exposures versus current ambient air exposures; or to

2. estimate pentavalent arsenic risks separately from trivalent arsenic risks — with pentavalent arsenic risks being estimated to be at least ten times lower than trivalent arsenic risks.

They also suggest reconsideration of the possibility of a threshold of no significant adverse effects since arsenic sulfhydryl bonding is an equilibrium process that supports the concept of a threshold, and evidence suggests a linear threshold model would fit the data better.

Comments from Dr. Kenny Crump are presented in Attachment B. These comments focus on the need to revise Part B to:

3. either replace the unsound and not understandable smoking interaction model, or at least develop a range of estimates that is more consistent with the data available; and

4. show the range of risk that would result from use of the Environmental Protection Agency (EPA) additive risk model assumptions.

Dr. Crump also suggests that Part B be revised to:

5. discuss/investigate more fully the implications of the Lee-Feldstein (198[illegible] data and the non-linear relation estimated by Enterline et al.;

6. reconsider or better justify the conclusion that the use of cumulative exposure may substantially underestimate risks from environmental exposures; and

7. discuss whether evidence from the epidemiological studies is consistent with no risk from environmental exposures of concern.

Comments from Dr. Paul Solomon are presented in Attachment C. These comments focus on ambient air monitoring. Dr. Solomon suggests that As(III) vapor emissions are likely to be detected by particle monitors located at least 500 meters downwind.

Comments by Ted Holcombe are presented in Attachment D. These comments focus on the alarmist and conjectural nature of some of the statements in Part A, a[illegible] on the significance of ingestion exposures and ingestion threshold theories o[illegible] inhalation exposures.

The highlights of a recent draft toxicological evaluation of arsenic by Dr. William Marcus, EPA Office of Drinking Water, are presented in Attachment E. Part B should be revised as needed to incorporate the statements and re[illegible]enc cited in the highlights.

PG&E believes the 30-day comment period on this draft risk assessment severel[illegible] limits the public's ability to comment. Given that this draft was released f[illegible] public comment on April 7, 1988, after 32 months of preparation by the agencies, additional review time would seem appropriate.

If you have any questions about these comments, or if the Scientific Advisory Panel would like Drs. Carter, Crump, Pike or Solomon to present oral testimon[illegible] please call me at (415) 972-7746, or Ted Holcombe at (415) 972-6910.

Victor C. Furtado

Attachments

cc w/attachments A through E only

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EnviroMe

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May 4, 1988

Mr. Ted Holcombe
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Room 1658
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San Francisco, California

Dear Mr. Holcombe,

Attached you will find comments prepared by Dr. Dean Carter and me regarding the Report on Arsenic in the Ambient Air prepared by the California Department of Health Services for submission to the Scientific Review Panel on Toxic Air Contaminants dated December 30, 1987. Our comments recommend:

1. Lowering the unit risk estimate for inorganic arsenic by at least a factor of 20 to 40 by incorporating differences in potency of As(III) compared to As(V); by recognizing that As(V) is the predominant species present in ambient air, and incorporating physical chemical properties of particles such as size and solubility into the risk estimates.

2. Addressing the physiological implications of the physical chemical properties of particles on such parameters as lung capture, retention, and bioavailability in the calculation of the unit risk estimates.

3. Incorporate the possibility of a threshold below which no significant adverse effects are likely to occur (considering the possibility that arsenic may be an essential metal) and fit the data to such a model.

You will be receiving Dr. Kenny Crump's comments under separate cover and will find that his comments will recommend among other modifications:

4. Abandoning the contorted and unsound DHS approach of "inferring data" to fit their model to account for a presumed interaction between smoking and arsenic in the production of lung cancer that is intermediate between linear and multiplicative.

5. DHS should reconsider the use of an additive risk model considering the weak arguments presented for using the relative

risk model in the derivation of their unit risk estimates. DHS's decision contrasts with the EPA's finding that additive risk models fit the data better than relative risk models.

Please feel free to contact Dr. Carter, Dr. Crump or me directly if you have specific questions relative to our comments.

Very truly yours,

Steven Pike, M.D.

Enc.

I. The risk assessment should incorporate the difference in potency of Arsenic III compared to Arsenic V in developing the unit risk estimate. Existing data are sufficient to warrant a unit risk at least ten times lower for Arsenic V than for Arsenic III. [Comments by Dean Carter, Ph.D. and Steven Pike, M.D.]

In Section 2.1.2 DHS suggests that inhalation of ambient arsenic may be more toxic than ingestion of an equivalent amount of dietary arsenic. DHS reasons that lack of methylation (detoxification) in the lung may be responsible. It is important to note that it is the trivalent arsenic that is taken up by hepatocytes for methylation and not the pentavalent. Speciation of arsenic plays an important role in metabolism, As(V) requiring reduction to As(III) to undergo methylation. Since the target for this risk assessment is the effect of arsenic on cells of the lung, a closer look at the effects of As(III) and As(V) on cells is warranted.

Section 7.1.1 cites reports in which arsenite As(III) inhibited DNA repair of damage caused by UV radiation in bacteria, while arsenate As(V) at five times the concentration had no effect on DNA repair.

In Section 7.3 concentrations of arsenate (As(V)) ten times greater than arsenite (As(III)) were required to inhibit mitogenesis. Furthermore, mutation of frequencies were negative in the mouse cell thymidine kinase (TK) locus assay when treated with As(V). Section 7.3 also reports positive responses for chromosomal abnormalities in mammalian cells exposed to As(III); As(V) was not tested.

In Section 7.3.1 DHS cites work reported on human lymphocytes exposed in vitro to sodium arsenite (As(III)) which resulted in chromatid breaks and gaps, but was negative when tested with sodium arsenate (As(V)).

It is apparent that there is at least a ten-fold difference in the potency of As(III) compared to As(V). When considering the lack of evidence of the lung's ability to metabolize As(V) to As(III) and detoxify As(III) by methylation, failing to factor in speciation of arsenic in considering toxicity combined with failing to consider ratios of As(III):As(V) in ambient air, risk is overestimated by at least a factor of 20 to 40.

II. The risk assessment should factor the relative contributions and potencies for the development of cancer that vary with particle size, solubility, and the proportion of As(III):As(V) in ambient air. The magnitude of such effects should be estimated and incorporated into the calculation of the unit risk for arsenic. Consideration of these factors will lower the resultant risk estimates. [Main comments by Steven Pike, M.D., some comments by Dean Carter, Ph.D.]

In Section 11.4.2C DHS recognizes that assuming ambient air and occupational exposure involve similar As(III):As(V) ratios may overestimate risk. Arsenic trioxide (As(III)) is probably nearly the exclusive form of exposure to the Anaconda and Tacoma smelter workers. Andreae, 1980 reports that nearly all the arsenic emitted from the Tacoma smelter is arsenic trioxide (As(III)) and that rainfall samples from the Anacortes, Washington site were 88% arsenite (As(III)) strongly supporting the argument that the Tacoma smelter is the dominant source of arsenic at this site. This result should be contrasted with the environmental ratio of As(III):As(V) reported in Appendix C of Part A [Solomon, 1987] to be close to 1 (i.e., equal mixture of both species, approx. 50% As(III)). However, this ratio was determined from samples collected in the City of Industry and thus may not truly reflect the ratio in the majority of urban and rural areas. Studies conducted in Tucson, Arizona, a city ringed by copper mines and smelters, revealed an As(III):As(V) ratio of about 0.31 +/- 0.29 (i.e., 24% As(III)) indicating that As(V) may be the species present in the atmosphere at up to three times the concentration of As(III), [Solomon, 1984]. Furthermore the ratio of 0.31 represents the mean of the highest total arsenic measured in 15 of 60 samples taken over a one year period [Solomon, 1988]. These samples were collected about 500 meters from an electric powerplant. Comparing the ratio of As(III) reported by Andreae to the ratios of As(III) reported by Solomon suggest that there is 1.8 (88/50) to 3.7 (88/24) times as much As(III) in Tacoma air as in powerplant or California smelter air. Failing to incorporate the difference in speciation of arsenic in air overestimates risk by a factor of two to four.

III. The risk assessment should be revised and modified based on an evaluation of physical state and should incorporate the differences in physical state that exist between the arsenic compounds measured in the epidemiologic studies and those measured in the ambient exposures for the development of unit risk estimates. [Main comments by Dean Carter, Ph.D., some comments by Steven Pike, M.D.]

CAPTURE:

The size of the particles should be considered in the exposure extrapolation. The deposition of particles of different sizes has been well studied in the human lung. The particle size distribution of the arsenic oxide particles at the Tacoma Washington smelter has been studied. A brief description can be found in Piver (1983). It appears that about 55% of the arsenic particles were smaller than 2.5 um. Although it is not possible to directly compare this with the findings described in the California DHS report (page A-78), it appears that the California environmental samples are considerably smaller than smelter samples with regard to their arsenic distribution. Smaller particles do go deeper into the lung but their deposition decreases to the point that most very small particles are exhaled with the breath without deposition. Data suggests that only approximately 30% to 50% of particles between 0.1 um and 1.0 um are retained by the lung parenchyma [Task Force Group on Lung Dynamics.

1966]. The arguments made in the California DHS report (page suggest that the bronchioles are the target site in the lung and no lower alveolar region. This would be consistent with the de ositic larger particles. Thus, a risk assessment should include an e. uatic the particle size distribution of the environmental samples as com with the smelter samples and an assessment of deposition rate and differences.

RETENTION:

There are several considerations for an evaluation of toxicity l on physical state. First, assuming that the lung is the target orga the DHS evaluation, the soluble compounds of arsenic described in evaluation would be rapidly dissolved and absorbed from the lung (Mara and Vahter, 1987). Arsenic is not retained in the body but is ra excreted into the urine (Cal DHS 2-6,7). Yet, smelter workers have found to have high concentrations of arsenic remaining in their several years after exposure ceased (Vahter, 1983). This suggests the workers may have been exposed to insoluble forms of arsenic sulfides, arsenite salts of calcium, lead, zinc, etc.) and the retentio these compounds may have been significant in the development of cancer.

BIOAVAILABILITY:

The hazard assessment discussion has ignored an evaluation of physical state of the arsenic. The review does briefly distinguis' 'etv arsenic compounds in the vapor phase and in the solid (partic.. p (Cal DHS A2-A3, A72-A79). However, there are many arsenic compo that are of environmental importance which have different water solubil (NRC, 1977). These compounds of different solubilities have diffe bioavailabilities (Marafante and Vahter, 1987; Webb et al., 1984) different forms of toxicity (Webb et al., 1986).

Insoluble arsenic (As(III)) salts are probably more hazardous than soluble salts because they are retained in the target organ (the l whereas the soluble forms can readily enter the bloodstream where can be taken up by the liver to undergo detoxification by methyla This concept is supported by the animal work by Pershagen and cowor which is cited in the California DHS report on page 8-3 as supportive arsenic being a lung carcinogen in animals after intratracheal instilla of arsenic. All animal groups in this study received the arsenic i carrier dust of charcoal carbon to increase the lung retention of ars as well as a solution of sulfuric acid. This supports both the con that arsenicals retained in the lung may have had an effect on development of lung cancer and that sulfur oxides may have a contribu effect on arsenic carcinogenicity. These critical experimental details v ignored in the California DHS report. Thus, a risk assessment sh include an evaluation of the physical form and solubility of the ars with special emphasis on how much can be retained.

IV. The DHS Risk Assessment should consider the possibility of a threshold below which there are no significant adverse effects. The use of a zero threshold may actually create significant adverse effects if arsenic is an essential element in humans and is regulated to a level which would create a deficiency state. Thus a zero threshold would not be biologically plausible. DHS is arbitrarily dismissing the possibility of a threshold; a conclusion contrary to the opinions of other scientists. Furthermore, if evidence for arsenic as an essential element in humans becomes compelling, some scientists would argue that there is a teleologically sound basis for the existence of a threshold below which no significant adverse effects would result. [Main comments by Dean Carter, Ph.D., some comments by Steven Pike, M.D.]

The California DHS report discounts the possibility of a threshold dose. There are several workers in the field who would have come to the opposite conclusion. There is one point on page 10-5 of the report which shows a lack of understanding of arsenic binding. The report states "A single instance of sulfhydryl group binding to an enzyme might result in misrepair or breakage of DNA." This type of argument has been used with alkylating agents of DNA which form a covalent bond after an irreversible reaction with the DNA. In that case, one molecule forming one bond may indeed result in breakage of DNA. However, arsenic binding to sulfhydryl groups is an equilibrium process in which the bonds are continually being formed and broken. The number of molecules which have bound to arsenic depends on the free arsenic concentration and the actual sulfhydryl groups which are bound change constantly. The dose-response relationships for such equilibrium processes have been well described in basic pharmacology texts and support the concept of a threshold.

The argument that DHS raises in Section 10.5.2 that a single instance of sulfhydryl group binding to an enzyme might result in misrepair or breakage of DNA is biologically not plausible. Enzymes have great reserve capacity for function in human physiology. This is most dramatically evident when one considers the ability of heterozygous genotypes for enzyme deficiency in persons with inborn errors of metabolism to be phenotypically normal. It is extremely unlikely that one altered enzyme molecule would bind to DNA and cause misrepair or breakage in the midst of overwhelming numbers of "normal" enzyme molecules.

The staff at DHS cite the possibility that "a single instance of arsenolysis might result in DNA damage." However the hypothesis that inorganic arsenic (As(V)) competes with phosphorus to form unstable arsenate DNA and RNA esters has never been proven in vivo. All experimental results have been based on isolated enzyme or single cell studies and there is no evidence that this mechanism is biologically plausible in mammalian systems. DHS has not shown that a threshold model fails to fit the data as well or better than a linear no threshold model and evidence suggests that the converse is true.

BIBLIOGRAPHY

Andreae, M.O. 1980. Arsenic in Rain and the Atmospheric Mass Balance of Arsenic. J. Geophys. Res. 85: 4512-4518.

Marafante, E. and M. Vahter. 1987. Solubility, retention and metabolism of intratracheally and orally administered inorganic arsenic compounds in the hamster. Environ. Res. 42: 72-82.

National Research Council. 1977. Arsenic. National Academy of Sciences, Washington, DC. p. 4-15.

Piver, W.T. 1983. Mobilization of arsenic by natural and industrial processes. In "Biological and environmental effects of arsenic" edited by B.A. Fowler. Elsevier, Amsterdam, p. 40.

Solomon, P.A., Rabano, E.S., Castillo, N.T. and Torre, K.J. Speciation of Arsenic in Ambient Aerosols Collected in Los Angeles. Final Report 1182R/0214A submitted to California Air Resources Board, May 19, 1987.

Solomon, P.A. Collection and Analysis Techniques for Studies of Atmospheric Arsenic Species, Ph.D. Thesis, Dept. of Chemistry, University of Arizona, Tucson, Arizona (1984).

Solomon, P.A. Personal communication, May 3, 1988.

Task Force Group on Lung Dynamics, Committee II IRCP, Deposition and retention models for internal dosimetry of the human respiratory tract. Health Phys., 12, 173, 1966.

Vahter, M. 1983. Metabolism of arsenic. In "Biological and environmental effects of arsenic" edited by B.A. Fowler. Elsevier, Amsterdam. p. 172.

Webb, D.R., I.G. Sipes and D.E. Carter. 1984. In vitro solubility and in vivo toxicity of gallium arsenide. Toxicol. Appl. Pharmacol. 76: 96-104.

Webb, D.R., S.E. Wilson and D.E. Carter. 1986. Comparative pulmonary toxicity of gallium arsenide, gallium oxide or arsenic oxide intratracheally instilled into rats. Toxicol. Appl. Pharmacol. 82: 405-416.

Comments on

Health Effects of Arsenic Compounds
Prepared by
Air Unit
Hazard Evaluation Section
Department of Health Services
Berkeley, CA

Kenny S. Crump
Clement Associates, Inc.
1201 Gaines Street
Ruston, Louisiana 71270

Overview of DHS's risk assessment

DHS's risk assessment was based upon lung cancer data from three studies. A recent study by Lee-Feldstein (1986) was not used. The risk assessment relies heavily upon the EPA review of the epidemiological studies, which was prepared before any of these four studies were published. DHS should review these these studies in more depth. It is possible that the Lee-Feldstein study should not be rejected out of hand, since all of the studies involve defficiencies of some sort.

DHS's model of smoking and arsenic interaction is unsound and their explanation of this feature of their model in Appendix E is not understandable. Further, their basic assumptions with regard to smoking and arsenic interaction are not well supported by the data. DHS should

abandon the current model of smoking and arsenic interaction and replace it with a simpler approach or, in view of the disparity of the data, develop a range of estimates that are more or less equally consistent with the data available.

DHS's justification of use of a linear dose-response is primarily theoretical. DHS should evaluate this crucial assumption in light of the dose-response data, and examine what level of departure from this assumption is consistent with the data. In particular, DHS should discuss whether the evidence from the epidemiological studies is consistent with no risk from environmental exposures of concern.

DHS's reliance upon a single risk assessment model is unfortunate, particularly since it appears to have methodological defects. DHS should develop a range of estimates for different assumptions that are all more or less consistent with the data and with current scientific understanding. For example, since DHS utilized new data from the Tacoma smelter that were not available to EPA and have not heretofore been used in risk assessment, it would be useful to determine the risk estimates obtained by applying the EPA methodology to these data. The fact that the new study estimates a considerably higher air concentration for a given urine level suggests that the EPA procedure would produce lower risk estimates from the newer data.

Specific Comments

DHS relied heavily upon the review by EPA (1984) of the epidemiological studies. However, four studies, including all of those used by DHS for its risk assessment, appeared after EPA's review. The risk assessment would have profited from a more thorough review of these studies. In particular, the reason for not using the Lee-Feldstein (1986) study should have been more thoroughly described. Perhaps this study should be utilized since all of the studies have defficiencies of one sort of another. Also, the non-linear relation estimated by Enterline *et al.* between urinary arsenic and airborne arsenic could have important implications for risk assessment and should investigated more fully.

DHS's discussion of possible bias in estimates made for persons exposed as children is speculative and itself potentially biased. For example, it is not clear whether they are referring to dermal or inhalation exposures that are claimed to result from children playing in dirt. Dermal exposures are not considered to be related to lung cancer risk. One can also easily think of reasons why risk from early exposures could be overestimated: children breathe less than adults and children may have a stronger immune system than the elderly. Further, it is highly speculative to assume that a smoking and arsenic interaction would hold for arsenic exposures that precede the onset of smoking; consequently, it would be reasonable to consider a model in which any joint effect of

smoking and arsenic only applies to arsenic exposures that occur after the advent of smoking. DHS's discussion of these issues should be presented in a more balanced fashion.

The statement (page 11-11) that "short-term exposures are considered equivalent to long-term low exposures provided the cumulative dose is the same" is not quite correct. It is true that DHS's method of accumulating dose predicts that *at a given age* risk is determined only by cumulative dose to that age. However, with a high short-term exposure, cumulative exposure will be higher at intermediate ages than with an equivalent long-term exposure; consequently, lifetime risk will be estimated by DHS as being higher from a short-term high level exposure.

Kodell *et al* (1987) (page 11-11) refer to using total average exposure as a surrogate for taking the actual exposure pattern into account; since DHS is taking the exposure pattern into account in both the epidemiological populations and the posited exposures in the risk assessment, the situation discussed by Kodell *et al* is not comparable to that being evaluated by DHS. Comparing the results of having an early stage effected to DHS's use of cumulative exposure is problematic without carrying out a detailed analysis. Consequently, DHS's conclusion that their use of cumulative exposure may substantially underestimate risk from environmental exposures seems premature and

should be either buttressed by a more detailed analysis or be deleted.

DHS was perhaps premature (page 11-13) to dismiss an additive risk model for arsenic. DHS cited two factors in this decision: first, the assumption that risk is independent of age for a given cumulative dose is biologically implausible and, second, age-specific data were lacking. With regard to the first factor, DHS indicated that an absolute risk model would predict the same additional hazard for a five-year-old as for a fifty year old, given the same cumulative exposure and that this was biologically implausible. However, an absolute risk model would not predict the same risk in these two circumstances if latency was taken into account realistically. Beyond this, it is not clear that an additive risk model is implausible. Further, EPA found that additive risk models fit the available data better than relative risk models.

The reasons cited for using a linear dose-response (page 11-14) should include a discussion of the observed dose-responses in the epidemiological studies. Further, the range of departures from this assumption which are consistent with the epidemiological data should be explored.

The model used by DHS assumes that the joint effect of arsenic and smoking multiplies the background risk of lung cancer. Based upon their conclusion that the joint effects of arsenic and smoking are intermediate between multiplicative and additive, DHS develops a very

complicated model of interaction that involves inferring SMRs (standardized mortality ratios) and observed cancers in nonsmoking populations. As discussed below, this approach seems ill-advised.

First of all, the limited evidence on the interaction between smoking and arsenic exposure has been overinterpreted by DHS. Even if the basic model is one of a multiplicative effect upon age-specific background rates, this model will not predict that the expected RRs (relative risks) will be multiplicative, as assumed by DHS. This is because the expected number of cancers in a dose group is a sum of terms for each age- and calendar-year and even though a multiplicative relationship holds for each group, this will not in general result in a multiplicative relationship for the overall RRs. (It would be multiplicative if the multiplicative factors for both smoking and arsenic were constant; however, this will not be true in general because, for example, the relative risk associated with a worker's exposure to arsenic will increase with his exposure.) Moreover, even if the expected relationship was to be multiplicative, the observed relationship would be subject to random error. DHS, in deciding that a multiplicative relationship is not appropriate, did not investigate whether the disagreement could be explained by random error. It seems likely that some of the relative risks, for non-smokers in particular, were based on small numbers of cases; consequently, the disagreement with a multiplicative relation could well be due to random deviations.

DHS incorporated the effect of a non-multiplicative relationship between arsenic and smoking by including a parameter, ρ, that expresses the degree of departure from a multiplicative model. This parameter is assumed to decrease with increasing exposure to arsenic; the specific values used for this parameter are apparently not derived from data. A casual observation of the data in Appendix A did not support DHS's assumptions regarding this parameter. Values of ρ suggested by the Welch *et al* (1982) data vary from 0.4 to 3 depending upon how they are calculated and do not appear to vary with arsenic exposure in a consistent manner. Thus, DHS's selection of values for this parameter are not clearly supported by data.

DHS's dose-response modelling procedure is contorted and not well explained. There appear to be errors in the discussion of the implementation. The complications arise mainly from DHS's modelling of the joint effect of arsenic and smoking. To do this they calculate new "data" which they call "inferred nonsmokers data" and fit a linear dose-response model to this data by a least squares method (not explicitly defined).

I was not able to follow the mathematical explanation of the model contained in Appendix E. The basis for the derivation is overly simplistic; relative risks are actually calculated as ratios of sums

with each term in the sum being similar to the expressions used by DHS, but with different factors due to different background incidences, arsenic doses, and smoking categories. The formula for SMR on page E-3 must be incorrect (the SMR will be negative if ρ is less than one). Also, the mathematical derivation does not lead to this equation and I was unable to infer the formula used for the results in Table E-1.

The properties of statistical procedures applied to the "inferred data" are unknown. DHS warns at one point that the confidence limits calculated from the inferred data may not share the properties that would hold had they been applied to real, as opposed to inferred, data. However, the conclusion that "an excellent fit was obtained for both data sets" was not tempered by such a warning.

DHS indicates that the inferred observed deaths are treated as Poisson random variables. It is not clear what role this assumption plays in the sequel.

The data used in the risk assessment are not in Table 11-3 as stated on page 11-12. Presumably the data for Tacoma can be obtained by combining data from Tables 9-4 and 11-2, and the data for Anaconda by combining data from Tables 9-6 and 11-2. However, it is important that the actual data used be clearly designated.

The implication (pages 11-6 and 11-18) that Welch *et al.* (1982) and Higgins *et al.* (1985) were "incorrect" in their apportioning of person-years of exposure according to final exposure is too strong. "Less appropriate for the particular risk assessment approach applied by DHS" would be preferred.

ATTACHMENT E

A SUMMARY OF HIGHLIGHTS
OF
"QUANTITATIVE TOXICOLOGICAL EVALUATION OF INGESTED ARSENIC"
BY

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This is a preliminary draft, dated approximately April 17, 1988, not yet officially released — and therefore not yet official agency policy. Dr. Marcus has advised that he will publish this evaluation as a book in May 1988.

Highlights of the evaluation include:

A. AVERAGE EXPOSURES

1. One can estimate that approximately 112,000 people are receiving drinking water from public water supplies with arsenic levels at or above 50 ug/l, the federal maximum contaminant level. These people would be exposed to more than 100 ug of arsenic per day (assuming an average daily consumption of 2 liters of water). On average, ground water supplies show higher levels of arsenic in some of the western United States (pg. 4).

2. Recent FDA surveys indicate an average daily dietary intake in the United States of approximately 50 ug arsenic.... Although most of the trimethyl arsenic compounds in prawns were excreted unchanged, three to five percent is changed to mono- and di- methylated forms or to inorganic arsenic (pp 5-6).

3. Assuming a daily inhalation rate of 20 m^3, and an average national exposure of 0.006 ug As/m^3 (6 ng/m^3), the inhalation exposure of the general public to water soluble forms of arsenic in the ambient air can be estimated as almost 0.12 ug/day (pg. 5).

†NOTE: 3% of 50 ug/day is 1.5 ug/day. This suggests that even assuming that all food arsenic was 100% organic, exposures from conversion of such arsenic would be ten times greater than inhalation exposures assuming 6 ng/m^3, and effective drinking water exposures would likely be even higher. This suggests that inhalation exposures to soluble As (III) compounds in California may be insignificant, since the highest annual average exposures identified by the California Air Resources Board in their April 1988 Preliminary Draft Report on Public Exposure to Airborne Inorganic Arsenic in California was only 3.5 ng/m^3 (ARB Table 1-2 pg. A-12).†

B. ESSENTIALITY

1. One can project a nutritional requirement of between about 12 and 50 ug/day (pg. 7).

2. [Animal studies in rats, chicks, goats and pigs all indicated adverse effects from arsenic deficient diets (pp77-79)].

3. If [arsenic is essential in humans] the required daily intake in humans is estimated to be approximately 10 to 30 ug/day (US EPA 1987)(pg. 79).

C. REVERSIBILITY OF TOXIC MECHANISM

1. Paul Erhlich showed that glutathione and other sulfydryl containing chemicals prevented the toxic effects of arsenic (pg. 24).

2. Voegtlin postulated that the toxic action of trivalent arsenical compounds was the result of a toxic reversible interaction of arsenite [As(III)] with the SH groups of glutathione in cells or with other SH groups occurring in cell protoplasm. This conclusion has been supported by extensive studies... [indicating] that the major toxic action of trivalent arsenicals is their interaction with thiol groups of critical enzymes (Squiff and Flower, 1983) (pp 24-25).

D. POSSIBLE SAFE THRESHOLD

Dr. Marcus suggests that daily ingestion of more than 200 to 250 ug of arsenic is needed in order for [significant adverse] effects to be demonstrated. He bases this threshold phenomenon theory on the following:

a. conversion of inorganic arsenic to dimethylarsinic acid (DMA) appears to be the rate limiting step in detoxification (VIII-40);

b. the methylation capacity of the liver is exceeded [at exposures above] 250 ug/day (VIII-43);

c. [when the methylation capacity has been reached, excess As(III), by binding directly to sulfhydryl groups in essential enzymes and in the dithiol cofactor, inhibits the enzymatic conversion of monomethylarsonic acid (MMA) to DMA (VIII-37 and VIII-47)]; and

d. [overwhelming the detoxification mechanism allows direct deposition of As(III) in the blood and tissues and can result in excess arsenite ion being available to interfere with DNA methylation and repair (VIII-37 and VIII-47)].

The following other references in the report support Dr. Marcus's threshold conclusions:

1. [Valentine et al (1979) showed that arsenic concentrations in blood increased at a far higher linear rate after drinking water concentrations exceeded 100 ug/l. (Fig 1A & pg. 28)]

SUMMARY OF HIGHLIGHTS OF APRIL 1988 DRAFT
QUANTITATIVE TOXICOLOGICAL EVALUATION OF INGESTED ARSENIC
BY WILLIAM L. MARCUS, U.S.E.P.A. OFFICE OF DRINKING WATER

2. Buchet et al (1981) showed that the rate of conversion to methylated forms diminished starting at 250 ug, but not until the dose range exceeded 500 ug did the absolute amount of DMA decline, indicating saturation of methylating capacity. In addition, the biological half-life of total recovered arsenic increased with increasing dose (39 hours at 125 ug to 59 hours at 1,000 ug)(pg. 39).

3. Questions have arisen as to why the American population does not show signs of arsenic skin lesions in areas with high arsenic concentrations in drinking water. The levels all correspond to doses less than 500 ug/day. However, in Millard County, Utah (Southwick, 1983), where some of the highest U.S. drinking water concentrations are found, specific signs associated with arsenic ingestion have been observed (pg. 46 and Fig 7).

4. Higgins et al (1982) reported on a sample of 1800 workers at the Anaconda Smelter. Higgins stratified his cohort based upon extrapolated exposure levels. The authors analyzed the data using five different exposure/follow-up methods. None of the methods found a significantly ($p < 0.05$) increased respiratory cancer risk for ceiling level categories less than 500 ug/m^3 of arsenic. For the respiratory cancer SMR analysis by time weighted average exposure, no increase was found in the lowest [exposure] category. The authors concluded that if a worker in the study had not been exposed to concentrations of arsenic in excess of 500 ug/m^3, he would have little, if any, excess cancer risk (pg. 21).

5. Bluchet and Lauwreys (1985) showed that As (III) is transformed into MMA non-enzymically; in contrast, the formation of DMA was proven to be an enzymatic process.... At higher substrate concentrations, DMA formation was inhibited, while MMA appeared to accumulate in the system. Thus it is our conclusion that at high enough concentrations of substrate relative to cytosolic enzymes, an excess of arsenite is available to react with thiol groups in the enzymes and cofactors critical to the dimethylation reaction, namely glutathione, SAMe and lipolic acid (pp 32-33).

6. Kram and Montalbano note that arsenic appears to be clastogenic to DNA by interfering with DNA synthesis, rather than by directly damaging it.... They postulate that the mode of action may be dependent on valence state. As a sulfhydryl reagent, trivalent arsenic is capable of inhibiting a number of thiol-dependent enzyme systems, and in this way may inhibit DNA repair enzymes. Arsenic in the pentavalent form may effect DNA synthesis by substituting for phosphorus in DNA (pg. 22-23).

E. AS(V) vs AS(III)

1. Recent studies have shown that at environmental levels, pentavalent arsenic [As(V)] is rapidly converted to trivalent arsenic [As(III)] in the blood (Marafante, Vather and Envall, 1985) (pg. 23).

2. Cullen et al (1984) demonstrated that in vitro there is a direct attack on As (V) by sulfur-containing reducing agents leading to formation of As (III) (pp 31-32).

3. Lerman et al (1985) found that dimethyl arsenic acid formed when As(III), but not As(V) was added to the (hepatocytes) culture medium. No metabolism of As(V) was seen, nor was the As(V) taken up by the liver cells (pg. 33).

4. Squibb and Flower have shown that arsenate can replace phosphate in enzyme catalyzed reactions. However, arsenical esters are readily hydrolyzed and thus are unstable compared to phosphate esters (pg. 25-26).

5. Lindgren, Vahter and Dencker (1982) injected mice with radiolabeled (inorganic) arsenic... Arsenate was cleared more rapidly than arsenite from all tissues but the kidneys and the skeleton (pp 28-29).

F. ESTIMATED SKIN CANCER RISK FROM INGESTION OF ARSENIC

1. EPA's Risk Assessment Council concluded that the percentage of fatal tumors could range from 1% (based upon the experience of Caucasian in the U.S. with non-melanoma sun-induced skin cancers, which are similar in type, but not location, to arsenic-induced tumors) and 14% (based upon the experience of Taiwan population, which may have standards of nutrition and health care which are different from those in the U.S.)(pg. 54).

2. Risks of skin cancers associated with the ingestion of inorganic arsenic be estimated using a cancer potency of $5*10^{-5}$ per ug/liter (pg. 55).

3. [Risk estimates be reduced one order of magnitude to reflect the limited likelihood of lethal cancer (pg. 55)].

NOTE: Words in [] have been paraphrased from Marcus's text.

Words enclosed in † were added by J. T. Holcombe.

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Victor C. Furtado, Ph.D
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December 1, 1989

Mr. Robert Barham, Chief
Toxic Air Contaminant Identification Branch
Air Resources Board
Attention: Inorganic Arsenic
P.O. Box 2815
Sacramento, CA 95812

Dear Mr. Barham:

PG&E COMMENTS ON DRAFT ARSENIC EXPOSURE AND RISK ASSESSMENT

PG&E appreciates this opportunity to comment on the October 31, 1989 "DRAFT REPORT ON INORGANIC ARSENIC".

As you know, on May 9, 1988 PG&E submitted extensive comments on the preliminary draft exposure and risk assessment. Although we appreciate the improvements the Air Resources Board (ARB) and Department of Health Services (DHS) have made in this draft exposure and risk assessment, it is clear that the major issues raised in our previous comments have not yet been adequately addressed.

During this phase of the process, the critical issue is the cancer risk from exposure. In both the preliminary draft and this draft, data is presented which suggests that cancer risk differs in accordance with a variety of factors including: **route of exposure** (inhalation versus ingestion), **time of retention in the lungs** (or perhaps more specifically in the bronchioles), and **bioavailability while present in the lungs.** While both drafts correctly distinguish between inhalation and ingestion exposures, both drafts ignore the effect of particle size and solubility upon capture and retention in the bronchioles. Similarly, while both drafts correctly distinguish between organic and inorganic arsenic, both drafts ignore the demonstrated lower toxicity and lower lung retention of pentavalent arsenic [As(V)] versus trivalent arsenic [As(III)].

This risk assessment is based upon historical cancer data relating to high exposures to insoluble As(III) particles which are retained in the bronchioles for years after exposures ended. The historic smelter emissions which caused these exposures [up to and beyond 416 million ng/m^3-years (pg. 9-29)] differ significantly from, for example, geothermal power plant cooling tower water drift exposures [estimated in the report as roughly 1-2 ng/m^3 yearly (pg. A-35)]. Geothermal drift exposures are not only lower in magnitude, but probably also different in particle size distribution, higher in As(V), and more soluble.

Both drafts assume that risks from geothermal drift exposures ar proportional to risks from smelter exposures. We think it would be more appropriate for the risk estimate to either be applied only to smelter type exposures, or to include formulae for adjusting unit risks for differences in the ratio of As(III) to As(V), the fraction of As(III) particles in the air likely to be captured by the bronchioles, and the time of retention of the captured As(III) fraction in the lungs.

PG&E has a direct interest in risk estimate adjustment factors since both the preliminary draft and this draft suggest that PG&E's geothermal power plant emissions may be contributing to borderline arsenic risks which will be further reviewed for possible control. The consideration of relative As(III) to As(V) ratios, bronchiole capture rates, or other factors might not be allowed in the control decision phase unless those factors are properly addressed in this phase.

Attached are comments from Doctors Pike and Carter elaborating upon their previous comments. Their comments reflect the logic that:

1. We accept that inhaled As(III) is not detoxified through methylation while in the lungs. Therefore it is more hazardous than ingested arsenic -- particularly when inhaled as larger, less soluble particles which are retained by the lungs for long periods of time. However, inhaled As(V) is not readily metabolized to As(III) in the lungs. Since direct attempts to test the relative potency of As(III) and As(V) suggest that As(V) causes either no effect, or the same effect only when present in ten times higher concentrations, inhaled As(V) cancer risk estimates should be at least ten times lower than inhaled As(III) cancer risk estimates. Since ingested arsenic exposures far exceed inhaled arsenic exposures, the fraction of the inhaled As(III) and As(V) which clears the lungs and enters the blood stream would insignificantly contribute to total body exposures and could be ignored.

2. There are differences in As(III) to As(V) ratios between the historical conditions upon which the draft risk is based, and conditions expected for average ambient exposures in California. These differences suggest that this risk estimate, which does not distinguish between As(III) & As(V) and is based upon historic As(III) to As(V) ratios, should be reduced by a factor of at least 2 to 4. The correct adjustment factor might be even greater for specific exposure sources. Therefore the risk assessment should either only apply to As(III) exposures, or should include a formula for adjusting unit risk in response to differences in the As(III) to As(V) ratio.

3. Deposition in the bronchioles may be a critical factor. Historically cancer has occurred in human bronchioles. Also, the DHS postulates (on page 10-6) that differences between human bronchiole cells and animal bronchiole cells may explain why arsenic has not induced lung cancer in animals. This risk estimate, which is proposed to be applied equally to all particle sizes, should be re-proposed to include an adjustment for differences between historical exposure bronchiole deposition, and California exposure bronchiole deposition. This adjustment could perhaps best be a risk adjustment formula related to particle size.

4. In addition to the above, there may be an important consideration regarding solubility and subsequent bioavailability in the lungs. In general, soluble arsenic compounds would be rapidly dissolved and cleared from the lungs. Soluble As(V) has also been shown to clear from the lungs faster than soluble As(III). Furthermore, some evidence suggests that reducing the solubility of arsenic increases the resultant risk. This draft should be revised to adjust the estimated risk for differences in solubility and biovailability between the historic and California exposures.

In the absence of any better basis for adjusting for solubility and bioavailability, PG&E recommends consideration of relative lung retention time for the As(III) fraction of the total arsenic exposure. This should be calculatable through the consideration of the specific compounds in the historic and California exposures, and the rates of release, uptake into lung cells, and particle clearance for each of those compounds. In the event that available data do not support such precise calculations, then the relative solubility of the captured As(III) fraction could be taken as a reasonable adjustment parameter.

We therefore recommend **adjustment of the unit risk estimates for the relative ratio of insoluble As(III) likely to be captured by the bronchioles.** Ignoring factors such as As(III) to As(V) ratios, bronchiole capture ratios, and bioavailability ratios simplifies the risk estimation and control decision process. But if such simplicity forces industries emitting less hazardous forms of arsenic to expend millions of dollars on unnecessary controls, such simplicity is false economy.

We were unable, in the limited time allowed us, to arrange for Dr. Crump's review of DHS's response to his earlier comments that:

1. "Their basic assumptions with regard to smoking and arsenic interation are not well supported by the data. DHS should abandon the current model of smoking and arsenic interaction

and replace it with a simpler approach or, in view of the disparity of the data, develop a range of estimates that are more or less equally consistent with the data available": and

2. "Further, it would be highly speculative to assume that a smoking and arsenic interaction would hold for arsenic exposures that precede the onset of smoking".

Since smoking is voluntary, any cancer risk due to interaction with smoking should also be considered as voluntary. While Dr. Crump has highlighted key concerns with DHS's approach, these concerns are important only if control decisions are to be based upon the voluntary, rather than the involuntary, risk level.

Arsenic risks due to smoking interaction are estimated in this draft to be 10^{-5}. This level of voluntary risk is insignificant relative to the 10^{-3} risk of smoking one pack of cigarettes per day (Science, 17 April 1987, pg. 268). This level of voluntary risk is also far lower than other commonly accepted voluntary risks such as those estimated for horse racing, mountain climbing, sunbathing, or playing football. We therefore recommend that Part B be expanded to place this voluntary risk into perspective. We further recommend that if any mention of smoking interaction risks is made in the Executive Summary, that it be clearly identified as a voluntary risk in the summary, and as a risk that is probably insignificant (for ambient air exposures) in relation to the smoking risk itself.

Also attached are additional comments from Dr. Paul Solomon. In his comments Dr. Solomon notes, among other things, that:

1. The DHS risk estimate is based upon 1985 data, while the exposure data in Part A has been updated for 1986 data.

2. The ARB's suggestion on Pg. A-35 that "the surrounding area is being impacted" should be reconsidered. Since more than 95% of the data points were below the 3 ng/m^3 detection limit, it is difficult to draw any definitive "impacted area" conclusions from the data. Furthermore, the estimated 1-2 ng/m^3 exposures are right in line with the estimated average statewide exposures. Impacted areas are generally those with higher than average, not average, exposures.

3. As(V) was present in all Tucson ambient monitoring samples analyzed, but As(III) was only detectable ($\geq$1 ng/m^3) in half of the samples.

4. Currently, the Executive Summary and Part A summarizes arsenic concentrations in a way which overemphasizes As(III) concentrations. Previous and attached comments include suggestions to correct that. For example, the Executive Summary should note that As(V) is the predominate form of arsenic in the ambient air.

5. In addition to source variations, meteorology also plays an important role in determining atmospheric concentrations.

The Executive Summary section on pg. 4 entitled "Are there Other Routes of Exposure to Inorganic Arsenic?" implies that total intake from drinking water exposures only exceeds inhalation exposures in some areas of the San Joaquin valley. The ARB table of average surface and ground water arsenic concentrations has not changed (see preliminary draft page A-38, current draft page A-26). As noted in Ted Holcombe's May 9, 1988 comment #1, these average arsenic concentrations suggest than intake of arsenic from drinking water is far higher than intake from inhalation throughout the entire state.

If the staffs (or Science Panel) believe that it would be productive, PG&E would welcome an opportunity to ask our consultants to come to a public meeting with the staff (or Science Panel) on the comments received.

As previously indicated, PG&E is also available, and can arrange to make its consultants available, to answer any ARB/DHS staff or Science Review Panel questions regarding these comments. If you have any questions please call me at (415) 972-7746, or Ted Holcombe at (415) 972-6910.

Victor Furtado

Attachments

cc with all attachments
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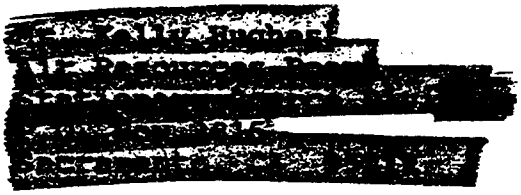

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Shelly G. Sharp
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Attachment 1

Additional comments by

STEVEN PIKE, M.D. and DEAN CARTER, Ph.D.

on the

October 1989 ARB/DHS DRAFT ARSENIC Report

EnviroMD

3443 E. FORT LOWELL ROAD • TUCSON, AZ 85716 • (602) 881-1000 • FAX (602) 327-1572

November 30, 1989

Mr. Robert Barham, Chief
Toxic Air Contaminant Identification Branch
Air Resources Board
Attn: Inorganic Arsenic
P.O. Box 2815
Sacramento, CA 95812

Dear Mr. Barham:

We wish to clarify our comments presented to the Air Resources Board (ARB) on May 9, 1988 by Dr. Furtado for PG&E. We agree with the ARB staff that our comment suggesting that the risk estimate for total airborne arsenic should be lowered by a factor of 20-40 is in error. The sentence should have read that the risk is overestimated by at least a factor of 2-4 (not 20-40). The corrected comment is included as Attachment A to this letter. While risk is overestimated by at least a factor of 2-4 it may be overestimated by as much as a factor of 10 when As(V) is the sole species present in air.

Speciation is still an important consideration in performing a risk assessment for inorganic arsenic due to the following considerations:

1) in-vitro As(V) is less toxic than As(III) based on experimental results, cited by the ARB staff in Part B of their October 1989 draft, with end points ranging from genotoxicity to lethality.[1 2 3 4]

2) mechanisms of action of As(III) and As(V) appear to differ:

   As(V) is believed to substitute for inorganic phosphate in vivo thus affecting ATP synthesis.

   As(III) binds to sulfhydryl and inactivates sensitive enzymes such as pyruvate dehydrogenase.

3) There is still no evidence of the lung's ability to convert As(V) to As(III). If the lung were to convert As(V) to As(III), we would expect the metabolic excretion profile for each species should be identical after administration of each

species to the lung. The data in Attachment B, presented by Rosner and Carter (1987), demonstrate marked differences in metabolic excretion profiles for As(III) compared to As(V), thus the bioavailability for As(V) is not the same as As(III) in the lung.

4) Rosner and Carter demonstrate that intratracheal deposition of arsenate (As(V)) results in a markedly different metabolic excretion profile compared to intratracheally administered arsenite (As(III)).[5] They show that intratracheal As(V) is eliminated more rapidly than As(III), attained significantly lower blood levels than As(III) at 24h post dosing, as well as significantly lower levels in the liver than As(III), and is excreted predominantly as inorganic arsenic and more rapidly than As(III). It is also significant to note that As(V) was cleared more completely from the lung than As(III) at 24, 48, and 96 hours post dosing by an average factor of 1.56 +/- 0.26 (see Table 1 in Attachment B).

We do recognize that there is no epidemiologic evidence that As(V) is less carcinogenic to humans than As(III) but, likewise there is no direct evidence that As(V) is carcinogenic. Furthermore, the epidemiologic studies linking As(III) to respiratory tract cancer in humans have not been conclusively confirmed in animal experiments without the use of confounding factors. Lacking evidence to the contrary, it is a prudent and reasonable assumption, based on the available scientific evidence, that the toxicity and carcinogenic potency of As(III) is greater than that of As(V) and should be factored into the risk assessment.

Very truly yours,

Steven Pike, M.D.

Dean E Carter
Dean Carter, Ph.D.

Enclosure

NOTES

1. Amacher DE and Paillet SC. Induction of trifluorothymidine-resistant mutants by metal ions in L5178Y/TK$^{+/-}$ cells. Mutation Research 78:279-288 (1980).

2. Okada S, Yamanaka K, Ohba H and Kawazoe Y. Effect of inorganic arsenics on cytotoxicity and mutagenicity of ultraviolet light on Escherichia coli and the mechanism involved. J Pharm Dyn 6:496-504 (1983).

3. Rossman TG. Enhancement of UV-mutagenesis by low concentrations of arsenite in E. coli. Mutation Res 91:207-211 (1981).

4. Nordenson I and Beckman L. Chromosome aberrations in cultured human lymphocytes exposed to trivalent and pentavalent arsenic. Scand J Work Environ Health 7:277-281 (1981).

5. Rosner MH and Carter DE. Metabolism and excretion of gallium arsenide and arsenic oxides by hamsters following intratracheal installation. Fundamental and Applied Toxicology 9:730-737 (1987).

Review of California DHS Draft Report on Inorganic Arsenic

I. The risk assessment should incorporate the difference in potency of Arsenic III compared to Arsenic V in developing the unit risk estimate. Existing data are sufficient to warrant a unit risk at least ten times lower for Arsenic V than for Arsenic III. [Comments by Dean Carter, Ph.D. and Steven Pike, M.D.]

In Section 2.1.2 DHS suggests that inhalation of ambient arsenic may be more toxic than ingestion of an equivalent amount of dietary arsenic. DHS reasons that lack of methylation (detoxification) in the lung may be responsible. It is important to note that it is the trivalent arsenic that is taken up by hepatocytes for methylation and not the pentavalent. Speciation of arsenic plays an important role in metabolism, As(V) requiring reduction to As(III) to undergo methylation. Since the target for this risk assessment is the effect of arsenic on cells of the lung, a closer look at the effects of As(III) and As(V) on cells is warranted.

Section 7.1.1 cites reports in which arsenite As(III) inhibited DNA repair of damage caused by UV radiation in bacteria, while arsenate As(V) at five times the concentration had no effect on DNA repair.

In Section 7.3 concentrations of arsenate (As(V)) ten times greater than arsenite (As(III)) were required to inhibit mitogenesis. Furthermore, mutation of frequencies were negative in the mouse cell thymidine kinase (TK) locus assay when treated with As(V). Section 7.3 also reports positive responses for chromosomal abnormalities in mammalian cells exposed to As(III); As(V) was not tested.

In Section 7.3.1 DHS cites work reported on human lymphocytes exposed in vitro to sodium arsenite (As(III)) which resulted in chromatid breaks and gaps, but was negative when tested with sodium arsenate (As(V)).

It is apparent that there is at least a ten-fold difference in the potency of As(III) compared to As(V). When considering the lack of evidence of the lung's ability to metabolize As(V) to As(III) and detoxify As(III) by methylation, failing to factor in speciation of arsenic in considering toxicity combined with failing to consider ratios of As(III):As(V) in ambient air, risk is overestimated by at least a factor of 2 to 4.

II. The risk assessment should factor the relative contributions and potencies for the development of cancer that vary with particle size, solubility, and the proportion of As(III):As(V) in ambient air. The magnitude of such effects should be estimated and incorporated into the calculation of the unit risk for arsenic. Consideration of these factors will lower the resultant risk estimates. [Main comments by Steven Pike, M.D., some comments by Dean Carter, Ph.D.]

In Section 11.4.2C DHS recognizes that assuming ambient air and occupational exposure involve similar As(III):As(V) ratios may overestimate risk. Arsenic trioxide (As(III)) is probably nearly the exclusive form of exposure to the Anaconda and Tacoma smelter workers. Andreae, 1980 reports that nearly all the arsenic emitted from the Tacoma smelter is arsenic trioxide (As(III)) and that rainfall samples from the Anacortes, Washington site were 88% arsenite (As(III)) strongly supporting the argument that the Tacoma smelter is the dominant source of arsenic at this site. This result should be contrasted with the environmental ratio of As(III):As(V) reported in Appendix C of Part A [Solomon, 1987] to be close to 1 (i.e., equal mixture of both species, approx. 50% As(III)). However, this ratio was determined from samples collected in the City of Industry and thus may not truly reflect the ratio in the majority of urban and rural areas. Studies conducted in Tucson, Arizona, a city ringed by copper mines and smelters, revealed an As(III):As(V) ratio of about 0.31 +/- 0.29 (i.e., 24% As(III)) indicating that As(V) may be the species present in the atmosphere at up to three times the concentration of As(III), [Solomon, 1984]. Furthermore the ratio of 0.31 represents the mean of the highest total arsenic measured in 15 of 60 samples taken over a one year period [Solomon, 1988]. These samples were collected about 500 meters from an electric powerplant. Comparing the ratio of As(III) reported by Andreae to the ratios of As(III) reported by Solomon suggest that there is 1.8 (88/50) to 3.7 (88/24) times as much As(III) in Tacoma air as in powerplant or California smelter air. Failing to incorporate the difference in speciation of arsenic in air overestimates risk by a factor of two to four.

III. The risk assessment should be revised and modified based on an evaluation of physical state and should incorporate the differences in physical state that exist between the arsenic compounds measured in the epidemiologic studies and those measured in the ambient exposures for the development of unit risk estimates. [Main comments by Dean Carter, Ph.D., some comments by Steven Pike, M.D.]

CAPTURE:

The size of the particles should be considered in the exposure extrapolation. The deposition of particles of different sizes has been well studied in the human lung. The particle size distribution of the arsenic oxide particles at the Tacoma Washington smelter has been studied. A brief description can be found in Piver (1983). It appears that about 55% of the arsenic particles were smaller than 2.5 um. Although it is not possible to directly compare this with the findings described in the California DHS report (page A-78), it appears that the California environmental samples are considerably smaller than smelter samples with regard to their arsenic distribution. Smaller particles do go deeper into the lung but their deposition decreases to the point that most very small particles are exhaled with the breath without deposition. Data suggests that only approximately 30% to 50% of particles between 0.1 um and 1.0 um are retained by the lung parenchyma [Task Force Group on Lung Dynamics,

1966]. The arguments made in the California DHS report (page 10-7) suggest that the bronchioles are the target site in the lung and not the lower alveolar region. This would be consistent with the deposition of larger particles. Thus, a risk assessment should include an evaluation of the particle size distribution of the environmental samples as compared with the smelter samples and an assessment of deposition rate and site differences.

RETENTION:

There are several considerations for an evaluation of toxicity based on physical state. First, assuming that the lung is the target organ in the DHS evaluation, the soluble compounds of arsenic described in this evaluation would be rapidly dissolved and absorbed from the lung (Marafante and Vahter, 1987). Arsenic is not retained in the body but is rapidly excreted into the urine (Cal DHS 2-6,7). Yet, smelter workers have been found to have high concentrations of arsenic remaining in their lungs several years after exposure ceased (Vahter, 1983). This suggests that the workers may have been exposed to insoluble forms of arsenic (i.e., sulfides, arsenite salts of calcium, lead, zinc, etc.) and the retention of these compounds may have been significant in the development of lung cancer.

BIOAVAILABILITY:

The hazard assessment discussion has ignored an evaluation of the physical state of the arsenic. The review does briefly distinguish between arsenic compounds in the vapor phase and in the solid (particle) phase (Cal DHS A2-A3, A72-A79). However, there are many arsenic compounds that are of environmental importance which have different water solubilities (NRC, 1977). These compounds of different solubilities have different bioavailabilities (Marafante and Vahter, 1987; Webb et al., 1984) and different forms of toxicity (Webb et al., 1986).

Insoluble arsenic (As(III)) salts are probably more hazardous than the soluble salts because they are retained in the target organ (the lung) whereas the soluble forms can readily enter the bloodstream where they can be taken up by the liver to undergo detoxification by methylation. This concept is supported by the animal work by Pershagen and coworkers which is cited in the California DHS report on page 8-3 as supportive of arsenic being a lung carcinogen in animals after intratracheal instillation of arsenic. All animal groups in this study received the arsenic in a carrier dust of charcoal carbon to increase the lung retention of arsenic as well as a solution of sulfuric acid. This supports both the concept that arsenicals retained in the lung may have had an effect on the development of lung cancer and that sulfur oxides may have a contributory effect on arsenic carcinogenicity. These critical experimental details were ignored in the California DHS report. Thus, a risk assessment should include an evaluation of the physical form and solubility of the arsenic with special emphasis on how much can be retained.

IV. The DHS Risk Assessment should consider the possibility of a threshold below which there are no significant adverse effects. The use of a zero threshold may actually create significant adverse effects if arsenic is an essential element in humans and is regulated to a level which would create a deficiency state. Thus a zero threshold would not be biologically plausible. DHS is arbitrarily dismissing the possibility of a threshold; a conclusion contrary to the opinions of other scientists. Furthermore, if evidence for arsenic as an essential element in humans becomes compelling, some scientists would argue that there is a teleologically sound basis for the existence of a threshold below which no significant adverse effects would result. [Main comments by Dean Carter, Ph.D., some comments by Steven Pike, M.D.]

The California DHS report discounts the possibility of a threshold dose. There are several workers in the field who would have come to the opposite conclusion. There is one point on page 10-5 of the report which shows a lack of understanding of arsenic binding. The report states "A single instance of sulfhydryl group binding to an enzyme might result in misrepair or breakage of DNA." This type of argument has been used with alkylating agents of DNA which form a covalent bond after an irreversible reaction with the DNA. In that case, one molecule forming one bond may indeed result in breakage of DNA. However, arsenic binding to sulfhydryl groups is an equilibrium process in which the bonds are continually being formed and broken. The number of molecules which have bound to arsenic depends on the free arsenic concentration and the actual sulfhydryl groups which are bound change constantly. The dose-response relationships for such equilibrium processes have been well described in basic pharmacology texts and support the concept of a threshold.

The argument that DHS raises in Section 10.5.2 that a single instance of sulfhydryl group binding to an enzyme might result in misrepair or breakage of DNA is biologically not plausible. Enzymes have great reserve capacity for function in human physiology. This is most dramatically evident when one considers the ability of heterozygous genotypes for enzyme deficiency in persons with inborn errors of metabolism to be phenotypically normal. It is extremely unlikely that one altered enzyme molecule would bind to DNA and cause misrepair or breakage in the midst of overwhelming numbers of "normal" enzyme molecules.

The staff at DHS cite the possibility that "a single instance of arsenolysis might result in DNA damage." However the hypothesis that inorganic arsenic (As(V)) competes with phosphorus to form unstable arsenate DNA and RNA esters has never been proven in vivo. All experimental results have been based on isolated enzyme or single cell studies and there is no evidence that this mechanism is biologically plausible in mammalian systems. DHS has not shown that a threshold model fails to fit the data as well or better than a linear no threshold model and evidence suggests that the converse is true.

BIBLIOGRAPHY

Andreae, M.O. 1980. Arsenic in Rain and the Atmospheric Mass Balance of Arsenic. J. Geophys. Res. 85: 4512-4518.

Marafante, E. and M. Vahter. 1987. Solubility, retention and metabolism of intratracheally and orally administered inorganic arsenic compounds in the hamster. Environ. Res. 42: 72-82.

National Research Council. 1977. Arsenic. National Academy of Sciences, Washington, DC. p. 4-15.

Piver, W.T. 1983. Mobilization of arsenic by natural and industrial processes. In "Biological and environmental effects of arsenic" edited by B.A. Fowler. Elsevier, Amsterdam, p. 40.

Solomon, P.A., Rabano, E.S., Castillo, N.T. and Torre, K.J. Speciation of Arsenic in Ambient Aerosols Collected in Los Angeles. Final Report 1182R/0214A submitted to California Air Resources Board, May 19, 1987.

Solomon, P.A. Collection and Analysis Techniques for Studies of Atmospheric Arsenic Species, Ph.D. Thesis, Dept. of Chemistry, University of Arizona, Tucson, Arizona (1984).

Solomon, P.A. Personal communication, May 3, 1988.

Task Force Group on Lung Dynamics, Committee II IRCP, Deposition and retention models for internal dosimetry of the human respiratory tract. Health Phys., 12, 173, 1966.

Vahter, M. 1983. Metabolism of arsenic. In "Biological and environmental effects of arsenic" edited by B.A. Fowler. Elsevier, Amsterdam. p. 172.

Webb, D.R., I.G. Sipes and D.E. Carter. 1984. In vitro solubility and in vivo toxicity of gallium arsenide. Toxicol. Appl. Pharmacol. 76: 96-104.

Webb, D.R., S.E. Wilson and D.E. Carter. 1986. Comparative pulmonary toxicity of gallium arsenide, gallium oxide or arsenic oxide intratracheally instilled into rats. Toxicol. Appl. Pharmacol. 82: 405-416.

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Metabolism and Excretion of Gallium Arsenide and Arsenic Oxides by Hamsters following Intratracheal Instillation[1]

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Metabolism and Excretion of Gallium Arsenide and Arsenic Oxides by Hamsters following Intratracheal Instillation. ROSNER, M. H., AND CARTER, D. E. (1987). *Fundam. Appl. Toxicol.* 9, 730–737. The increasing use of gallium arsenide (GaAs) in the electronics industry has produced the need for pharmacokinetic and toxicologic data on GaAs. The disposition in male Syrian golden hamsters ($n = 4$) following intratracheal instillation of GaAs (mean volume diameter 5.8 μm), arsenic(III) oxide (arsenite), and arsenic(V) oxide (arsenate) at a dose of 5 mg/kg body weight was examined. Blood, kidney, liver, and lung samples were collected at 1, 2, and 4 days after administration. Excreta were collected daily. Urinary metabolite profiles were determined after separation on a mixed anion–cation-exchange column. Total As content was analyzed by direct hydride flame atomic absorption spectrophotometry after digestion. Arsenic blood levels after GaAs, arsenite, and arsenate administration were 0.185 ± 0.041, 0.596 ± 0.117, and 0.310 ± 0.045 ppm, respectively, after Day 1. Arsenic blood levels after GaAs administration increased to 0.279 ± 0.021 ppm on Day 2 indicating continued absorption while levels decreased for the arsenite and arsenate groups. At Day 1 the liver contained 0.565 ± 0.036, 2.62 ± 0.26, and 0.579 ± 0.144% of the arsenic dose of GaAs, arsenite, and arsenate, respectively. The arsenite and arsenate were rapidly excreted in the urine with almost half the dose appearing after 4 days; in contrast, only about 5% of the GaAs was found at the corresponding time. Total recoveries, as arsenic equivalents, for the three compounds were between 75 and 80%. Ratios of the two major urinary metabolites (dimethylarsinic acid/total inorganic As species) were 1.41, 1.71, and 0.983 for GaAs, arsenite, and arsenate, respectively. GaAs is metabolized to the same compounds as arsenite and arsenate, and shows a metabolic profile most similar to that observed for sodium arsenite.

Due to its unique physical characteristics, gallium arsenide (GaAs) has several applications in the electronics industry. The integral components of discrete microwave devices, lasers, light emitting diodes, photoelectric chemical cells, and semiconductor devices may be composed of GaAs (Robinson, 1983). Exposure to GaAs in the semiconductor industry is a possible occupational risk since cleaning and slicing GaAs ingots to yield the desired wafers can generate GaAs particles (Briggs and Owen, 1980). Current manufacturing processes use 5 to 10 tons of arsenic in GaAs devices, and it is thought that the production will increase 3- to 10-fold by 1990 (Willardson, 1983).

GaAs has been shown to be soluble in aqueous solutions and forms unidentified gallium and arsenic species upon dissolution (Webb *et al.*, 1984). The various species of arsenic which are formed following inhalation may lead to both pulmonary and systemic effects. This study was designed to compare the metabolism and excretion after intratracheal instillation of GaAs and the soluble arsenic oxides, sodium arsenate (As(V)) and sodium arsenite (As(III)). The hamster was chosen as the animal model since its urinary metabolic profile most closely resembles that of humans following inorganic arsenic exposure.

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METHODS

Preparation of particles. Particles of GaAs were prepared as described by Webb *et al.* (1984) except that the pulverized GaAs was ultimately sieved through a 10-μm precision microsieve (No. L3-M10, ATM Corp., Milwaukee, WI). This fraction was determined to have a mean count diameter of 1.63 μm and a mean volume diameter of 5.82 μm by an electrozone celloscope fitted with a 48-μm orifice probe. Particle shape was determined to be approximately spherical by scanning electron microscopy.

Analytical determination of arsenicals. The procedure of Webb and Carter (1984) was employed for quantification of total arsenic in all biological samples. Standards for dimethylarsinic acid (DMAA), monomethylarsonic acid (MMAA), arsenic(V), and arsenic(III) were prepared as described by Webb and Carter (1984). The chromatographic procedure of Maiorino and Aposhian (1985) was used for separation of the urinary metabolites. A modification of the spectrophotometric method of Lasko *et al.* (1979) was used as a confirmatory method for both the total arsenic and the metabolites. This was done on samples containing greater than 1 μg As, the detection limit of the method. The apparatus used to generate the various arsines was similar to the arsine generator used by Webb and Carter (1984). The exit line was fitted with a lead acetate trap and the nitrogen entrained flow (0.1 ml/min) was terminated in a 10 × 150-mm borosilicate tube fitted with a serum cap with an outlet for the nitrogen gas and filled with a 0.5% silver diethyldithiocarbamic acid in pyridine solution. The sodium borohydride ($NaBH_4$) was introduced into the reaction vessel dropwise via a 1-ml gas-tight syringe as a 10% (w/v) $NaBH_4$ in 1 N NaOH solution. A volume of 20 ml of pH 5.2 citrate–acetate buffer or 3 N HCl was used in the reaction vessel. The buffer was used to evolve dimethylarsine and arsine derived from arsenite.

Dose solution. The GaAs particles were continually mixed using a magnetic stirrer to yield a suspension of 5 mg As/ml (96.53 mg GaAs/10 ml) in a 0.05% Tween 80 (No. 1754, Sigma Chemical Co., St. Louis, MO) physiological saline solution. The dose solution was delivered immediately to the animals to ensure minimal particle dissolution. Sodium arsenite (No. S 225, Fisher Chemical Co., Fair Lawn, NY) and sodium arsenate (No. SO 4145, Pfaltz and Bauer, Stamford, CN) were used to prepare 10 ml of the dosing solutions by initially dissolving the powders (86.7 and 208.2 mg, respectively) in 0.1 N NaOH and subsequently adjusting the pH to 7.4 with HCl. The final volume was diluted with a 0.05% Tween 80 saline solution. These solutions were quantified by both analytical procedures to determine the purity and form of the arsenic dosed. All arsenate and arsenite dosing solutions were found to be at least 98% pentavalent and trivalent, respectively, as determined by the combined ion exchange–atomic absorption technique. The spectrophotometric technique showed greater than 95% purity. A solution of saline and Tween 80 was given as the vehicle to the control animals.

Treatment of animals. Male Syrian golden hamsters (130 ± 15 g) were obtained from Charles River Breeding Laboratories (Boston, MA) and allowed to acclimate for at least 1 week prior to dosing. Water and food (Wayne Lab Blox) were provided *ad libitum* throughout the studies. A 12-hr light cycle was maintained with artificial lighting. The hamsters were randomly divided into groups of four animals. Groups administered GaAs, arsenite, and arsenate were killed at 1, 2, and 4 days, and a control group was included at Day 1. The hamsters were dosed intratracheally with 5 mg/kg As of the appropriate solution by a modified method of Brain *et al.* (1976). A plastic speculum was placed into the trachea as a guide for the needle and to prevent expiration of the dose. After dosing, the hamsters were placed into individual polycarbonate metabolism cages (No. 1114-ALS, Thomas Scientific, Philadelphia, PA) for the daily collection of excreta. To aid in the collection of the viscous hamster urine, the cages were washed down with water and the washings were added to the urine. The urine and feces were stored frozen at −15°C until analysis.

The animals were sacrificed by carbon dioxide inhalation. A chest incision was made, the rib cage was removed, and 1 ml of blood was drawn by cardiac puncture and placed in 4 ml of a saturated EDTA solution. Only three major organs were collected for assessing the distribution of the three compounds: the lung (site of administration), the liver (major site of metabolism), and the kidney (major site of concentration for urinary elimination). The lungs were separated into the individual lobes and the liver and kidneys were trimmed of extraneous fat and connective tissues and weighed. All three organs were homogenized with a Ultra-Turrax Tissumizer (Tekmar Model SDT, Cincinnati, OH) in 15 ml of water and adjusted to a final volume of 20 ml. After thawing, the urine volume was adjusted to 10 ml. Feces were digested overnight in 20 ml of 1 N NaOH and mixed vigorously. Aliquots of the homogenates and the blood were analyzed for total As and expressed as percentage of As administered. Blood was analyzed for total arsenic similarly but reported as concentration (μg As/ml blood) for easier comparison to literature data. An aliquot of urine was analyzed for metabolites and expressed as percentage of the total urinary As metabolites.

Statistics. The results expressed as ratios and percentages were mathematically transformed to induce approximate normality since the distributions of these values are naturally skewed. The transformed values followed more closely a normal distribution. The blood concentration values were assumed to fit a normal distribution. Results expressed as percentage of dose administered were transformed by arc sin $(p)^{1/2}$, where p is the percentage divided by 100. The metabolite ratio results were transformed by taking the log of the ratio value. The

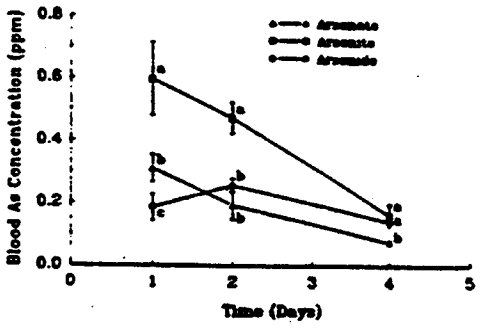

FIG. 1. Mean total arsenic blood concentrations expressed as As equivalents as determined by direct hydride FAAS. Animals were dosed intratracheally with 5 mg/kg As equivalents of the appropriate compound. Values are means ± SD ($n = 4$). [a,b,c]Values not sharing common letters are significantly different at corresponding times ($p \leq 0.05$). Only arsenic levels at the same time point were compared for significance.

transformed values were employed to establish statistically significant differences ($p < 0.05$) by two-way ANOVA and Newman–Keuls multiple means comparisons.

RESULTS

Controls. The control animals were tested for trace levels of arsenic in the tissues, blood, and excreta and yielded no significant amounts of arsenic. Although the urine had traces of arsenic, the levels present could not be quantified by the atomic absorption method employed.

Absorption and distribution. All three compounds were absorbed from the lung into the blood (Fig. 1). The blood concentrations at 24 hr corresponded to 0.418 ± 0.069 (arsenate), 0.827 ± 0.141 (arsenite), and 0.230 ± 0.056% (GaAs) of the dose administered. The peak concentration for GaAs at 48 hr was equivalent to 0.347 ± 0.026% of the GaAs given. Total arsenic blood values from arsenite were significantly higher than those after arsenate at the time points examined. Both compounds showed a continued decrease in blood level with time, suggesting the terminal elimination phase of both arsenicals was reached by 24 hr. The GaAs arsenic blood levels peaked at 2 days after dosing, suggesting that the absorption phase of GaAs was incomplete by Day 1. Even after 4 days the blood arsenic levels were not significantly lower than after 24 hr, suggesting a continuous absorption phase or steady-state conditions.

The absorbed arsenicals were distributed to various tissues (Table 1). The solutions of arsenite and arsenate were almost entirely cleared from the lung by the first day; less than 1% of the dose administered remained. Large amounts of arsenic were present in the lung after GaAs dosing: more than 40% of the dose still remained in the pulmonary region of the respiratory tract after 24 hr. Lung clearance of the particles continued until the end of the experiment. The liver concentrations at 24 hr were 3300 ± 350, 752 ± 189, and 731 ± 103 ppb for arsenite, arsenate, and GaAs, respectively. The arsenite-treated animals had significantly greater arsenic levels in the liver at Days 1 and 4 than did the arsenate-treated animals; arsenic levels in the liver following GaAs administration were significantly lower than either soluble arsenical after the 24-hr time point. The concentrations of arsenic in the kidneys at Day 1 were 3.82 ± 0.83 (arsenite), 3.42 ± 0.48 (arsenate), and 7.62 ± 1.33 ppm (GaAs). No significant differences were found in the kidney after arsenite or arsenate administration; a significantly higher amount of arsenic was found at Day 1 and a smaller amount was found in the kidney at Day 2 after GaAs administration.

Metabolism and excretion. The cumulative percentages of the dose excreted in the urine and feces are shown in Table 2. There is significantly more arsenic eliminated in urine at 24 and 48 hr after the arsenate than after the arsenite dose; after 4 days about 50% of both compounds had been eliminated in the urine. After the GaAs dose, only about 5% of the arsenic was excreted in the urine after 96 hr. Only 10% of the administered dose of soluble arsenic oxides was eliminated in the feces after Day 1; however, 27% of the GaAs-derived As was found in the feces. An addi-

TABLE 1

PERCENTAGE DOSE OF ARSENIC EQUIVALENTS IN TISSUE[a]

Compound	Day	Liver	Kidney	Lung
Arsenate	1	0.579 ± 0.144[b]	0.520 ± 0.081[b]	0.185 ± 0.029[b]
	2	0.545 ± 0.153[b]	0.541 ± 0.058[b]	0.070 ± 0.025[b]
	4	0.266 ± 0.067[b]	0.334 ± 0.114[b]	0.040 ± 0.014[b]
Arsenite	1	2.62 ± 0.26[c]	0.589 ± 0.111[b]	0.329 ± 0.046[c]
	2	0.652 ± 0.136[b]	0.541 ± 0.051[b]	0.089 ± 0.020[b]
	4	0.464 ± 0.070[c]	0.251 ± 0.082[b,c]	0.065 ± 0.013[c]
Arsenide	1	0.565 ± 0.036[b]	1.207 ± 0.218[d]	41.78 ± 5.83[d]
	2	0.312 ± 0.040[d]	0.365 ± 0.056[d]	29.69 ± 1.91[d]
	4	0.144 ± 0.017[d]	0.152 ± 0.026[c]	23.58 ± 1.82[d]

[a] Tissue levels are expressed as percentage of administered dose (as As equivalents) as determined by direct hydride flame atomic absorption spectroscopy (FAAS). Animals were dosed intratracheally with 5 mg/kg As equivalents of the appropriate compound. Values are means ± SD ($n = 4$). Arsenide is GaAs.

[b,c,d] Values not sharing common letters for corresponding tissue and time are significantly different at $p \leq 0.05$. Only arsenic levels at the same time point were compared for significance.

tional 10% of the As was eliminated the next day and a total of almost half of the administered As was found in the feces 4 days after exposure to GaAs. Both arsenic oxide salts showed a large increase in the fecal elimination of arsenic after 48 hr; about 30% of each soluble arsenical was excreted in feces after 4 days.

Metabolite levels in urine after doses of the three inorganic arsenicals is showed in Table 3. A fraction of the arsenate administered was eliminated unchanged in the urine 17.4, 11.3, and 11.2% by 1, 2, and 4 days, respectively. A portion of the arsenite was also eliminated unchanged; 3.7, 9.2, and 9.8% of the arsenite was eliminated as the parent compound on

TABLE 2

CUMULATIVE PERCENTAGE DOSE EXCRETED AS ARSENIC EQUIVALENTS[a]

Compound	Day	Urine	Feces	Total
Arsenate	1	24.64 ± 2.07[b]	7.44 ± 0.49[b]	32.07 ± 1.69[b]
	2	43.43 ± 5.42[b]	20.34 ± 2.41[b]	63.77 ± 7.07[b]
	4	48.49 ± 2.91[b]	29.25 ± 5.49[b]	77.74 ± 7.84[b]
Arsenite	1	15.24 ± 1.49[c]	3.43 ± 0.81[c]	18.67 ± 0.81[c]
	2	32.07 ± 0.88[c]	18.48 ± 1.57[b]	50.55 ± 2.16[c]
	4	48.52 ± 2.60[b]	31.57 ± 3.30[b]	80.08 ± 4.99[b]
Arsenide	1	1.94 ± 0.37[d]	27.01 ± 4.35[d]	28.94 ± 4.48[b]
	2	4.15 ± 0.68[d]	36.74 ± 5.21[d]	40.89 ± 4.67[d]
	4	5.42 ± 0.26[d]	46.34 ± 3.15[d]	51.75 ± 3.00[d]

[a] Levels are expressed as percentage of administered dose (as As equivalents) excreted as determined by direct hydride FAAS. Hamsters were dosed intratracheally with 5 mg/kg As equivalents of the appropriate compound. Values are means ± SD ($n = 4$). Arsenide is GaAs.

[b,c,d] Values not sharing common letters for corresponding excreta and time are significantly different at $p \leq 0.05$. Only arsenic levels at the same time point were compared for significance.

TABLE 3

URINARY METABOLITES AS PERCENTAGE ARSENIC[a]

	As(III)	As(V)	MMAA	DMAA	UA
Arsenate					
Day 1	18.77 ± 1.59[b]	30.24 ± 5.50[b]	8.69 ± 0.59[b]	38.62 ± 0.59[b]	3.69 ± 0.39[b]
Day 2	23.94 ± 4.83[b]	26.01 ± 4.40[b]	10.51 ± 1.83[b]	35.67 ± 3.40[b]	3.86 ± 0.49[b]
Day 4	22.94 ± 4.83[c]	23.16 ± 0.94[b]	4.76 ± 1.52[b]	45.32 ± 1.22[b]	3.82 ± 0.36[b]
Arsenite					
Day 1	24.40 ± 2.98[c]	13.62 ± 1.08[c]	7.64 ± 0.74[b]	52.06 ± 2.89[c]	2.29 ± 0.41[c]
Day 2	30.27 ± 2.45[b]	8.79 ± 1.65[c]	8.17 ± 1.92[b,c]	48.91 ± 3.89[c]	3.86 ± 1.37[b,c]
Day 4	20.29 ± 1.90[b]	12.08 ± 1.05[c]	8.65 ± 2.00[c]	55.46 ± 1.96[c]	3.52 ± 0.82[b,c]
Arsenide					
Day 1	19.70 ± 3.76[b,c]	10.12 ± 1.41[d]	5.38 ± 1.04[d]	58.90 ± 4.29[c]	5.99 ± 0.85[d]
Day 2	13.54 ± 0.96[d]	23.01 ± 3.67[b]	7.48 ± 0.97[c]	51.92 ± 3.20[c]	4.04 ± 0.34[b,c]
Day 4	11.83 ± 1.62[d]	25.77 ± 1.49[d]	6.52 ± 0.91[b,c]	52.88 ± 2.76[c]	3.00 ± 0.52[b,c]

[a] Values are expressed as percentage of cumulative urinary arsenic values (from Table 2). Each metabolite was determined by mixed-bed strong anion- and cation-exchange column chromatography followed by direct hydride FAAS. Values are means ± SD ($n = 4$). MMAA, monomethylarsonic acid. DMAA, dimethylarsinic acid. UA, unknown arsenic containing metabolite. Arsenide, GaAs.

[b,c,d] Values not sharing letters for corresponding metabolite and time point are significantly different at $p \leq 0.05$. Comparisons were made only between treatment groups at a single time point.

Days 1, 2, and 4 respectively. In all cases, DMAA was the major metabolite. An unidentified arsenic metabolite accounted for between 2 and 6% of the total dose found in the urine. MMAA was another minor metabolite for the compounds, accounting for 5–10% of the total urinary arsenic. The variation of values found probably reflects the use of different animals for each time point for each compound in our experimental design.

The levels of As derived from GaAs were less than 5-μg As equivalents of trivalent arsenic, so significant oxidation may have occurred on the chromatographic column. This would only affect the relative amounts of As(III) and As(V). If the total inorganic arsenic (the sum of arsenite and arsenate) was used to compare the results, DMAA was the major metabolite after arsenite and GaAs exposure, but total inorganic arsenic was the major urinary form of As following arsenate administration. The ratio of these two major metabolite fractions (DMAA/total inorganic arsenic: DMAA/TIA) was used to compare the urinary metabolite profiles (Fig. 2). On Day 1, the DMAA/TIA ratio values from the studies were statistically different from each other. At 48 and 96 hr, the metabolite ratio after arsenate administration was significantly different from that of the arsenite and GaAs; ratios for the arsenite and GaAs doses

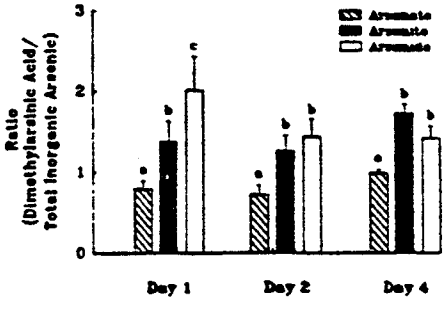

FIG. 2. Cumulative urinary metabolite profile analysis expressed as the ratio of dimethylarsinic acid to inorganic As species, As(III) + As(V), expressed as As equivalents as determined by chromatographic separation followed by direct hydride FAAS. Animals were dosed intratracheally with 5 mg/kg As equivalents of the appropriate compound. [a,b,c]Values not sharing common letters are significantly different at corresponding times ($p \leq 0.05$).

were not statistically different from each other.

Total recoveries. The total recoveries of the administered dose for the three compounds were 78.49 ± 7.92, 81.05 ± 5.04, and 75.83 ± 4.59% for arsenate, arsenite, and GaAs at 96 hr, respectively. The recovery of As after the arsenate and arsenite doses increased with time. Arsenic recoveries of 33.78 ± 1.90 and 65.21 ± 6.87% of the arsenate dose were found in the tissue and excreta collected for 24 and 48 hr, respectively; recoveries of 23.04 ± 0.99 (Day 1) and 52.51 ± 2.74% (Day 2) of the administered arsenite were found.

DISCUSSION

The dissolution of GaAs in aqueous media and animals has been demonstrated from *in vitro* and *in vivo* experiments (Webb *et al.*, 1984); however, these studies did not attempt to characterize the dissolved species. Our results show that the arsenic in the GaAs zinc-blend crystal was biotransformed to arsenic metabolites like arsenic and arsenous acids once it was released from the solid. These results after intratracheal dosing support those found previously (Yamauchi *et al.*, 1986) for GaAs administered orally.

Webb and co-workers (1984) showed that the rat absorbed about 10% of the arsenic after intratracheal instillation of GaAs at doses ranging from 10 to 100 mg/kg. To determine absorption, we have compared the relative levels of arsenic in the urine and tissues for the different treatments. Insufficient time points were collected to determine absorption by area under the blood concentration–time curve calculations. (The individual hamster blood arsenic values are only an indicator of the amount of arsenic in the systemic circulation at the specified time.) About 5% of the As given in the form of GaAs was excreted in the urine by 96 hr. This represents about one-tenth as much urinary arsenic as was found after arsenite and arsenate administration. If the urinary excretion can be related to the cumulative arsenic absorbed, an absorption of about 5–10% of the As from GaAs could be estimated from the excretion data. The urinary excretion data of Yamauchi and co-workers (1986) showed that less than 1% of the total dose was excreted following oral administration of 10–1000 mg/kg GaAs.

The 27% fecal elimination of the GaAs dose after 24 hr was probably due to the lung clearance into the gastrointestinal tract since the completely absorbed soluble arsenicals had values of less than 10% at the same time point. Some gastrointestinal absorption may occur. Webb *et al.* (1984) reported that 56% of the GaAs-derived total arsenic was found in the feces of rats administered a 10 mg/kg oral dose. Yamauchi *et al.* (1986) found 87.5% of the total As from GaAs in the feces of hamsters after a 10 mg/kg oral dose. This expectoration and subsequent gastrointestinal absorption may explain the apparent continuous absorption phase observed with GaAs.

The data we obtained demonstrated a slower rate of arsenic elimination of arsenite when compared to arsenate. Regardless of the route of administration, this relationship held true for most mammals tested (Inamasu, 1983; Odanaka *et al.*, 1980; Vahter, 1981). Mice retained 12% of the dosed arsenite in the body compared to 7% of the administered arsenate at 48 hr when given 4 mg/kg orally (Vahter, 1981). By 96 hr the amount of total arsenic found in the excreta of both soluble arsenicals was about the same in our experiments. GaAs was eliminated more slowly than either arsenite or arsenate. A large amount of the dose of GaAs was still present in the lungs; this shows the much slower rate of absorption and pulmonary clearance when compared to the trivalent and pentavalent arsenic oxyacids. The GaAs retained in the lungs is a source for a prolonged pulmonary exposure as the particulate and has the potential for absorption into the systemic circulation during that time.

Due to the decreased pulmonary absorption and the relatively poor absorption from the gastrointestinal tract, GaAs had a much lower calculated bioavailability following equimolar doses of the three compounds. Distribution of the bioequivalent doses of arsenate and arsenite were compared to allow further evaluation of our results. Arsenite showed significantly greater levels in the blood (596 ppb) than arsenate (310 ppb) at 24 hr. One day after administration of arsenite, liver tissue levels (3300 ppb) were significantly greater than arsenate liver values (752 ppb). These trends agreed favorably with the literature results for hamsters (Lindgren *et al.*, 1982); 1 day following intravenous injection of arsenite and arsenate, arsenic blood levels were 3 times greater and liver levels were 3.5 times higher for arsenite as compared to arsenate. Absolute levels 24 hr after the intravenous dosing were substantially lower than those found after intratracheal dosing. Lindgren *et al.* (1982) also found the kidney concentration for both arsenicals to be 20 ppb at 24 hr. Our kidney concentrations for arsenite (3.82 ppm) and arsenate (3.42 ppm) were substantially higher but were not significantly different from each other either.

The urinary metabolite profile after arsenite exposure was different from that of arsenate at the time points tested. The values obtained compared favorably with hamster experiments by Inamasu (1983); DMAA, total inorganic arsenic, and MMAA were reported as 48.7, 38.4, and 12.8% of the arsenic excreted in the urine following a 10 mg/kg arsenite treatment. Although the absolute amounts of the arsenic metabolites were much lower in the urine of GaAs pretreated animals, the normalized values, expressed as percentage of total urinary arsenic, showed that the GaAs results were not statistically different from those for arsenite at 48 and 96 hr. Thus, the systemic arsenic released from GaAs appeared to be treated like trivalent arsenic by the body. The increased DMAA levels in the urine of the GaAs group may be related to the different amounts of arsenic in the circulation between the two groups. Methylation of inorganic arsenic is a saturable process at higher doses or following low-level chronic exposure (Bencko *et al.*, 1976). The lower amount of arsenic from GaAs at 24 hours may have been methylated more efficiently than the higher level of arsenic from arsenite. An unknown arsenic metabolite was measured at levels which agreed with the literature, between 2 and 3% of the total urinary arsenic (Charbonneau *et al.*, 1980). This compound is probably trimethylarsine oxide (Cullen *et al.*, 1984) or arsenobetaine (Yamauchi and Yamamura, 1984).

Trivalent arsenic has been shown to be relatively more toxic than pentavalent arsenic (NAS, 1977). However, arsenite has been shown to be oxidized to arsenate *in vivo* (Bencko *et al.*, 1976) and As(V) was reduced to As(III) in mice and rabbits (Vahter and Envall, 1983). Careful interpretation of results for comparing inorganic arsenic exposures must be made. Our metabolism results suggest that the systemic arsenic from GaAs is metabolized similar to As(III) and may be As(III). If so, it would be the more toxic arsenic species. Recall that the relative amount of GaAs absorbed over the 4 days was estimated to be one-tenth of the amount absorbed following sodium arsenite exposure. The actual species of arsenic in the lung was not determined so it is difficult to assess the effects of the soluble arsenic present. The GaAs particles still remaining in the lung have been reported to cause numerous pathological lesions consistent with the onset of an acute progressive fibrogenic response (Webb *et al.*, 1984).

In summary, lung arsenic was rapidly cleared after sodium arsenate and arsenite exposure, but GaAs was cleared more slowly following intratracheal instillation. Arsenic blood levels had peaked for arsenic(III) and arsenic(V) before Day 1 but GaAs levels peaked at Day 2. Absorption of GaAs after 4 days was estimated to be one-tenth of that found for arsenite or arsenate if calculations

were based on tissue and excretion data. Thus, the soluble arsenicals had a relative bioavailability at least one magnitude greater than GaAs. The greater fecal elimination of GaAs was probably due to a large lung clearance into the gastrointestinal tract. Arsenic absorbed from GaAs was metabolized to DMAA, MMAA, As(III), and As(V). The urinary metabolite profile of GaAs was similar to both inorganic arsenicals, but the ratio of the major metabolites was statistically different from arsenate only. The DMAA/total inorganic As ratio for GaAs was about twice the value calculated for arsenate. The *in vivo* solubility and large lung retention show that the particulate nature of GaAs must be considered in assessing the toxic effects of this semiconductor material in addition to the systemic toxicity of arsenic.

REFERENCES

BENCKO, V., BENES, B., AND CIKRT, M. (1976). Biotransformation of As (III) to As (V) and arsenic tolerance. *Arch. Toxicol.* 36, 159–162.

BRAIN, J. D., KNUDSON, D. E., SOROKIN, S. P., AND DAVIS, M. A. (1976). Pulmonary distribution of particles given by intratracheal instillation or by aerosol inhalation. *Environ. Res.* 11, 13–33.

BRIGGS, T. M., AND OWENS, T. W. (1980). *Industrial Hygiene Characterization of the Photovoltaic Solar Cell Industry.* NIOSH Technical Report, DHEW (NIOSH) Publication No. 80-112, U. S. Dept. of Health, Education, and Welfare, Cincinnati, OH.

CHARBONNEAU, S. M., HOLLINS, J. G., TAM, G. K. H., BRYCE, F., RIDEWAY, J. M., AND WILES, R. F. (1980). Whole-body retention, excretion and metabolism of (^{74}As) arsenic acid in the hamster. *Toxicol. Lett.* 5, 175–182.

CULLEN, W. R., MCBRIDE, B. C., AND REGLINSKI, J. (1984). The reduction of trimethylarsine oxide to trimethylarsine by thiols: A mechanistic model for the biological reduction of arsenicals. *J. Inorg. Biochem.* 21, 45–60.

INAMASU, T. (1983). Arsenic metabolites in urine and feces of hamsters pretreated with PCB. *Toxicol. Appl. Pharmacol.* 71, 142–152.

LASKO, J. U., ROSE, L. J., PEOPLES, S. A., AND SIRACHI, D. Y. (1979). A colorimetric method for the determination of arsenite, arsenate, monomethylarsonic acid, and dimethylarsinic acid in biological and environmental samples. *J. Agric. Food Chem.* 27(6), 1229–1233.

LINDGREN, A., VAHTER, M., AND DENCKER, L. (1982). Autoradiographic studies on the distribution of arsenic in mice and hamsters administered ^{74}As-arsenite or -arsenate. *Acta Pharmacol. Toxicol.* 51, 253–265.

MAIORINO, R. M., AND APOSHIAN, H. V. (1985). Dimercaptan metal-binding agents influence the biotransformation of arsenite in the rabbit. *Toxicol. Appl. Pharmacol.* 77, 240–250.

NAS (1977). *Medical and Biological Effects of Environmental Pollutants: Arsenic.* Natl. Acad. Sci., Washington, DC.

ODANAKA, Y., MATANO, O., AND GOTO, S. (1980). Biomethylation of inorganic arsenic by the rat and some laboratory animals. *Bull. Environ. Contam. Toxicol.* 24, 452–459.

ROBINSON, A. L. (1983). GaAs readied for high-speed microcircuits. *Science* 219, 275–277.

VAHTER, M. (1981). Biotransformation of trivalent and pentavalent inorganic arsenic in mice and rats. *Environ. Res.* 25, 286–293.

VAHTER, M., AND ENVALL, J. (1983). *In vivo* reduction of arsenate in mice and rabbits. *Environ. Res.* 32, 14–24.

WEBB, D. R., AND CARTER, D. E. (1984). An improved wet digestion procedure for the analysis of total arsenic in biological samples by direct hydride atomic absorption spectrophotometry. *J. Anal. Toxicol.* 8, 118–123.

WEBB, D. R., SIPES, I. G., AND CARTER, D. E. (1984). *In vitro* solubility and *in vivo* toxicity of gallium arsenide. *Toxicol. Appl. Pharmacol.* 76, 96–104.

WILLARDSON, R. K. (1983). Arsenic in electronics. In *Arsenic: Industrial, Biomedical, Environmental Perspectives* (W. H. Lerderer and R. J. Fensterheim, Eds.), pp. 72–88. Van Nostrand, New York.

YAMAUCHI, H., TAKAHASHI, K., AND YAMAMURA, Y. (1986). Metabolism and excretion of orally and intraperitoneally administered gallium arsenide in the hamster. *Toxicologist* 40, 237–246.

YAMAUCHI, H., AND YAMAMURA, Y. (1984). Metabolism and excretion of orally administered dimethylarsinic acid in the hamster. *Toxicol. Appl. Pharmacol.* 74, 134–140.

Attachment 2

Additional comments by

DR. PAUL SOLOMON

on the

October 1989 ARB/DHS DRAFT ARSENIC Report

SUGGESTIONS BY DR. PAUL SOLOMON ENHANCING THE DRAFT REPORT TO THE AIR RESOURCES BOARD ON INORGANIC ARSENIC

EXECUTIVE SUMMARY

Page 3, Does Arsenic Exist in More Than One Form?;

While As(III) may be the most predominant form of arsenic emitted from some high temperature sources, in the ambient atmosphere the As(III)/As(V) ratio in atmospheric particulate matter and in rain water is typically less than one [i.e., As(V) is the predominant form]. This section should be revised to include this fact, otherwise readers are lead to believe that all arsenic in the atmosphere is in the most carcinogenic form, As(III).

Page 3, What Are the Ambient Concentrations of Inorganic Arsenic in the State?;

The text of the report (Part A) summarizes data obtained in 1986; and therefore, this section should summarize the 1986 data and not the 1985 data. 1986 was used in the October 1989 version because it included information from 9 additional sampling sites located throughout the state and for the complete year.

Page 5, What Is the Risk Assessment for Exposure to Inorganic Arsenic?;

This section needs to changed to reflect the 1986 data (see the page 3 comment immediately above). In 1986 the statewide population-weighted exposure was 1.5 ng/m3, which would lower the risk assessment reported in this section by about 32%, assuming a linear model, as was done in Part B of the report.

PART A - PUBLIC EXPOSURE TO AIRBORNE INORGANIC ARSENIC IN CALIFORNIA

This draft shows much improvement over the previous one and I commend the authors on a job well done. Of course, I believe some portions of this draft still require additional work, especially since 1986 data are discussed rather than the 1985 data described and discussed in the previous draft.

Comments suggested in this section address specifics in Part A and are listed in order as they would appear in the text and not in order of importance.

Comments by Dr. Paul A. Solomon (continued)

Page A-1, paragraph 5, sentence 3;

I suggest adding the following sentence after sentence 3: "In the air, arsenic can exist as the +3 or +5 oxides, oxyacids, or salts of the oxyacids." Give examples if you wish or refer to Table III-1.

Page A-1, paragraph 5, sentences 4-6;

Delete sentence 5. As_2O_3 sublimes in high temperature sources to form As_4O_6 and in the atmosphere condenses onto existing particles as As_2O_3. This is correctly stated in the next paragraph, sentence 4.

I suggest starting a new paragraph with sentence 4 and changing sentences 4 and 6 to: "Arsenic trioxide (as As_4O_6), a species with arsenic in the +3 oxidation state, is the ... and combustion sources (Eatough et. al., 1979). In the air, it can react with water to form a less volatile and more water-soluble oxyacid (e.g., H_3AsO_3) or can be oxidized to arsenic pentoxide (As_2O_5), a species with arsenic in the +5 oxidation state. Arsenic pentoxide also is less volatile and more water-soluble than the trioxide form."

Page A-2, paragraph 6 and paragraphs 1-3 on page A-3;

The use of 1985 data appears to be a carry over from the previous draft. This summary should be updated to discuss the data presented in the text of the report, that is, the data from 1986. The health risk assessment data summarized here should be changed accordingly. Discussions and data in Part B of this report also should be changed to reflect the one full year of data from 1986.

Page A-3, paragraph 2, sentence 1;

According to results presented in Table I-3, high peak-to-mean ratios occurred at only two sites, which I do not consider common. However, I suspect high peak-to-mean ratios would be observed near sources, and if that is what they are referring to it should be stated.

Page A-3, paragraph 4;

This paragraph should be changed to reflect the 1986 data set. For example, the overall geographic mean arsenic concentration for 1986 was 1.5 ng/m3. The mean statewide population-weighted exposure for 1986 was 1.5 ng/m3 with an lower bound of 1.2 ng/m3 and an upper bound of 2.0 ng/m3, based on the data in Table I-4.

Comments by Dr. Paul A. Solomon (continued)

Page A-5, paragraph 2;

What do these data suggest? Should arsenic +3 and +5 speciation be considered in the health risk assessment, since both species appear to be present in the atmosphere?

Page A-8, Table I-2;

I suggest adding the sample number (n) to this table.

Page A-9, line 17;

I suggest adding "at a given site" after the first word on that line "data."

Pages A-9, paragraph 2, sentence 1;

Insert "for the period July 1985 - August 1987" after "by month". The text up to here is summarizes only 1986 data.

Also, can the seasonal trends observed in Figures I-2 to -4 be explained in terms of meteorology or other factors. Do fine particle mass concentrations follow the same trend. In SCAB, PM10 and fine particles show a summer minimum and winter maximum. See Solomon et. al., 1989, February JAPCA, and the reference therein by Gray et. al. and the ARB Final report by Solomon et. al., March, 1988, ARB contract No. A4-144-32.

Page A-17, Table I-4;

The values for the population-weighted exposure for SCAB are incorrect, if they are the arithmetic mean of the values for each site within the basin. The values should be:

lower bound	2.0
mean	2.6
upper bound	3.4

The values for the overall population-weighted exposure are also incorrect, if they are the arithmetic mean of the values for each site. The values should be:

lower bound	1.2
mean	1.5
upper bound	2.0

The text needs to be changed accordingly.

A value of 1.7 ng/m3 should be used as the estimated population-weighted exposure for the SCAB and SFBAAB for the health risk estimate calculations described in Part B of this report.

Comments by Dr. Paul A. Solomon (continued)

Page A-20, lines 1 and 2;

The overall geographic arithmetic mean by sites, based on the data in Table I-2, should be "1.5 ng/m3" not "2.2 ng/m3". This is consistent with the results reported on page 9 for the average values for northern and southern California of 1.2 and 2.0 ng/m3, respectively. The value of "2.2 ng/m3" appears to be carried over from the previous version.

Page A-20, paragraph 1, sentence 3;

What high peak-to-mean ratios are they referring to? Most in Table I-3 are less than 5.

Page A-20, paragraph 1, last sentence;

This sentence should be repeated at the end of the discussion on the variability of the peak-to-mean ratios on page A-13, paragraph 1.

Page A-21, text line 3;

Add at the end of the sentence "observed in 1985" or change the value of "2.4 ng/m3" to "2.6 ng/m3" and add at the end of the sentence "observed in 1986". I believe the latter is preferred, since the hot spot data was obtained in 1986.

Page-24, paragraph 2, last sentence;

Delete this sentence.

Page A-23, Table I-7, the first footnote (*);

Reference this data. Andreae, 1980 conducted rain water studies along the eastern coast of the U.S. Is this the data you are referring to? If so, what is the point of this footnote, since Andreae observed both As(III) and As(V) in most rain water samples he collected.

Page A-33, Table II-2;

The Table number was not reproduced.

Page A-35, paragraph 3;

This paragraph is poorly written and presents the results in a biased worst case manner. Suggestions for improving this paragraph are given below.

Comments by Dr. Paul A. Solomon (continued)

Page A-35, paragraph 3, sentence 1;

The phrase "is being impacted" is to strong of a statement considering that greater than 95% of the data were below the detection limit of 3 ng/m3. I suggest changing this phrase to "may be impacted". In fact, the paragraph on page A-52 of the previous draft along with my comment to that paragraph (Part C of the current version, page C-5) is preferred, since it summarizes the GAMP data in a less biased manner. I have attached three tables that summarize the GAMP data for arsenic for the years 1983/1984 and 1986/1987. Since most of the data were below the detection limit of the analytical method it is difficult to draw a definitive conclusion about the impact of The Geysers on the surrounding area.

Page A-35, paragraph 3, sentence 2;

This sentence is inaccurate. I suggest changing it to the following: "Fine particle arsenic concentrations obtained at two sites located east of the developed steam field have shown maximum 24-hour averages up to 14 ng/m3 (second high was 6 ng/m3) during 1983-1984, and 4 ng/m3 (second high was <3 ng/m3) during 1986-1987. Maximum coarse particle concentrations were always less than the detection limit of 3 ng/m3 (GAMP, 1987)."

Page A-35, paragraph 3 sentence 3;

Insert "the detection limit of" after "or below".

Page A-35, paragraph 3, sentence 5;

I suggest deleting this sentence because it is not accurate, since large fluctuations in concentrations can also be due to variable meteorology. Also, there is insufficient data to reach this conclusion, since less than 5% (12 samples) of the data were above the detection limit of 3 ng/m3. Of the 12 samples (out of 248) above the detection nine were equal to 4 ng/m3 and one each were equal to 5, 6, and 14 ng/m3 and they were all observed in the fine particle fraction.

Page A-35, paragraph 3, sentence 6;

If sentence 2 is not modified as suggested here than move sentence 6 to after sentence 2 of this paragraph. Also, change "as fine particles" to "in the fine particles".

Comments by Dr. Paul A. Solomon (continued)

Page A-51, paragraph 4;

I suggest adding the following to the end of paragraph 4: "However, these levels of arsenic have not been observed in the atmosphere. This is probably because the thermodynamic calculations of Murray et. al. and Pupp et. al. do not consider the reaction of water with As_2O_3 to form the less volatile and more water soluble species oxyacid or the oxidation of As(III) to As(V)."

Page A-54, paragraph 1, sentence 1;

Insert "(Eatough et. al., 1979)" at the end of the sentence.

Page A-55, paragraph 2, sentence 6;

This statement has not been proven for the ambient environment; however, it probably is true for occupational exposures. Current ambient arsenic speciation data (Andreae, 1980; Solomon, 1984, Rabano et. al., 1989 and Appendix B of Part A) indicate that the concentration of As(III) in the atmosphere is on the average equal to or less than As(V).

Page A-55, paragraph 3, sentence 1;

I suggest changing "arsenic trioxide" to "As(III)" and "arsenic pentoxide" to "As(V)". They are assuming to know the species.

Actually, arsenic trioxide may first undergo or be very competitive with a reaction with water to form the As(III) oxyacid before oxidation to As(V)."

Page A-56, paragraph 1, sentence 3;

Andreae contributes the variation in the As(III)/As(V) ratio to several factors, only one of which was the presence of industrial sources that emit arsenic trioxide. Other factors included sources of As(V) (e.g., ocean spray), the age of the aerosol, and the effective oxidation-reduction potential of the aerosol.

Page A-56, paragraph 2, sentence 3;

This sentence should be changed to the following so that the results are not bias toward As(III), which was actually at lower concentrations than As(V). "Trivalent arsenic was present above the detection limit (approximately 1 ng/m3) in only half of the samples, whereas, As(V) was present in all samples analyzed. A wide variation also was observed in the relative amounts of trivalent and pentavalent arsenic in the samples."

Comments by Dr. Paul A. Solomon (continued)

Page A-56, paragraph 3, sentence 1;

Insert at the end of the sentence after "in Los Angeles", "near a known high temperature source of arsenic".

Appendix B;

Enclosed, please find an improved version of the first paper in this appendix. It has been peer reviewed and published in JAPCA. I would remove the sentence "To be submitted JAPCA May, 1987." from the current title page, leave in the table of contents changing the page numbers accordingly, and then reproduce the paper directly.

I have also enclosed a higher quality copy of the second paper by Solomon et. al., 1983.

PART B - HEALTH EFFECTS OF ARSENIC COMPOUNDS

1. The health risk assessment conducted by the DHS and described in this report considers only arsenic in the +3 oxidation state. This is because the assessment is based on data obtained from occupational exposure studies at three copper smelters, where As(III) is believed to be the predominant species inhaled. While little if any data exist that relates As(V) concentrations to carcinogenicity, there is evidence that As(V) species make up a substantial fraction (> 50%) of the arsenic observed in atmosphere particulate matter in the ambient environment. Therefore, a risk assessment based just on As(III) may be inaccurate and premature.

2. The population-weighted annual average arsenic concentration of 2.2 ng/m3 used in the risk assessment calculation in Part B is based on the 1985 data discussed in the previous draft of Part A of this report. Based on the 1986 data (current version of Part A) the health risk assessment should be based on a population-weighted average value of 1.7 ng/m3 (SCAB and SFBAAB). This would effectively lower the risk by about 25% from 1-29 per million to about 0.8 -23 per million.

3. The 1985 data were obtained only at 10 sites in the SCAB and SFBAAB, whereas, the 1986 data were obtained at those 10 sites as well as nine other sites located throughout California. Therefore, it would seem reasonable to base the health risk assessment on the entire state, as defined in Part A, pages A-13 to A-20. The overall population-weighted exposure value would be 1.5 ng/m3. The statewide risk would be lower than currently reported using the 1985 data by about 32%, resulting in a estimated risk of about 0.7-20 cases per million. The risk assessment can be calculated for both the entire state and for the SCAB and SFBAAB, since about 60% of the states population resides in these two areas.

Comments by Dr. Paul A. Solomon (continued)

SUMMARY OF ARSENIC CONCENTRATION DATA OBSERVED DURING GAMP 1983/84 AND 1986/87

TABLE 1

Fine (≤2.5μm) Particulate Matter

	Anderson Springs		Glenbrook	
	1983-84	1986-87	1983-84	1986-87
Total Number Samples	62	62	62	64
Number of Samples With As Concs. >3ng/m^3	6 (7%)	5 (8.1%)	1 (1.6%)	0 (0%)
Avg. As Conc.*(ng/m^3)				
Lower Limit	1.1	0.7	0.4	0.3
Upper Limit	3.3	3.1	3.0	3.0
Maximum As Conc. (ng/m^3)	14	4	4	3
2nd Highest As Conc. (ng/m^3)	6	3	3	2
As Conc. Reported as 0	61%	69%	79%	83%

*Arithmetic Mean - Lower limit average was calculated using the values as reported in the data, even though 10-30 percent of the reported concentrations were below the detection limit.

- Upper limit average was calculated assuming all values less than or equal to the limit of detection were equal to the detection limit of 3ng/m^3.

Comments by Dr. Paul A. Solomon (continued)

SUMMARY OF ARSENIC CONCENTRATION DATA OBSERVED DURING GAMP 1983/84 AND 1986/87

TABLE 2

Coarse (>2.5um and <10um) Particulate Matter

	Anderson Springs		Glenbrook	
	1983-84	1986-87	1983-84	1986-87
Total Number Samples	62	62	62	64
Number of Samples With As Concs. >3ng/m^3	0	0	0	0
Avg. As Conc.*(ng/m^3)				
Lower Limit	0.3	0.3	0.3	0.2
Upper Limit	3.0	3.0	3.0	3.0
Maximum As Conc. (ng/m^3)	3	2	3	2
2nd Highest As Conc. (ng/m^3)	2	1	2	1
As Conc. Reported as 0	84%	79%	82%	91%

*Arithmetic Mean - Lower limit average was calculated using the values as reported in the data, even though 100 percent of the reported concentrations were below the detection limit.

- Upper limit average was calculated assuming all values less than or equal to the limit of detection were equal to the detection limit of 3ng/m^3.

SUMMARY OF ARSENIC CONCENTRATION DATA OBSERVED DURING GAMP 1983/84 AND 1986/87

TABLE 3

Samples With As Concentrations >3ng/m^3*

Date	Site	Fraction	As Conc. (ng/m^3)
09-27-83	Anderson Springs	Fine	4
11-14-83			14
12-02-83			4
03-31-84			4
04-24-84			5
07-05-84			6
08-30-86			4
01-09-87			4
01-14-87			4
04-27-87			4
06-02-87	V		4
11-02-83	Glenbrook	V	4

*The detection limit for Arsenic was equal to 3ng/m^3 and was based on 3 times the uncertainty of the filter blank.

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Speciation of Arsenic in Ambient Aerosols Collected in Los Angeles

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First-time measurements of the potentially toxic inorganic species of arsenic (arsenite and arsenate) have been obtained in fine (<2.5 μm AD) and coarse (>2.5 μm AD) atmospheric particles in the Los Angeles area. A recently developed method that includes procedures for sample collection, preparation, and analysis was used in this study. Size-fractionated aerosol samples were collected with a high-volume dichotomous virtual impactor that employed polytetrafluoroethylene filters. Results were obtained for the recovery of arsenic standards added to unexposed and collected filters. Data from this study, indicated that the recently developed speciation method can be used to determine concentrations of As(III) and As(V) in atmospheric particulate matter samples.

Size-fractionated aerosol samples were collected in the city of Industry during January and February 1987. In most samples, As(III) and As(V) were above the detection limit (approximately 1 ng m^{-3} of either species) in both aerosol size fractions. A greater portion (about 75 percent) of the two species were observed in the fine particles. The As(III)/As(V) ratio for both particle sizes was close to 1 (i.e., an equal mixture of both species). Comparison of total suspended particulate arsenic measured by the speciation method to that measured by a routine California Air Resources Board-approved procedure showed good agreement ($r = 0.94$), indicating both methods were approximately equivalent for the collection and analysis of aerosol arsenic.

California's air toxic law became effective in January 1985, and defines California's air toxic program (Health and Safety Code Sections 39650 et seq.).[1] Under this legislation, a statutory mandate was created for the identification and control of toxic air contaminants found in California.

One of the mandated criteria used in the identification process to prioritize compounds that are believed to be hazardous to human health is ambient concentration. The California Air Resources Board (ARB) has developed a list of potentially toxic substances based on the mandated ambient criteria. One such element under consideration is arsenic. The measurement of individual species of this element is particularly important because of the variations in toxicity and carcinogenity of the different arsenic compounds found in the environment. Arsenic(III) is not only more toxic, but also may represent a greater carcinogenic hazard than As(V).[2–5]

Arsenic is emitted into the atmosphere from both anthropogenic and natural sources and is present in the atmosphere in trace amounts. Its atmospheric concentration ranges from about 0.01 to 0.1 ng m^{-3} in clean areas such as Antarctica[6] and up to 500 ng m^{-3} near certain industrial environments such as copper smelters.[7] The average measured arsenic level in U.S. urban areas is approximately 20 ng m^{-3}.[8] The primary source of arsenic in the Los Angeles area, approximately 33 kg per day, is from stationary high-temperature combustion processes (e.g., glass furnaces, primary metallurgical processes, and fuel oil combustion).[9] This is important, since several researchers[10,11] suggest As_4O_6 (As_2O_3 sublimes to form the gas phase species As_4O_6) is the predominant arsenic species emitted into the atmosphere from these types of industrial sources.

A variety of analytical methods currently exist for measuring total arsenic at concentrations present in the atmosphere. However, Solomon has proposed a method for determining the inorganic species of arsenic [arsenite, As(III); arsenate, As(V)] in atmospheric particulate matter.[12] In that study, particular attention was given to the measurement of these species, while maintaining the initial As(III)/As(V) ratio during the sample collection, preparation, and analysis steps. An analytical detection limit of 25 ng was obtained for each species in a given sample aliquot. An average As(III)/As(V) ratio of about 0.31 ± 0.29 with a range from less than 0.04 to 0.97 was reported for total suspended particulate matter (TSP) collected in Tucson, Arizona. The average atmospheric concentrations of As(III) and As(V) were about 1.6 ± 1.4 ng m^{-3} and 5.4 ± 3.3 ng m^{-3}, respectively.

To help assess the impact of these potentially toxic species on human health, size-fractionated samples of atmospheric particulate matter should be obtained, with an emphasis on particles that are most efficiently collected in the lungs (i.e., particles less than 2.5 μm aerodynmic diameter).[13,14] A preliminary study, employing the commercially available low-volume virtual dichotomous sampler (VDS) (Model 241, Sierra-Andersen Corp., Inc.), indicated this sampler collected an insufficient amount of material for the analysis of As(III) and/or As(V) by the sensitive analytical method reported by Solomon. In addition, replicate analysis could not be performed, since the entire filter sample was used to obtain maximum sensitivity. To help overcome these problems, a high-volume dichotomous virtual impactor (HVDVI) was employed.[15] This sampler can collect up to 30 times the mass of efficiently size-fractionated material and has a sample-to-blank ratio that is twice that of the VDS.

The objective of this work is to verify the method reported by Solomon[12] for the collection and analysis of inorganic species of arsenic (arsenite and arsenate) in size-fractionat-

HVDVI and a collocated standard high-volume sampler. The latter is used for routine monitoring of TSP by the ARB. Experiments also were carried out to examine the efficiency of recoveries of aqueous arsenite and arsenate standards added both to unexposed filters and to filters containing aerosol particles.

Experimental

Atmospheric Particulate Matter Collection

Atmospheric particulate matter samplers were sited on the roof of the two-story U.S. Post Office building located in the middle of an industrial area in the City of Industry, Los Angeles County, California. Previous routine monitoring by the ARB indicated high ambient concentrations of total arsenic can typically be found in this area.

Two samplers were employed at this site. One was a standard high-volume aerosol sample (hi-vol)[16] that employed 8 × 10-inch Whatman glass microfiber filters and operated at a flow rate of about 1.1 m^3 min^{-1}. This sampler collected total suspended particulate matter (TSP) and is currently employed by the ARB for routine aerosol monitoring of many atmospheric species. The other sampler was a high-volume dichotomous virtual impactor[15] (HVDVI) that collected atmospheric particles in two size ranges (fine and coarse) on 102-mm polytetrafluoroethylene (PTFE) filters (Zefluor, 2.0 μm, Gelman Sciences). This particular filter type required several rinsings in deionized, metal-free water prior to sample collection to obtain reliable, reproducible results.

The HVDVI, when operated at about 400 L min^{-1}, has a cutpoint (50 percent collection efficiency) of about 2.5 μm aerodynamic diameter (AD). Thus, the fine particle filter collected particles smaller than 2.5 μm AD, whereas the coarse particle filter collected particles larger than 2.5 μm AD.

Immediately following sample collection, the loaded filters were removed from the sampler and brought to the lab. The HVDVI filters were placed individually into glass petri dishes, sealed, and then placed into plastic ziplock bags. The samples were then stored in a freezer for one day to several weeks, until they were analyzed.

Sample Preparation and Analysis

The semimicro sample preparation procedure developed by Solomon[12] was used in this study for determining the inorganic species of arsenic (arsenite and arsenate) collected on PTFE filters. A second preparation method was employed for the analysis of total arsenic collected on glass fiber filters.

Arsenic speciation. In the speciation method, one-eighth of the 102-mm Zefluor filter was sectioned and placed in a 7-mL Teflon vial fitted with a threaded screw cap (Savillex Corporation). For PTFE filters, 0.05 mL of 100 percent ethanol was pipetted directly onto the filter surface. This was done to reduce the hydrophobic nature of the PTFE material and to allow for the interaction of the leaching solution with the sample.[12,17] A PTFE rod (3/8 × 1/2-inch) was then placed on top of the filter pieces to keep them submerged, and 2.0 mL of 10^{-4} N HCl was added. The Teflon container was closed tightly and placed in an oven at 85 to 90°C for one hour. The vial and sample were allowed to cool to room temperature before analysis. A 1.0-mL aliquot of the sample leachate was then analyzed for As(III) and As(V) by the Zn-$NaBH_4$ method described below.

In the Zn-$NaBH_4$ analysis procedure, As(III) and As(V) were efficiently separated in a two-step reduction process reduce As(III) to arsine (AsH_3). Immediately following the first reaction, $NaBH_4$ was used to reduce As(V) to AsH_3. The arsine produced during each step was detected in the N_2-H_2 air-entrained flame of an atomic absorption spectrophotometer (Model 3030, Perkin-Elmer Corporation). A complete description of the apparatus and the experimental conditions used can be found in the literature.[12] This procedure resulted in a routine (day-to-day) analytical detection limit of about 20 to 25 ng for each species. The direct analysis of aqueous arsenite and arsenate mixed standards by this method resulted in an analytical measurement precision for As(III) and As(V) of 11 and 9 percent, respectively, at the 200 ng level of each species, and 2 and 4 percent, respectively, at the 600 ng level for each species.

Total arsenic. A procedure developed by the California Air Resources Board's Haagen-Smit Laboratory (Method 107) was used for the analysis of total arsenic.[18] In this procedure, one-quarter of a glass fiber filter was sectioned and placed into a 100-mL graduated mixing cylinder to which 50 mL of 0.5 N HNO_3 was added. The cylinder and contents were placed in an ultrasonic bath (450 watts) for one hour at about 70°C. After cooling, 50 mL of deionized, metal-free water were added, and the cylinder contents were leached for a second hour. The sample was then filtered and a 0.02-mL aliquot was analyzed for total arsenic by graphite furnace atomic absorption spectroscopy (Perkin-Elmer 3030, Perkin-Elmer Corporation).

Standards and reagents. Arsenic(III) standards were diluted daily from a 1000-mg L^{-1} stock solution of As(III) that was prepared from As_2O_3 and obtained directly from Fisher Scientific (arsenic reference standard solution, 1000 ppm As, Fisher Scientific). The As(V) standards were diluted daily from a 1000-mg L^{-1} stock solution of As(V) that was prepared from As_2O_5 and obtained directly from EM Reagents (1000 ppm, 0.002 gm L^{-1} of As in water). Sodium tetrahydroborate (NaBH) pellets ($NaBH_4$, 99 percent purity, 5/16-inch, Alpha Products), each weighing approximately 0.25 gm, and zinc powder (8 micron, 99.9 percent pure, Aesar) were used as the reductants. Concentrated hydrochloric acid (reagent grade) with no measurable arsenic blank was obtained from Mallinckrodt Chemical Company. All solutions were prepared in deionized, metal-free water (Milli-Q, Millipore Corporation).

Results and Discussion

The effect of the amount of ethanol pipetted directly onto the PTFE filter surface, prior to leaching the sample for speciation analysis, was studied. Improved recoveries for both arsenic species (about equal to the amount of arsenic added to the filter) were observed when ethanol (0.05 or 0.10 ml) was added to unexposed filters, relative to recoveries when no ethanol was employed. These were similar to results observed by Solomon.[12]

A limited number of experiments were performed to study the recovery of standards added to unexposed PTFE filters. In each case, an aqueous standard containing equal amounts of As(III) and As(V) (in the range of 200 to 600 ng) was pipetted directly onto the filter surface after the surface was wet with ethanol (100 percent). The additions were allowed to dry and then analyzed by the arsenic speciation method. Excellent recoveries were obtained for both As(III) and As(V) (95 ± 7 and 100 ± 8 percent, respectively).

Aqueous standards, similar to those added to the unexposed filters, also were directly pipetted onto the particles on collected filters after the filter surface was wet with ethanol (100 percent). These filter samples were allowed to dry and then analyzed by the speciation method. The average recovery of As(III) and As(V) (including both the fine and coarse aerosol fractions) was 79 ± 22 and 97 ± 23 percent, respectively. These results suggested that the complex matrix of collected particulate matter may slightly affect the recovery

Table I. Comparison of two methods for the collection and analysis of total arsenic[a] (concentrations in ng m^{-3}).

Date collected	Collected by HVDVI[b,d]	Collected by standard hi-vol[c]
12 Jan 87	74.1	69.4
13 Jan 87	22.3	24.4
14 Jan 87	12.8	5.5
15 Jan 87	6.4	4.4
19 Jan 87	9.9	16.2
20 Jan 87	8.9	12.1
21 Jan 87	8.9	11.8
22 Jan 87	24.8	34.0
25 Jan 87	4.1	2.8
26 Jan 87	22.6	35.9
27 Jan 87	5.2	15.0
28 Jan 87	24.6	21.2
29 Jan 87	5.6	6.8
1 Feb 87	9.4	12.7
2 Feb 87	12.7	14.4
3 Feb 87	12.9	15.8

[a] Total arsenic equals the sum of As(III) and As(V) in total suspended aerosol.
[b] Employed Zefluor (PTFE) filters and was analyzed by the arsenic speciation method.
[c] Employed Whatman glass fiber filters and was analyzed by the ARB-HSL Method 107, see Reference 18.
[d] Sum of both arsenic species in the fine and coarse particle fractions. Less than values in Table II were set equal to the detection limit for this calculation.

ment of individual arsenic species. Similar results (i.e., a slight change up to about 20 percent) have been previously reported.[12] Therefore, to obtain the most accurate results, the method of standard additions can be used to compensate for these small changes.

Results obtained from the two types of recovery experiments (i.e., recoveries from unexposed and collected filters) can be used to estimate the precision for the combined sample preparation and analysis procedure employed for the determinations of the inorganic species of arsenic. The estimated error for As(III) and As(V) ranged from about 8 percent for unexposed filters to about 23 percent for filters containing particles. The larger error obtained for the arsenic species determined on the loaded filters was most likely due to the effect that variations in the complex matrix of the collected particles can have on the analysis of As(III) and As(V).

Concentrations of arsenic [sum of As(III) and As(V)] measured in total suspended aerosol (TSA) collected by the HVDVI (sum of fine and coarse fractions) and in TSP collected by the standard high-volume sampler are presented in Table I. Samples collected by the HVDVI were analyzed according to the arsenic speciation method, whereas those collected by the standard high-volume sampler were analyzed by the total arsenic procedure (ARB Method 107).[18] The method of standard additions was not applied to the arsenic speciation results presented in this paper (Tables I and II) because the possible sample matrix effect due to particles is believed to be small, certainly less than 20 percent (see Reference 12 and this paper). In addition, data presented by Solomon[12] indicate that TSA arsenic results (Table I) should not be affected, since the effect due to collected atmospheric particles is most likely the oxidation of As(III) to As(V); that is, total arsenic is conserved.

As can be seen in Table I, the concentration of total arsenic observed in samples collected by the HVDVI ranged from 4.1 to 74.1 ng m^{-3} with a mean and standard error of the mean of 16.6 ± 4.2 ng m^{-3} (this is an upper limit which includes less than values as equal to the detection limits indicated in Table II). Values reported for samples collected by the hi-vol sampler range from 2.8 to 69.4 ng m^{-3} with a mean and standard error of the mean of 18.9 ± 4.1 ng m^{-3}. The average ratio of total arsenic collected by the HVDVI to that of the hi-vol sampler was 0.88. Linear regression analysis [hi-vol (x) versus HVDVI (y)] of these data yielded a slope and intercept of 0.97 and −1.7, respectively, and a correlation coefficient (r) of 0.95 (n = 16). This agreement was very good considering the two samplers employed different collection substrates, the samples were prepared and analyzed by different methods, and the samplers probably have different inlet collection efficiencies.

With respect to the collection by different filter substrates, it should be noted that while PTFE filters are virtually inert, gas phase oxides or oxyacids of arsenic (most likely As_4O_6)[10,11] may be adsorbed and even oxidized by the more reactive glass fiber filter substrate. This would result in a positive artifact for aerosol arsenic. Similar results of positive artifact formation on glass fiber filters have been reported for the collection of aerosol nitrate and sulfate. In these cases, the oxides or oxyacids of nitrogen and sulfur (e.g., NO, NO_2, HNO_3, SO_2, and H_2SO_4) are adsorbed, or adsorbed and oxidized by the reactive filter material.[19-21]

Table II presents the As(III) and As(V) concentrations (ng m^{-3}) measured in the fine and coarse particle fractions collected in the City of Industry from January 12 to February 3, 1987. All analyses were performed using the arsenic speciation method. Once again, these data were not corrected for the small but possible sample matrix effect discussed previously. Arsenic(III) was observed on all but two filters in the fine particle fraction and was above the detection limit on about half the collected coarse particle samples. Arsenic(V) was measured on about 85 percent of the collected coarse and fine particle samples. On the average, approximately 13 to 20 percent of the As(III) and 29 to 30 percent of the As(V) were observed in the coarse particle fraction. The range of values indicates an upper and lower limit (see Table II, footnotes b and c).

The coarse particle fraction for As(III), and especially for As(V) observed in this study, is larger then one would typically expect if the major source of arsenic, in the Los Angeles

Table II. Arsenic(III) and As(V) concentrations (ng m^{-3}) and the As(III)/As(V) ratio observed in fine and coarse particles collected at the City of Industry in Los Angeles.[a]

Date collected	As(III) ng m^{-3} Fine	As(III) ng m^{-3} Coarse	As(V) ng m^{-3} Fine	As(V) ng m^{-3} Coarse	As(III)/As(V) Fine	As(III)/As(V) Coarse
12 Jan 87	44.0	4.8	18.7	6.6	2.4	0.7
13 Jan 87	10.9	1.8	6.6	3.0	1.7	0.6
14 Jan 87	4.2	<1.8	4.6	2.2	0.9	—
15 Jan 87	2.0	<1.1	1.9	1.4	1.1	—
19 Jan 87	2.9	1.4	3.4	2.2	0.9	0.6
20 Jan 87	5.3	1.2	2.4	<1.0	2.2	—
21 Jan 87	4.5	1.5	2.9	<1.2	1.6	—
22 Jan 87	14.1	4.1	4.9	1.7	2.9	2.4
25 Jan 87	<1.2	<0.9	<1.0	<0.8	—	—
26 Jan 87	10.2	2.2	5.9	4.3	1.7	0.5
27 Jan 87	1.5	<1.0	1.8	0.9	0.8	—
28 Jan 87	6.3	<2.4	12.0	3.9	0.5	—
29 Jan 87	2.2	<0.9	<0.9	1.6	—	—
1 Feb 87	3.7	1.0	3.4	1.3	1.1	0.8
2 Feb 87	<1.7	<1.7	7.0	2.3	—	—
3 Feb 87	4.2	<1.1	6.1	1.5	0.7	—
$\bar{x} \pm \sigma$[b]	7.4 ±10.4	1.8 ±1.1	5.2 ±4.6	2.2 ±1.5		
$\bar{x} \pm \sigma$[c]	7.3 ±10.6	1.1 ±1.5	5.1 ±4.7	2.1 ±1.7	1.4 ±0.7	0.9 ±0.7

[a] Values not corrected for 10 percent flow through coarse particle filter, see Reference 15.
[b] Upper limit, includes less than values (indicated by <) in the average as equal to the detection limit indicated.
[c] Lower limit, includes less than values in the average as equal to zero.

these sources predominantly emit As(III) as gas phase As_4O_6)[9,10] and if only gas-to-particle conversion processes were occurring. However, arsenic(III) oxide (most likely As_4O_6), a Lewis acid and the most probable precursor for particulate As(III) and As(V) species, may be behaving similar to the gas phase precursors of particle nitrate and sulfate [i.e., the oxyacids of nitrogen (e.g., NO, NO_2, HNO_3) and sulfur (e.g., SO_2, H_2SO_4), respectively] both of which exhibit coarse particle modes in the South Coast Air Basin.[22-24] This hypothesis simply considers the same type of acid-base chemistry, gas-to-particle transformations, and oxidation process that can occur in the formation of coarse particle NO_3^- and $SO_4^=$ (i.e., similar to the reactions of the gas phase weak acids NO, NO_2, and SO_2 with alkaline coarse particles to form coarse particle nitrate and sulfate). Obviously, this hypothesis does not completely extend itself to reactions of the strong acids, HNO_3 and H_2SO_4 with coarse particles, since the oxyacids of arsenic are only weak acids (e.g., oxyacids of arsenic would be incapable of displacing HCl from large sea-salt or NaCl particles, however, both the strong and weak acids are capable of sitting down on or reacting with alkaline coarse particles, e.g., coarse particles derived from crustal material).

The ratio of As(III)/As(V) also is presented for each sample in Table II. The average of this ratio was greater than one for the fine particles and slightly less than one for the coarse particles. For samples where both species were above their minimum detectable level, the As(III)/As(V) ratio ranged from about 0.5 to about 2.9 in both the fine and the coarse particle fractions. These results are somewhat different from those obtained in Tucson, Arizona.[12] In that study, the average As(III)/As(V) ratio observed in TSP collected by a high-volume sampler employing quartz fiber filters, was about 0.3, with a range from less than 0.04 to 0.97. These differences were most likely due to the impact of the various sources in the surrounding areas, on the age of the aerosol measured at the sampling sites, and/or on the rate at which As(III) was oxidized in the atmosphere (i.e., variations in the effective oxidation potential of the atmospheric environment).

Conclusion

A recently developed method[12] for the determination of inorganic species of arsenic (arsenite and arsenate) in atmospheric particulate matter was applied to aerosols collected in the Los Angeles area. Fine (<2.5 μm AD) and coarse (>2.5 μm AD) particle samples were collected in the City of Industry by a high-volume dichotomous virtual impactor (HVDVI). The use of this sampler allowed for the collection of a sufficient amount of sample so that both As(III) and As(V) could be routinely detected in both particle size fractions. In addition, use of the HVDVI, instead of the commercially available low-volume virtual dichotomous impactor, allowed for replicate analyses on individual filter samples. This is important since more accurate results for the analysis of As(III) and As(V) can be obtained by applying the method of standard additions.

Results obtained from recovery experiments, where arsenic standards were directly added to unexposed and collected filters, indicated that the arsenic speciation method can be used to determine concentrations of As(III) and As(V) in atmospheric particulate matter samples collected in the Los Angeles area. In addition, comparison of total suspended aerosol arsenic determined by the speciation method to that measured by a routine ARB-approved method showed good agreement. These results indicated the two methods were approximately equivalent for the monitoring of aerosol arsenic.

Size-fractionated aerosol samples were collected in the City of Industry and analyzed for their concentrations of were found in the fine particle fraction of the aerosol. The average As(III)/As(V) ratio observed in both the fine and coarse particle fractions was close to 1 (i.e., an equal mixture of the two species). For both particle size ranges, the As(III)/As(V) ratio varied from about 0.5 about 2.9.

This study should be helpful in assessing the potential adverse health effects due to public exposure to arsenic in ambient air in California. This is especially true since the data presented here indicate that both As(III) and As(V) species are present in ambient aerosols. Thus, assuming all arsenic in atmospheric particulates is As(III), the health risk assessment of inhaled arsenic may over-estimate the unit risk for public populations in California. In addition, the chemical physical information obtained from speciation measurements of this type will certainly help to evaluate source-sink strengths more thoroughly and to gain a better understanding of the complex geochemical cycles of arsenic and other related species in the environment.

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Disclaimer

This report has been reviewed by the staff of the California Air Resources Board and has been approved for publication. Approval does not signify that the contents necessarily reflect the views and policies of the Air Resources Board, nor does mention of trade names or commercial products constitute endorsement or recommendation for use.

References

1. Department of Health Services, Health and Safety Code Sections 39650 et seq. California State Law Library, 914 Capitol Mall, Room 305, Sacramento, CA 95814, January 1984.
2. D. J. Lisk, "Ecological aspects of metals," *N.Y. State J. Med.* 71: 2541 (1971).
3. *Medical and Biological Effects of Environmental Pollutants: Arsenic*, National Academy of Sciences, Washington, D.C. 1971, Chapter 5, p. 117.
4. *Medical and Biological Effects of Environmental Pollutants: Arsenic*, National Academy of Sciences, Washington, D.C. 1971, p. 185.
5. S. Hernberg, *Origins of Human Cancer*, Vol. 4, H. H. Hiatt, Ed; Cold Spring Harbor Laboratories, New York, N.Y. 1972, p. 147.
6. W. Maenhaut, W. H. Zoller, R. A. Duce, G. L. Hoffman, "Concentration and size distribution of particulate trace elements in the south polar atmosphere," *J. Geophys. Res.* 84: 2421 (1979).
7. P. R. Walsh, R. A. Duce, J. L. Fasching, "Impregnated filter sampling system for the collection of volatile arsenic in the atmosphere," *Environ. Sci. Technol.* 11: 163 (1977).
8. E. Sawicki, "Airborne carcinogens and allied compounds," *Arch. Environ. Hlth.* 14: 46 (1967).
9. G. R. Cass, G. J. McRae, "Source-Receptor Reconciliation of South Coast Air Basin Particulate Air Quality Data," California Air Resources Board. Final Report. NTIS No. PB-82-250093.
10. Lowenbach and Schlesinger Associates, Inc., "Arsenic: A Preliminary Materials Balance," U.S. EPA Report 560/6-79-005, 1979.
11. D. J. Eatough, N. L. Eatough, M. W. Hill, N. F. Mangelson, J. Ryder, L. D. Hansen, R. G. Meisenheimer, J. W. Fishcher, "The chemical composition of flue dust," *Atmos. Environ.* 13: 489 (1979).
12. P. A. Solomon, "Collection and Analysis Techniques for Studies of Atmospheric Arsenic Species," Ph.D. Thesis, Dept. of Chemistry, University of Arizona, Tucson, Arizona, 1984.

13. F. Perea, A. Karin Ahmed, *Respirable Particles: Impact of Airborne Fine Particles on Health and Environment*, Ballinger Press, Cambridge, MA, 1979.
14. J. H. Brown, K. M. Cook, F. G. Ney, T. Hatch, "Influence of particle size upon the retention of particulate matter in the human lung," *Amer. Jour. of Public Health* 40: 450 (1950).
15. P. A. Solomon, J. L. Moyers, R. A. Fletcher, "High-volume dichotomous virtual impactor for the fractionation and collection of particles according to aerodynamic diameter," *Aerosol Sci. Technol.* 2: 455 (1983).
16. "National primary and secondary ambient air quality standards," U.S. Environmental Protection Agency, *Federal Register* 36: 8186 (1971).
17. M. R. Derrick, J. L. Moyers, "Precise and sensitive water soluble ion extraction method for aerosol samples collected on polytetrafluoroethylene filters," *Anal. Lett.* 14: 1637 (1981).
18. "Method 107," State of California, Air Resources Board, Haagen-Smit Laboratory, El Monte, California 91731, 1986.
19. B. R. Appel, E. L. Kothny, Y. Tokiwa, M. Haik, J. J. Wesolowski, Fourth Quarterly Report to ARB (Contract No. ARB-5-1032), State of California, Air Resources Board, Sacramento, California, 1977.
20. B. R. Appel, S. M. Wall, Y. Tokiwa, M. Haik, "Interference effects in sampling particulate nitrate in ambient air," *Atmos. Environ.* 13: 319 (1979).
21. R. W. Coutant, "Effect of environmental variables on collection of atmospheric sulfates," *Environ. Sci. Technol.* 11: 873 (1977).
22. W. R. Pierson, W. W. Brachaczek, "Coarse- and fine-particle atmospheric nitrate and HNO_3(g) in Claremont, California, during the 1985 Nitrogen Species Methods Comparison Study," *Atmos. Environ.* 22: 1665 (1988).
23. P. A. Solomon, T. Fall, L. Salmon, P. Lin, F. Vasquez, G. R. Cass, "Acquisition of Acid Vapor and Aerosol Concentration Data for Use in Dry Deposition Studies in the South Coast Air Basin," Final Report to ARB (Contract No. A4-144-32), State of California, Air Resources Board, Sacramento, California, March 1988.
24. S. V. Hering, "Field Comparison of Measurement Methods for Nitric Acid," Final Report to ARB (Contract No. A4-164-32), State of California, Air Resources Board, Sacramento, California, April 1987.

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High-Volume Dichotomous Virtual Impactor for the Fractionation and Collection of Particles According to Aerodynamic Size

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A prototype dichotomous virtual impactor (DVI) using a single acceleration nozzle, operating at approximately 500 l/min, and having an aerodynamic particle cutpoint diameter of about 2–3 μm has been constructed and tested. Under these conditions the flow through the acceleration nozzle is calculated to be turbulent. This sampler was calibrated with a monodisperse aerosol, and the measured particle size-dependent collection efficiencies demonstrate that the sampler size fractionates atmospheric particulate matter as efficiently as the low-volume dichotomous virtual impactors. Analysis of test data indicates that the high-volume sampler can be described by classical impaction theory. These data also indicate that over the range of Reynolds numbers from 24,000 to 81,000 there is little, if any, dependence of inferred acceleration nozzle turbulence on the performance characteristics of the sampling system. A comparison of the concentration of atmospheric particulate matter, sulfate, and calcium on the fine filter samples collected with colocated high- and low-volume virtual impactors also shows that the two samplers are operating with similar performance characteristics. Additionally, the high-volume DVI collects at least 10–30 times the mass of particulate matter that the presently available virtual impactors collect and thus allows one to obtain improved precision in the measurement of those airborne species that are near the minimum detectable level of current analytical methods.

NOMENCLATURE

C	Cunningham's slip correction factor (dimensionless)
D_c	diameter of the collection probe (cm)
D_j	diameter of the acceleration nozzle (cm)
D_p	diameter of the particle (cm)
D_{p50}	diameter of the particle at 50% collection efficiency (cm)
f	large particle air flow transport ratio (%)
J	nozzle-to-probe spacing (cm)
Q	total flow rate (l/min)
Re_j	Reynolds number calculated for the acceleration nozzle (dimensionless)
St	Stokes number (dimensionless)
T	throat length of the acceleration nozzle (cm)
V_j	particle velocity at the acceleration nozzle exit plane (cm/sec)
θ	one-half the entrance angle of the acceleration nozzle (deg)
μ	viscosity of the air (1.81×10^{-4} g/sec cm)
ρ_a	density of the air (1.2×10^{-3} g/cm^3)
ρ_p	density of the particle (g/cm^3)
ψ	impaction parameter (dimensionless)
ψ_{50}	impaction parameter at 50% collection efficiency (dimensionless)

INTRODUCTION

Suspended particulate matter in the atmosphere exists primarily in two size ranges. The large or coarse particles are considered to have an aerodynamic diameter of greater

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than about 2–3 μm. Willeke and Whitby (1975), Dzubay and Stevens (1975), and others have shown that the large particles are primarily produced by mechanical processes (e.g., soil erosion or disruption). The small or fine particles are considered to have an aerodynamic diameter of less than a few micrometers and are composed primarily of nonvolatile gas phase reaction products and the more volatile chemical compounds and elements. Fine particles have long atmospheric residence times, typically on the order of weeks, and therefore they can be transported over long distances (Jaenicke, 1980). Middleton (1952), Charlson (1969), and Jaenicke (1980) indicate that fine particles have the potential to affect visibility and climate, since they efficiently scatter and absorb solar radiation. Brown et al. (1950) and Perera and Karim Ahmed (1979) have studied or reviewed the collection characteristics of atmospheric particulate matter in the human respiratory tract; their work indicates that fine particles are most efficiently collected deep in the lungs, where they have the potential to cause adverse health effects.

For these reasons, many air samplers have been designed to collect size-fractionated samples of atmospheric particulate matter. One class of particle size fractionators, originally developed by May (1945), is the impactors, where particle size fractionation is performed by inertial separation. Ranz and Wong (1952), Mitchell and Pilcher (1959), Cohen and Montan (1967), and others have described the real, or classical, impactor, for which size fractionation of the particles takes place at a surface. In classical impaction a small plate is placed such that the surface is perpendicular to the air flow at the exit of a particle acceleration nozzle. The large particles are impacted on the plate, while the small particles, having smaller inertia, follow the air streamlines around the plate. Lundgren (1967) and Dzubay et al. (1976) have demonstrated that this method of collecting size-fractionated samples can suffer from large-particle bounce or reentrainment problems, which result in contamination of the small particles by large particles.

The virtual impactor, first developed by Hounam and Sherwood (1965) and later modified by Conner (1966), Dzubay and Nelson (1975), and Loo et al. (1976), eliminates the particle bounce problem associated with classical impactors. In a virtual impactor a collection probe replaces the plate, and the size fractionation of the particles occurs in the space between the nozzle and probe. Typically, 90% of the air is removed perpendicular to the acceleration nozzle, and 10% flows down through the large particle collection probe. In this type of system the fine particles follow the streamlines of the major air flow and are collected on a fine-particle filter, while the coarse particles, with greater inertia, are accelerated across the space between the nozzle and probe and are collected on a coarse-particle filter. The use of filters and the replacement of the impaction surface with a collection probe in a virtual impactor eliminates the particle bounce problem associated with real impaction surfaces. As a result of the air flow design of the virtual impactor, 10% of the small particles are collected on the large-particle filter. However, the fine-particle sample is essentially free from large-particle contamination.

The present day commercial low-volume dichotomous virtual impactor, (LVDVI), using a single acceleration nozzle and operating under laminar flow conditions, separates particles into two size ranges (Loo et al., 1979). In these samplers the coarse particles have an aerodynamic diameter greater than about 2.5 μm, while the fine particles are those with an aerodynamic diameter of less than 2.5 μm. The LVDVI typically collects suspended atmospheric particulate matter on polytetrafluoroethylene (PTFE) membrane filters, operates at low flow rates (less than 20 l/min), and, depending on the concentration of atmospheric particulate matter, collects from less than 10 to several hundred micrograms of sample in a 24-hr period. This

results in particulate matter filter loadings (defined here as the volume of air collected in 24 hr per unit area of filter collecting surface) of about 4 m^3/cm^2. Because of the use of the PTFE membrane filter medium with its smooth collection surface, these samples are well-suited for analysis by x-ray fluorescence techniques. In addition to elemental analysis by x-ray fluorescence, these filters can also be analyzed for mass and various ionic species (Stevens and Dzubay, 1978). However, these samplers still collect relatively small amounts of particulate matter mass, and for this reason, when these low-volume samplers are used, many chemical species of interest are at or near the minimum detectable limit (MDL) of the analytical method. For example, it is difficult to analyze for individual organic species, ^{14}C, and several trace elements (Se, As, Sb, etc.) by present analytical methods. Additionally, contamination or blank problems associated with these low-volume samplers often limit the sampling time resolution to longer than desirable for many investigations. Loo et al. (1976) developed a medium-volume dichotomous virtual impactor (MVDVI) that uses three acceleration nozzles, operates at 50 l/min, and has a filter loading of 11.7 m^3/cm^2. The MVDVI provides great improvement relative to situations where the analytical measurement is limited by contamination or blank problems. However, the MVDVI still collects relatively small amounts of particulate matter.

In order to overcome some of the situations where the analysis of size-fractionated samples is limited by the small amount of particulate mass collected (i.e., measurements at or near the MDL of the analytical method) a single-jet high-volume dichotomous virtual impactor (HVDVI) has been developed. In addition to the advantages obtained when more sample is collected, the HVDVI also provides for an increased filter loading advantage relative to the LVDVI while maintaining essentially the filter loading obtained with the multijet MVDVI. The HVDVI was calibrated by two methods: (1) a laboratory calibration was obtained using a monodisperse aerosol, and (2) a field test was obtained by comparing the chemistry of the small-particle fraction of atmospheric particulate samples collected with colocated HVDVI and LVDVI samplers. In this paper the design and performance characteristics of the HVDVI sampler are presented and discussed.

EXPERIMENT

Laboratory Calibration

A monodisperse aerosol was generated by a Berglund–Liu vibrating orifice monodisperse particle generator from Thermal Systems Inc., model No. 3050[1] (Berglund and Liu, 1973). This generator produces solid or liquid monodisperse particles of a known size from approximately 0.50 to 50 μm in diameter with a standard deviation of approximately 1%. In this work, the aerosol was generated from an ethanol solution of oleic acid and fluorescein. The aerodynamic diameter of particles greater than 3 μm was determined by measuring their terminal velocity in still air and calculating the diameter using the Stokes equations. These particle diameters are accurate to about $\pm 2\%$. The diameter of particles less than 3 μm was calculated based on the dilution of solutions used to generate larger particles of specified diameter, with the accuracy being better than $\pm 5\%$. All particle sizes were monitored on-line for an estimate of the particle size distribution by using an optical particle counter (Climate model No. 208) equipped with a multichannel analyzer (Tracor, Northern Inc., model No. TN 1705).

[1]Certain commercial equipment, instruments, and materials are identified in this paper to specify adequately the experimental procedure. Such identification does not imply recommendation or endorsement by the National Bureau of Standards, nor does it imply that the materials or equipment identified are necessarily the best available for the purpose.

Circular Whatman 41 filter paper (10-cm diameter) was used in the sampler to collect the generated particles. The fluorescein dye was leached from the filters using 0.1N NH_4OH, and the absorbance of the resulting solution was measured at 490 nm using a standard laboratory spectrophotometer. The fine-particle collection efficiency was determined by measuring the ratio of fine-particle absorbance to the sum of the fine and coarse or total absorbance. An approximate value for wall losses was determined by disassembling the impactor and wiping the exposed surfaces with a piece of Whatman 41 filter paper wet with 0.5 ml of 0.1N NH_4OH.

Chemical Analysis of Airborne Particles

An empirical calibration of the sampler was obtained by comparing various chemical species on samples collected with colocated LVDVI and HVDVI samplers. The LVDVI uses 37 mm 2.0-μm-pore-size PTFE membrane filters (Membrana Corp.), and the HVDVI sampler uses 10.0-cm-diam quartz filters (Pallflex Corp., Pallflex 2500 QAST).

The concentrations of the mass of collected particulate matter were determined by gravimetric analysis. The quartz filters were weighed on an analytical balance and the PTFE filters on a microanalytical balance. For sulfate analysis a section of each quartz filter was placed in a Teflon bomb with distilled/deionized water and extracted at 90°C for 2 hr. A microprocedure developed by Derrick and Moyers (1981) was used to extract sulfate from the PTFE filters. In this procedure one-half of each PTFE filter is placed in a Teflon bomb, "wet" with ethanol, and then extracted with 5×10^{-5}N $HClO_4$ at 90°C for 2 hr. The extraction solutions were analyzed for SO_4^{-2} by ion chromatography (Mulik et al., 1976). For metal analysis, the quartz filters were extracted with 6N nitric acid at 90°C for 2 hr while the PTFE filters were first "wet" with ethanol and extracted with 6N nitric acid at 90°C for 2 hr. These solutions were then analyzed by flame atomic absorption spectroscopy.

RESULTS AND DISCUSSION

Impaction Theory and Design Parameters

There have been numerous studies of both real and virtual impactors, including experimental and theoretical studies designed to measure or define the motion of particles in this type of sampling system (Ranz and Wong, 1952; Mitchell and Pilcher, 1959; Cohen and Montan, 1967; Marple and Liu, 1974; Marple et al., 1974; Marple and Chien, 1980).

Assuming that the gravitational and electrical effects are small compared with the inertial effects, the classical impaction process can be characterized by a single dimensionless parameter ψ, as defined by Ranz and Wong (1952):

$$\psi = C\rho_p V_j D_p^2 / 18\mu D_j. \quad (1)$$

The Stokes number St as defined by Fuchs (1964), also a dimensionless parameter, is equal to 2ψ and is the ratio of the stopping distance of the particle to $D_j/2$. Each of these dimensionless parameters is used throughout the literature to describe the performance characteristics of impactors. The collection efficiency curve is a plot of the efficiency of collection (number collected/number incident) versus either the aerodynamic particle diameter or $\psi^{1/2}$. Experimental values of ψ_{50} (impaction parameter for 50% collection efficiency) range from about 0.06 (Swartz et al., 1973) to about 0.4 (Mercer, 1963), with most values falling between $0.1 \leq \psi_{50} \leq 0.3$ (Ranz and Wong, 1952; Cohen and Montan, 1967; McFarland, 1978).

Based on the classical impaction theory of Ranz and Wong (1952) and the design of the present day dichotomous virtual impactor, an HVDVI was constructed and is illustrated in Figure 1. It is approximately 50 cm in height and about 11.5 cm in diameter. The HVDVI uses two 10-cm diameter filters supported in individual filter cassettes, leaving a sample collection diameter of just under 9 cm. Approximately 90% of the total air flow $(Q - f)$ is removed perpendicular to the acceleration nozzle and collection probe

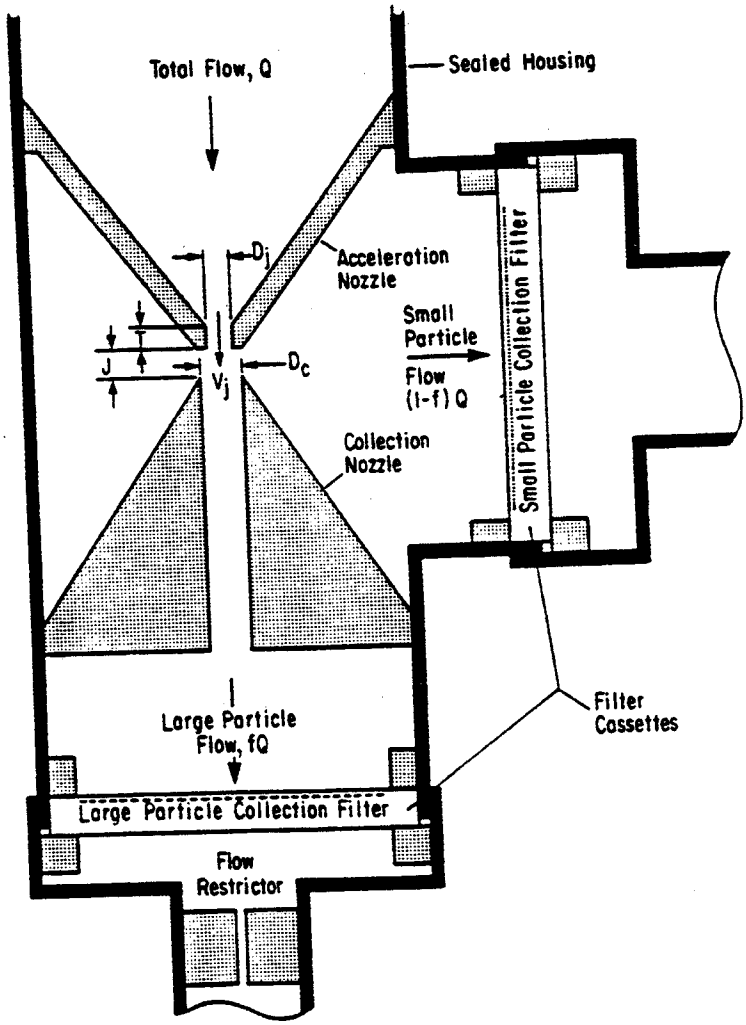

FIGURE 1. Physical design parameters of the HVDVI.

through the small-particle filter, while the remaining 10% (f) passes through the large-particle filter. Presently, the HVDVI uses the same high-volume pump that is used with the standard high-volume sampling system. When such a pump is used, the sampler can operate at a flow rate of up to approximately 500 l/min.

Table 1 compares some sampling flow rates, filter loadings, and particulate matter masses obtained with the LVDVI, MVDVI, HVDVI, and standard high-volume (HV) sampling systems. The HVDVI sampler, when operated at 500 l/min for 24 hr, collects about 10 and 30 times the mass of the MVDVI and LVDVI samplers, respectively, and about 40% of the mass collected by the HV sampler. Under standard operating conditions, the LVDVI and the HV sampler have filter loadings of about 4 m^3/cm^2, while the MVDVI and HVDVI have filter loadings of about 11.5 m^3/cm^2. Therefore, the HVDVI and the MVDVI have obtained an increase in the sample-to-blank ratio of about 3 over the LVDVI and HV samplers. It should be noted that with higher loadings filter clogging becomes more important and may become a serious problem in highly polluted

TABLE 1. Comparison of Typical Collection Parameters for the HVDVI, MVDVI, LVDVI, and Standard HV Samplers

	HVDVI	MVDVI	LVDVI	Standard HV Sampler
flow rate (m^3/hr)	30	3	1	70
volume per day (m^3)	720	72	24	1700
mass per day[a] (μg)	43,200	4320	1440	102,000
filter area (cm^2)	62	6.1	6.1	400
filter loading (m^3/cm^2)	11.6	11.7	3.9	4.2

[a]Assuming an atmospheric particulate concentration of 60 $\mu g/m^3$.

areas. However, the advantages obtained by collecting more mass and having the higher filter loadings make the HVDVI especially favorable for collecting size-fractionated samples in remote areas where particulate concentrations are very low or where the required time resolution is too short to obtain a sufficient sample by other virtual impactors.

FIGURE 2. Comparison of HVDVI and DVI collection efficiency curves.

Laboratory Calibration

Calibration and evaluation of the system was performed by varying the parameters of known or suspected importance (i.e., D_j, Re_j, D_c, J). For all the experimentally determined cutpoints of this sampler the impaction parameter, ψ_{50}, was calculated; it ranged from about 0.1 to 0.36. These values fall within the range found in the literature for laminar flow real and virtual impactors. Figure 2 illustrates three typical collection efficiency curves for the HVDVI. Table 2 lists the operating conditions and physical

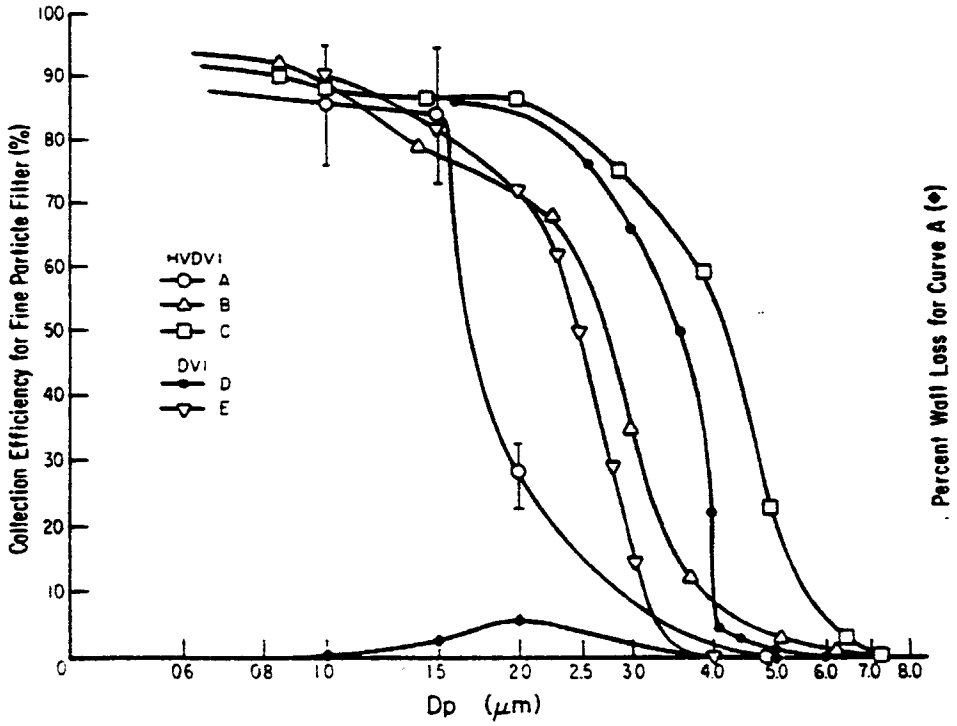

TABLE 2. Operating Conditions and Physical Design Parameters for the Efficiency Curves in Figure 2

	HVDVI			DVI[a]	
	Curve A[b]	Curve B[b]	Curve C[b]	Curve D[c]	Curve E[d]
Q (l/min)	420	500	200	14.0	16.7
$D_{p_{50}}$ (μm)	1.8	2.6	4.3	3.6	2.5
Re_j	78,000	81,000	32,000	4900	7700
D_j (cm)	0.76	0.87	0.87	0.40	0.31
D_c/D_j	1.33	1.33	1.33	1.31	1.38
J/D_j	1.43	1.25	1.25	0.89	1.04
f (%)	−9	−7	−11	10	10
T (cm)	0.75	0.85	0.85	0.89	0.32
θ (deg)	42.5	42.5	42.5	45	45

[a] Low-volume dichotomous virtual impactor.
[b] This work.
[c] McFarland (1978).
[d] Loo et al. (1979).

design parameters for the efficiency curves shown in Figure 2. Curve A, with a cutpoint of 1.8 μm, was obtained at a flow rate of 420 l/min and a nozzle diameter of 0.76 cm. Curves B and C, with cutpoints of 2.6 μm and 4.3 μm, were obtained at flow rates of 500 and 200 l/min, respectively, using an acceleration nozzle diameter of 0.87 cm. The Reynolds number is a parameter used to describe the flow through a pipe as either laminar or turbulent and is subsequently discussed. The Reynolds numbers calculated for the above acceleration nozzle diameters and flow rates are 78,000, 81,000, and 32,000, respectively. The error bars in curve A of Figure 2 represent the relative standard deviation associated with the measurement of the collection efficiency based on four individual determinations. In general, the measured relative standard deviation in the fine-particle collection efficiency was less than 5% near the 0% collection efficiency, about 15% near the cutpoint (the steepest slope), and about 10% when the particle collection efficiency was greater than about 75%. Curves D and E in Figure 2 are reported collection efficiency curves for two low-volume virtual impactors. Curve D was obtained by McFarland (1978), and Curve E was obtained by Loo et al. (1979). For each of the LVDVI systems, the Reynolds numbers are approximately 5000. As can be seen in Figure 2, the slope and shape of the efficiency curves determined for the HVDVI are qualitatively similar to those of the LVDVI.

Wall Losses

The wall losses obtained for each particle size for curve A are also plotted in Figure 2. As can be seen, the maximum wall loss occurs near the cutpoint and under these operating conditions is about 6%. Depending on the operating conditions, wall losses for the HVDVI sampler at the cutpoint ranged from approximately 5% to 20%. Wall losses obtained near the cutpoint for the DVI samplers were 10.7% and less than 1%, as reported by McFarland (1978) and Loo et al. (1979), respectively.

The nozzle-to-probe distance was optimized based on the amount and location of the internal wall losses. The wall loss was found in three locations: on the bottom of the acceleration nozzle, on the inside lip of the collection probe, and on the inside circumference of the main body of the sampler. The wall loss in this last area was located in a plane parallel to and equal in width to the spacing between the nozzle and probe. This type of wall loss occurred for most experiments when D_j was greater than or equal to 0.87 cm. Wall loss was eliminated on the bottom of the acceleration nozzle by increas-

ing the nozzle-to-probe distance to greater than 1 cm. For nozzle diameters greater than 0.85 cm, the nozzle-to-probe distance can fall in the range from $1.0D_j$ to at least $1.5D_j$, as described for real impactors by Marple and Liu (1974) and for virtual impactors by Marple and Chien (1980).

Reynolds Number

The Reynolds number Re, as discussed by Schlichting (1968), is a dimensionless parameter used to describe the flow of a fluid (liquid or gas) through a pipe as either laminar or turbulent. The Reynolds number Re_j within the acceleration nozzle can be defined as

$$Re_j = \rho_a V_j D_j / \mu. \quad (2)$$

Experiments reviewed by Schlichting (1968) have shown that the flow is laminar when the Reynolds number is less than about 2000. Above 2000 the flow can either be laminar or turbulent, depending on the flow characteristics of the system. For Reynolds numbers above about 10,000, it becomes increasingly difficult to maintain laminar flow, and for most situations turbulent flow exists. It is important to note that most previous real and virtual inertial-type impactors have been designed for particle size fractionation to be applied to laminar flow or assumed laminar flow conditions (i.e., Re_j typically less than about 9000).

A major objective of this study was to evaluate the potential effect on impactor performance of high Reynolds numbers (suggesting turbulent air flow conditions) as calculated for the acceleration nozzle. Marple and Chien (1980) provide a computer simulation of the performance characteristics of the LVDVI indicating that for Reynolds numbers between 5000 and 15,000 there is little effect on the particle size-dependent collection efficiency of the sampling device. McFarland's (1978) empirical study of the LVDVI also shows little effect on the shape and slope of the collection efficiency curve for values of the Reynolds number from 2000 to 9000.

Since the HVDVI operates at a much higher Reynolds number, an extensive set of experiments were conducted to evaluate the possible effect of turbulent air flow in the acceleration nozzle. Table 3 presents a summary of the measured D_{ps0} values and calculated ψ_{50} values for different Reynolds numbers and various values of the design parameters Q, V_j, and D_j. In Table 3 one can observe that there is no apparent or systematic effect of Re_j on impactor performance, where the impactor performance can

TABLE 3. Particle Diameter at 50% Collection Efficiency (D_{ps0}) and Impaction Performance Parameter (ψ_{50})

Design parameter			Performance parameter		Parameter approximate constant
D_j (cm)	V_j (cm/sec)	Re_j	D_{ps0} (μm)	ψ_{50}	
0.87	5,600	32,000	4.3	0.33	D_j
0.87	9,200	52,000	2.7	0.24	
0.87	13,000	74,000	2.8	0.32	
0.87	14,000	81,000	2.6	0.36	
0.52	8,000	27,000	2.0	0.19	V_j
0.56	8,300	31,000	2.1	0.20	
0.87	8,000	45,000	2.5	0.17	
1.03	7,700	52,000	3.3	0.25	
0.56	14,000	53,000	1.6	0.20	Re_j
0.64	12,000	52,000	1.8	0.19	
0.76	10,000	50,000	2.2	0.20	
0.87	9,200	52,000	2.7	0.24	
1.15	6,600	51,000	3.9	0.27	

be evaluated from the calculated values of the dimensionless impactor parameter ψ_{50}. The use of linear and nonlinear multiple regression analysis on these data indicates that $D_{p_{50}}^2$ is dependent on the same design parameters that describe laminar flow impactors (i.e., D_j and V_j^{-1}). The average ψ_{50} determined from these data is 0.24 ± 0.06. Thus, for the system configuration studied in this work, ψ_{50} falls within the range that has been demonstrated for laminar flow real and virtual impactor designs. This, of course, implies that for these types of systems classical impaction theory may be used in the design of systems even when apparently highly turbulent conditions would be expected to occur in the acceleration nozzles.

Field Comparison

A field comparison of the concentration of fine suspended particulate matter, fine sulfate, and fine Ca for 12 samples collected with colocated LVDVI and HVDVI samplers was made. These results are presented in Table 4. As can be seen in Table 4, the average concentrations of fine suspended particulate matter and fine sulfate (90% of the sulfate is found on particles less than 2.5 μm) agree within 5%, while the average fine Ca concentrations (10% of the calcium is found on particles less than 2.5 μm) agrees within 10%. The high standard deviation for Ca observed with the LVDVI samplers is a result of the Ca concentrations' being close to the detection limit of the analytical measurement method. The LVDVI is designed with a size-selective inlet, which theoretically allows only particles of less than 15 μm aerodynamic diameter to enter the sampler. The HVDVI has no such inlet. Therefore, no comparison can be made for the collection of coarse particles by the two sampling systems.

The increase in sample size and the analyte-to-blank ratio available with the HVDVI makes it especially promising for use with atmospheric organic chemistry investigations, including the newly developing area of ^{14}C measurements (Currie and Klouda, 1982). Any desired sampling media (e.g., quartz or PTFE) can be used, and thus the analytical methodology developed for the other sampling systems should be directly applicable to samples collected with the HVDVI.

CONCLUSION

These results provide convincing evidence that the dichotomous virtual impactor using a single acceleration jet can be operated as a high-volume sampler. Under these conditions, the HVDVI operates in the turbulent flow region (as calculated for the acceleration nozzle) but can still separate particles according to aerodynamic diameter as efficiently as the state-of-the-art laminar flow dichotomous virtual impactor. The analysis also indicates that the performance characteristics of this turbulent flow impactor can be described by the same theory that describes both real and virtual laminar flow impactors. The HVDVI sampler not only collects greater than 10–30 times the mass of particulate matter the MVDVI and LVDVI samplers collect, but it also has a sample-to-blank ratio that is about three times greater than the LVDVI or standard high-volume air

TABLE 4. Comparison of the HVDVI and the LVDVI Samplers for Observed Mass, Sulfate, and Calcium Concentrations

Measurement[a]	LVDVI ($\bar{x} \pm \sigma$ $\mu g/m^3$)	HVDVI ($\bar{x} \pm \sigma$ $\mu g/m^3$)	HVDVI/LVDVI ($\bar{x} \pm \sigma$)
Mass	9.2 ± 1.9	10.1 ± 3.0	0.95 ± 0.15
Sulfate	3.8 ± 0.8	3.8 ± 0.6	1.01 ± 0.17
Calcium	0.07 ± 0.03	0.08 ± 0.01	0.88 ± 0.42

[a] Fine particles (12 individual sampling periods).

sampler. The HVDVI and MVDVI have similar sample-to-blank ratios. The use of this sampler maintains the advantages of the LVDVI and MVDVI, but it will also allow for the analysis of size-fractionated samples for many atmospheric species that presently are near or below the minimum detectable level of present analytical techniques and cannot be determined using currently available size-fractionating virtual impactors. A potential disadvantage of this system is that more pronounced clogging problems will occur in these sampling situations where the particulate matter loading is high. This sampler is especially attractive for use in remote areas or for obtaining improved time resolution information on particulate species present in the atmosphere.

The HVDVI is a prototype sampler in its early stages of development. Future research should be directed toward the optimization of the sampler for both performance and convenience of operation. Additionally, the development of a size-selective inlet to operate at these flow rates would greatly enhance the comparability of the HVDVI to other thoracic or inhalable-type particulate matter samplers.

The authors would like to thank Dr. Harry Rook, Dr. Raymond McKenzie, and Dr. Dave Bright of the National Bureau of Standards for their support, space, and equipment, which helped make the calibration of this air sampler possible. We would also like to thank Dr. William Zoller and Dr. Glen Gordon at the University of Maryland for their support and suggestions in building and calibrating the HVDVI.

REFERENCES

Berglund, R. N., and Liu, B. Y. H. (1973). *Environ. Sci. Technol* 7:147–152.

Brown, J. H., Cook, K. M., Ney, F. G., and Hatch, T. (1950). *Am. J. Publ. Health* 40:450–458.

Charlson, R. J. (1969). *Environ. Sci. Technol.* 3:913–918.

Cohen, J. J., and Montan, D. N. (1967). *Amer. Ind. Hyg. Assoc. J.* 28:95–104.

Conner, W. D. (1966). *Air Pollut. Control Soc. J.* 16:35–38.

Currie, L. A., and Klouda, G. A. (1982). *Nuclear and Chemical Dating Techniques, Interpreting the Environmental Record* (L. A. Currie, ed.), ACS Symp. Series No. 176, pp. 159–185.

Derrick, M., and Moyers, J. (1981). *Analyt. Lett.* 14:1637–1652.

Dzubay, T. G., and Nelson, R. O. (1975). *Advances X-ray Anal.* 18:619–631.

Dzubay, T. G., and Stevens, R. K. (1975). *Environ. Sci. Technol.* 9:663–668.

Dzubay, T. G., Hines, L. E., and Stevens, R. K. (1976). *Atmos. Environ.* 10:229–234.

Fuchs, N. A. (1964). *The Mechanics of Aerosols*. Pergamon, New York, p. 154.

Hounam, R. F., and Sherwood, R. J. (1965). *Amer. Ind. Hyg. Assoc. J.* 26:122–131.

Jaenicke, R. (1980). *J. Aerosol Sci.* 11:577–588.

Loo, B. W., Jaklevic, J. M., and Goulding, F. S. (1976). In *Fine Particles* (B. Y. H. Liu, ed.), New York, pp. 311–350.

Loo, B. W., Adachi, R. S., et al. (1979). Lawrence Berkeley Laboratory Rep. No. LBL-8725, Berkeley, CA.

Lundgren, D. A. (1967). *Air Poll. Control Assoc. J.* 17:225–229.

Marple, V. A., and Chien, C. M. (1980). *Environ. Sci. Technol.* 14:976–984.

Marple, V. A., and Liu, B. Y. H. (1974). *Environ. Sci. Technol.* 8:648–654.

Marple, V. A., Liu, B. Y. H., and Whitby, K. T. (1974). *Fluids Eng. J.* 96:394–400.

May, K. R. (1945). *Sci. Instrum. J.* 22:187–195.

McFarland, A. R. (1978). *Environ. Sci. Technol.* 12:679–682.

Mercer, T. T. (1963). *Ann. Occup. Hyg.* 6:1–14.

Middleton, W. E. K. (1952). *Vision Through the Atmosphere*. University of Toronto Press, Toronto.

Mitchell, R. I., and Pilcher, J. M. (1959). *Ind. Eng. Chem.* 51:1039–1042.

Mulik, J., Puckett, R., Williams, D., and Sawicki, E. (1976). *Analyt. Lett.* 9:653–663.

Perera, F., and Karin Ahmed, A. (1979). *Respirable Particles: Impact of Airborne Fine Particulates on Health and the Environment*, Ballinger, Cambridge, MA.

Ranz, W. E., and Wong, J. B. (1952). *Ind. Eng. Chem.* 44:1371–1381.

Schlichting, H. (1968). *Boundary-Layer Theory*, 6th ed. (J. Kestin, transl.). McGraw-Hill, New York, p. 451.

Stevens, R. K., and Dzubay, T. G. (1978). *Atmos. Environ.* 12:55–68.

Swartz, D. B., Denton, M. B., and Moyers, J. L. (1973). *Am. Ind. Hyg. Assoc.* 34:429–439.

Willeke, K., and Whitby, K. (1975). *Air Poll. Control Assoc. J.* 25:529–534.

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Attachment 3

Comparative risk examples assembled by

TED HOLCOMBE

for smoking interaction significance consideration for the

October 1989 ARB/DHS DRAFT ARSENIC Report

Risk Assessment and Comparisons: An Introduction

RICHARD WILSON AND E. A. C. CROUCH

Risk assessment is presented as a way of examining risks so that they may be better avoided, reduced, or otherwise managed. Risk implies uncertainty, so that risk assessment is largely concerned with uncertainty and hence with a concept of probability that is hard to grasp. The results of even the simplest risk assessments need to be compared with similar assessments of commonplace situations to give them some meaning. We compare and contrast some risk estimates to display their similarities and differences.

EVERY DAY WE TAKE RISKS AND AVOID OTHERS. IT STARTS AS soon as we wake up. One of us lives in an old house that had old wiring. Each time he turned on the light, there was a small risk of electrocution. Every year about 200 people are electrocuted in the United States in accidents involving home wiring or appliances, representing a risk of death of about 10^{-6} per year, or 7×10^{-5} per lifetime. To reduce this risk, he got the wiring replaced. When we walk downstairs, we recall that 7000 people die each year in falls in U.S. homes. But most are over 65, so we pay little attention to this risk since both of us are younger than that.

How should we go to work? Walking is probably safer than using a bicycle, but would take five times as long and provide less healthful exercise. A car or, better, public transport would be both safer and faster. Expediency wins out, and the car comes out of the garage. Fortunately, the choice nowadays is not between horse or canoe—both of which are much more dangerous. The day has just begun, and already we are aware of several risks, and have made decisions about them.

Most of us act semi-automatically to minimize our risks. We also expect society to minimize the risks suffered by its members, subject to overriding moral, economic, or other constraints. In some cases these constraints will dominate, in others there will be trade-offs between the values assigned to risks and the constraints. Risk assessments, except in the simplest of circumstances, are not designed for making judgments, but to illuminate them (*1*). To effectively illuminate, and then to minimize, risks requires knowing what they are and how big they are. This knowledge usually is gained through experience, and the essence of risk assessment is the application of this knowledge of past mistakes (and deliberate actions) in an attempt to prevent new mistakes in new situations.

The results of risk assessments will necessarily be in the form of an estimate of probabilities for various events, usually injurious. The goal in performing a risk assessment is to obtain such estimates, although we consider the major value in performing a risk assessment is the exercise itself, in which (ideally) all aspects of some action are explored. The results, goals, and values of performing the risk assessment must be sharply contrasted with the cultural values assigned to the results. Such cultural values will presumably be factors influencing societal decisions and may differ even for risk estimates that are identical in probability.

Risk and Uncertainty

The concept of risk and the notion of uncertainty are closely related. We may say that the lifetime risk of cancer is 25%, meaning that approximately 25% of all people develop cancer in their lifetimes. Once an individual develops cancer, we can no longer talk about the risk of cancer, for it is a certainty. Similarly if a man lies dying after a car accident, the risk of his dying of cancer drops to near zero. Thus estimates of risks, insofar as they are expressions of uncertainty, will change as knowledge improves.

Different uncertainties appear in risk estimation in different ways (*2*). There is clearly a risk that an individual will be killed by a car if that person walks blindfolded across a crowded street. One part of this risk is stochastic; it depends on whether the individual steps off the curb at the precise moment that a car arrives. Another part of the risk might be systematic; it will depend on the nature of the fenders and other features of the car. Similarly, if two people are both heavy cigarette smokers, one may die of cancer and the other not; we cannot tell in advance. However there is a systematic difference in this respect between being, for instance, a heavy smoker and a gluttonous eater of peanut butter, which contains aflatoxin. Although aflatoxin is known to cause cancer (quite likely even in humans), the risk of cancer from eating peanut butter is much lower than that from smoking cigarettes. Exactly how much lower is uncertain, but it is possible to make estimates of how much lower and also to make estimates of how uncertain we are about the difference.

Some estimates of uncertainties are subjective, with differences of opinion arising because there is a disagreement among those assessing the risks. Suppose one wishes to assess the risk (to humans) of some new chemical being introduced into the environment, or of a new technology. Without any further information, all we can say about any measure of the risk is that it lies between zero and unity. Extreme opinions might be voiced; one person might say that we should initially assume a risk of unity, because we do not know that the chemical or technology is safe; another might take the opposite extreme, and argue that we should initially assume that there is zero risk, because nothing has been proven dangerous. Here and elsewhere, we argue that it is the task of the risk assessor to use whatever information is available to obtain a number between zero and one for a risk estimate, with as much precision as possible, together with an estimate of the imprecision. In this context, the statement "I do not know" can be viewed only as procrastination

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and not responsive to the request for a risk estimate (although this should not be read as condemning procrastination in all circumstances).

The second extreme mentioned, the assumption of zero risk, can arise because people and government agencies have a propensity to ignore anything that is not a proven hazard. We argue that this attitude is inconsistent if the objective is to improve the public health, may also lead to economic inefficiencies, and often leads to unnecessary contention between experts who disagree strongly. Fortunately, if risk assessors have been diligent in searching out hazards to assess, few hazards posing large risks will be missed in this way, so that there may be minor direct danger to human health from a continuation of the attitude.

Risk Estimation Based on Historical Data

The way in which risks are perceived is strongly correlated with the way in which they are calculated. Risks based on historical data are particularly easy to understand and are often perceived reliably. It is therefore easy to illustrate a risk calculated from historical data to understand some characteristics of risk estimation. There are plenty of data on automobile accidents (although never enough to make risk assessors happy). One thing that these data can tell us is the frequency of such accidents in the past and their trend through time. To make predictions, however, we must use a model. The simplest model is that there will be as many accidents next year as last, to within a statistical error of the square root of the number. A slightly more complicated, but perhaps more accurate, model might be to fit a mathematical function to numbers from previous years and to argue that next year's accidents will follow the trend given by this function. A possibly better and possibly more accurate model still might use all available information that might influence accident trends. For example, an oil embargo with a concomitant rise in oil price and reduction in automobile travel would be likely to reduce the risk of accident. In any event, it becomes clear that it is impossible to calculate any risk without a model of some sort, even the simple one that tomorrow will be like today.

Risks of New Technologies

We can only use the historical approach to estimating risks when the hazard (for example, technology, chemical, or simply some action) has been present for some time and the risk is large enough to be directly measured (although when it is not large enough to be measured, an upper limit may be calculated, if one assumes some sort of model). If there is no historical database for the hazard (a new power plant or industrial facility, for instance), one approach is to consider it in separate parts, calculating the risks from each part and adding them together to estimate a risk for the whole. For example, all possible chains of events from an initiator to a final accident are followed in an "event tree," with the probabilities of each event in the tree being estimated from historical data in different situations.

A particularly well-known example is the calculation of the probability of a severe accident at a nuclear power plant (*3*). That this procedure has at least a partial validity is due to the fact that the design of nuclear power plants proceeded in approximately this favorable way; attempts were made to imagine all major accident possibilities, "maximum credible accidents" or "design basis accidents," and then to add an independent device to prevent this accident from having severe consequences. To the extent that the added safety device is independent, the failure probability is independent, and the small overall accident probability is the product of individual failure probabilities which are larger.

Table 1. Comparison of several common radiation risks.

Action	Dose (mrem/year)	Cancers if all U.S. population exposed (assuming linearity)
Medical x-rays	40	1100
Radon gas (1.5 pCi/liter, equivalent dose)*	500	13,500
Potassium in own body	30	1000
Cosmic radiation at sea level	40	1100
Cosmic radiation at Denver	65	1800
Dose to average resident near Chernobyl first year	5000	Not relevant
One transcontinental round trip by air	5	135
Average within 20 miles of nuclear plant	0.02	>1

*The radon exposure is to the lungs and cannot be directly compared to whole body external exposure. The comparison here is on the basis of the same magnitude of risk. The uncertainty of the radon number is at least a factor of 3.

Table 2. Some commonplace risks (mean values with uncertainty).

Action	Annual risk	Uncertainty
Motor vehicle accident (total)	2.4×10^{-4}	10%
Motor vehicle accident (pedestrian only)	4.2×10^{-5}	10%
Home accidents	1.1×10^{-4}	5%
Electrocution	5.3×10^{-6}	5%
Air pollution, eastern United States	2×10^{-4}	Factor of 20 downward only
Cigarette smoking, one pack per day	3.6×10^{-3}	Factor of 3
Sea-level background radiation (except radon)	2×10^{-3}	Factor of 3
All cancers	2.8×10^{-3}	10%
Four tablespoons peanut butter per day	8×10^{-6}	Factor of 3
Drinking water with EPA limit of chloroform	6×10^{-7}	Factor of 10
Drinking water with EPA limit of trichloroethylene	2×10^{-9}	Factor of 10
Alcohol, light drinker	2×10^{-5}	Factor of 10
Police killed in line of duty (total)	2.2×10^{-4}	20%
Police killed in line of duty (by felons)	1.3×10^{-4}	10%
Frequent flying professor	5×10^{-5}	50%
Mountaineering (mountaineers)	6×10^{-4}	50%

Risks by Analogy: Carcinogenic Risks

Some carcinogenic risks may be estimated from historical data. But this is complicated by the time delay between the insult and the final cancer, one reason why causality is hard to prove if the risk is small. This is the difficult field of epidemiology.

Although some of the largest cancer risks have been identified through the use of epidemiology (*4*), preventive public health suggests that we endeavor to estimate risks even where no historical data exist and the risk is small. This is often done by analogy with the cancer risks to animals, usually rodents, which are deliberately exposed to large enough quantities of pollutant so that an effect is observed. To use these data to estimate the risk at low doses in people involves (to oversimplify matters) two difficult steps: the comparison of carcinogenic potency in animal and man (*5–7*) and the extrapolation from a high dose to a low dose. Because both steps require a certain amount of theory, they are controversial. Indeed, there are those who regard the uncertainty as so great that they prefer not to provide numerical estimates of risk (*8, 9*), although they may order materials in carcinogenic potency. The differe

Ranking Possible Carcinogenic Hazards

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This review discusses reasons why animal cancer tests cannot be used to predict absolute human risks. Such tests, however, may be used to indicate that some chemicals might be of greater concern than others. Possible hazards to humans from a variety of rodent carcinogens are ranked by an index that relates the potency of each carcinogen in rodents to the exposure in humans. This ranking suggests that carcinogenic hazards from current levels of pesticide residues or water pollution are likely to be of minimal concern relative to the background levels of natural substances, though one cannot say whether these natural exposures are likely to be of major or minor importance.

EPIDEMIOLOGISTS ESTIMATE THAT AT LEAST 70% OF HUMAN cancer would, in principle, be preventable if the main risk and antirisk factors could be identified (*1*). This is because the incidence of specific types of cancer differs markedly in different parts of the world where people have different life-styles. For example, colon and breast cancer, which are among the major types of cancer in the United States, are quite rare among Japanese in Japan, but not among Japanese-Americans. Epidemiologists are providing important clues about the specific causes of human cancer, despite inherent methodological difficulties. They have identified tobacco as an avoidable cause of about 30% of all U.S. cancer deaths and of an even larger number of deaths from other causes (*1, 2*). Less specifically, dietary factors, or their absence, have been suggested in many studies to contribute to a substantial proportion of cancer deaths, though the intertwined risk and antirisk factors are being identified only slowly (*1, 3, 4*). High fat intake may be a major contributor to colon cancer, though the evidence is not as definitive as that for the role of saturated fat in heart disease or of tobacco in lung cancer. Alcoholic beverage consumption, particularly by smokers, has been estimated to contribute to about 3% of U.S. cancer deaths (*1*) and to an even larger number of deaths from other causes. Progress in prevention has been made for some occupational factors, such as asbestos, to which workers used to be heavily exposed, with delayed effects that still contribute to about 2% of U.S. cancer deaths (*1, 5*). Prevention may also become possible for hormone-related cancers such as breast cancer (*1, 6*), or virus-related cancers such as liver cancer (hepatitis B) and cancer of the cervix (papilloma virus HPV16) (*1, 7*).

Animal bioassays and in vitro studies are also providing clues as to which carcinogens and mutagens might be contributing to human cancer. However, the evaluation of carcinogenicity in rodents is expensive and the extrapolation to humans is difficult (*8–11*). We will use the term "possible hazard" for estimates based on rodent cancer tests and "risk" for those based on human cancer data (*10*).

Extrapolation from the results of rodent cancer tests done at high doses to effects on humans exposed to low doses is routinely attempted by regulatory agencies when formulating policies attempting to prevent future cancer. There is little sound scientific basis for this type of extrapolation, in part due to our lack of knowledge about mechanisms of cancer induction, and it is viewed with great unease by many epidemiologists and toxicologists (*5, 9–11*). Nevertheless, to be prudent in regulatory policy, and in the absence of good human data (almost always the case), some reliance on animal cancer tests is unavoidable. The best use of them should be made even though few, if any, of the main avoidable causes of human cancer have typically been the types of man-made chemicals that are being tested in animals (*10*). Human cancer may, in part, involve agents such as hepatitis B virus, which causes chronic inflammation; changes in hormonal status; deficiencies in normal protective factors (such as selenium or β-carotene) against endogenous carcinogens (*12*); lack of other anticarcinogens (such as dietary fiber or calcium) (*4*); or dietary imbalances such as excess consumption of fat (*3, 4, 12*) or salt (*13*).

There is a need for more balance in animal cancer testing to emphasize the foregoing factors and natural chemicals as well as synthetic chemicals (*12*). There is increasing evidence that our normal diet contains many rodent carcinogens, all perfectly natural or traditional (for example, from the cooking of food) (*12*), and that no human diet can be entirely free of mutagens or agents that can be carcinogenic in rodent systems. We need to identify the important causes of human cancer among the vast number of minimal risks. This requires knowledge of both the amounts of a substance to which humans are exposed and its carcinogenic potency.

Animal cancer tests can be analyzed quantitatively to give an estimate of the relative carcinogenic potencies of the chemicals tested. We have previously published our Carcinogenic Potency Database, which showed that rodent carcinogens vary in potency by more than 10 millionfold (*14*).

This article attempts to achieve some perspective on the plethora of possible hazards to humans from exposure to known rodent carcinogens by establishing a scale of the possible hazards for the amounts of various common carcinogens to which humans might be chronically exposed. We view the value of our calculations not as providing a basis for absolute human risk assessment, but as a guide to priority setting. One problem with this type of analysis is that few of the many natural chemicals we are exposed to in very large amounts (relative to synthetic chemicals) have been tested in animals for carcinogenicity. Thus, our knowledge of the background levels of human exposure to animal carcinogens is fragmentary, biased in favor of synthetic chemicals, and limited by our lack of knowledge of human exposures.

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Ranking of Possible Carcinogenic Hazards

Since carcinogens differ enormously in potency, a comparison of possible hazards from various carcinogens ingested by humans must take this into account. The measure of potency that we have developed, the TD_{50}, is the daily dose rate (in milligrams per kilogram) to halve the percent of tumor-free animals by the end of a standard lifetime (*14*). Since the TD_{50} (analogous to the LD_{50}) is a dose rate, the lower the TD_{50} value the more potent the carcinogen. To calculate our index of possible hazard we express each human exposure (daily lifetime dose in milligrams per kilogram) as a percentage of the rodent TD_{50} dose (in milligrams per kilogram) for each carcinogen. We call this percentage HERP [*H*uman *E*xposure dose/*R*odent *P*otency dose]. The TD_{50} values are taken from our ongoing Carcinogenic Potency Database (currently 3500 experiments on 975 chemicals), which reports the TD_{50} values estimated from experiments in animals (*14*). Human exposures have been estimated from the literature as indicated. As rodent data are all calculated on the basis of lifetime exposure at the indicated daily dose rate (*14*), the human exposure data are similarly expressed as lifelong daily dose rates even though the human exposure is likely to be less than daily for a lifetime.

It would be a mistake to use our HERP index as a direct estimate of human hazard. First, at low dose rates human susceptibility may differ systematically from rodent susceptibility. Second, the general shape of the dose-response relationship is not known. A linear dose response has been the dominant assumption in regulating carcinogens for many years, but this may not be correct. If the dose responses are not linear but are actually quadratic or hockey-stick shaped or show a threshold, then the actual hazard at low dose rates might be much less than the HERP values would suggest. An additional difficulty is that it may be necessary to deal with carcinogens that differ in their mechanisms of action and thus in their dose-response relationship. We have therefore put an asterisk next to HERP values for carcinogens that do not appear to be active through a genotoxic (DNA damaging or mutagenic) mechanism (*15*) so that comparisons can be made within the genotoxic or nongenotoxic classes.

Table 1 presents our HERP calculations of possible cancer hazards in order to compare them within several categories so that, for example, pollutants of possible concern can be compared to natural carcinogens in the diet. A convenient reference point is the possible hazard from the carcinogen chloroform in a liter of average (U.S.) chlorinated tap water, which is close to a HERP of 0.001%. Chloroform is a by-product of water chlorination, which protects us from pathogenic viruses and bacteria.

Contaminated water. The possible hazards from carcinogens in contaminated well water [for example, Santa Clara ("Silicon") Valley, California, or Woburn, Massachusetts] should be compared to the possible hazard of ordinary tap water (Table 1). Of 35 wells shut down in Santa Clara Valley because of their supposed carcinogenic hazard, only two have HERP values greater than ordinary tap water. Well water is not usually chlorinated and typically lacks the chloroform present in chlorinated tap water. Water from the most polluted well (HERP = 0.004% per liter for trichloroethylene), as indicated in Table 1, has a HERP value orders of magnitude less than for the carcinogens in an equal volume of cola, beer, or wine. Its HERP value is also much lower than that of many of the common natural foods that are listed in Table 1, such as the average peanut butter sandwich. Caveats for any comparisons are given below. Since the consumption of tap water is only about 1 or 2 liters per day, the animal evidence provides no good reason to expect that chlorination of water or current levels of man-made pollution of water pose a significant carcinogenic hazard.

Pesticide residues. Intake of man-made pesticide residues from food in the United States, including residues of industrial chemicals such as polychlorinated biphenyls (PCBs), averages about 150 μg/day. Most (105 μg) of this intake is composed of three chemicals (ethylhexyl diphenyl phosphate, malathion, and chlorpropham) shown to be noncarcinogenic in tests in rodents (*16*). A carcinogenic pesticide residue in food of possible concern is DDE, the principal metabolite (>90%) of DDT (*16*). The average U.S. daily intake of DDE from DDT (HERP = 0.0003%) is equivalent to the HERP of the chloroform in one glass of tap water and thus appears to be insignificant compared to the background of natural carcinogens in our diet (Table 1). Even daily consumption of 100 times the average intake of DDE/DDT or PCBs would produce a possible hazard that is small compared to other common exposures shown in Table 1.

Nature's pesticides. We are ingesting in our diet at least 10,000 times more by weight of natural pesticides than of man-made pesticide residues (*12*). These are natural "toxic chemicals" that have an enormous variety of chemical structures, appear to be present in all plants, and serve to protect plants against fungi, insects, and animal predators (*12*). Though only a few are present in each plant species, they commonly make up 5 to 10% of the plant's dry weight (*12*). There has been relatively little interest in the toxicology or carcinogenicity of these compounds until quite recently, although they are by far the main source of "toxic chemicals" ingested by humans. Only a few dozen of the thousands present in the human diet have been tested in animal bioassays, and only some of these tests are adequate for estimating potency in rodents (*14*). A sizable proportion of those that have been tested are carcinogens, and many others have been shown to be mutagens (*12*), so it is probable that many more will be found to be carcinogens if tested. Those shown in Table 1 are: estragole (HERP = 0.1% for a daily 1 g of dried basil), safrole (HERP = 0.2% for a daily natural root beer), symphytine (a pyrrolizidine alkaloid, 0.03% for a daily cup of comfrey tea), comfrey tablets sold in health food stores (6.2% for a daily dose), hydrazines in mushrooms (0.1% for one daily raw mushroom), and allyl isothiocyanate (0.07% for a daily 5 g of brown mustard).

Plants commonly produce very much larger amounts of their natural toxins when damaged by insects or fungi (*12*). For example, psoralens, light-activated carcinogens in celery, increase 100-fold when the plants are damaged by mold and, in fact, can cause an occupational disease in celery-pickers and in produce-checkers at supermarkets (*12, 17*).

Molds synthesize a wide variety of toxins, apparently as antibiotics in the microbiological struggle for survival: over 300 mycotoxins have been described (*18*). They are common pollutants of human food, particularly in the tropics. A considerable percentage of those tested have been shown to be mutagens and carcinogens: some, such as aflatoxin and sterigmatocystin, are among the most potent known rodent carcinogens. The potency of aflatoxin in different species varies widely; thus, a bias may exist as the HERP uses the most sensitive species. The aflatoxin content of U.S. peanut butter averages 2 ppb, which corresponds to a HERP of 0.03% for the peanut butter in an average sandwich (Table 1). The Food and Drug Administration (FDA) allows ten times this level (HERP = 0.3%), and certain foods can often exceed the allowable limit (*18*). Aflatoxin contaminates wheat, corn (perhaps the main source of dietary aflatoxin in the United States), and nuts, as well as a wide variety of stored carbohydrate foodstuffs. A carcinogenic, though less potent, metabolite of aflatoxin is found in milk from cows that eat moldy grain.

There is epidemiologic evidence that aflatoxin is a human carcinogen. High intake in the tropics is associated with a high rate of cancer, at least among those chronically infected with the hepatit

virus (*19, 20*). Considering the potency of those mold toxins that have been tested and the widespread contamination of food with molds, they may represent the most significant carcinogenic pollution of the food supply in developing countries. Such pollution is much less severe in industrialized countries, due to refrigeration and modern techniques of agriculture and storage, including use of synthetic pesticides and fumigants.

Preparation of foods and beverages can also produce carcinogens. Alcohol has been shown to be a human carcinogen in numerous epidemiologic studies (*1, 21*). Both alcohol and acetaldehyde, its

Table 1. Ranking possible carcinogenic hazards. *Potency of carcinogens*: A number in parentheses indicates a TD_{50} value not used in HERP calculation because it is the less sensitive species; (−) = negative in cancer test. (+) = positive for carcinogenicity in test(s) not suitable for calculating a TD_{50}; (?) = is not adequately tested for carcinogenicity. TD_{50} values shown are averages calculated by taking the harmonic mean of the TD_{50}'s of the positive tests in that species from the Carcinogenic Potency Database. Results are similar if the lowest TD_{50} value (most potent) is used instead. For each test the target site with the lowest TD_{50} value has been used. The average TD_{50} has been calculated separately for rats and mice, and the more sensitive species is used for calculating the possible hazard. The database, with references to the source of the cancer tests, is complete for tests published through 1984 and for the National Toxicology Program bioassays through June 1986 (*14*). We have not indicated the route of exposure or target sites or other particulars of each test, although these are reported in the database. *Daily human exposure*: We have tried to use average or reasonable daily intakes to facilitate comparisons. In several cases, such as contaminated well water or factory exposure to EDB, this is difficult to determine, and we give the value for the worst found and indicate pertinent information in the References and Notes. The calculations assume a daily dose for a lifetime; where drugs are normally taken for only a short period we have bracketed the HERP value. For inhalation exposures we assume an inhalation of 9,600 liters per 8 hours for the workplace and 10,800 liters per 14 hours for indoor air at home. *Possible hazard*: The amount of rodent carcinogen indicated under carcinogen dose is divided by 70 kg to give a milligram per kilogram of human exposure, and this human dose is given as the percentage of the TD_{50} dose in the rodent (in milligrams per kilogram) to calculate the *Human Exposure/Rodent Potency* index (HERP).

Possible hazard: HERP (%)	Daily human exposure	Carcinogen dose per 70-kg person	Potency of carcinogen: TD_{50} (mg/kg)		References
			Rats	Mice	
		Environmental pollution			
0.001*	Tap water, 1 liter	Chloroform, 83 μg (U.S. average)	(119)	90	*96*
0.004*	Well water, 1 liter contaminated (worst well in Silicon Valley)	Trichloroethylene, 2800 μg	(−)	941	*97*
0.0004*	Well water, 1 liter contaminated, Woburn	Trichloroethylene, 267 μg	(−)	941	*98*
0.0002*		Chloroform, 12 μg	(119)	90	
0.0003*		Tetrachloroethylene, 21 μg	101	(126)	
0.008*	Swimming pool, 1 hour (for child)	Chloroform, 250 μg (average pool)	(119)	90	*99*
0.6	Conventional home air (14 hour/day)	Formaldehyde, 598 μg	1.5	(44)	*100*
0.004		Benzene, 155 μg	(157)	53	
2.1	Mobile home air (14 hour/day)	Formaldehyde, 2.2 mg	1.5	(44)	*28*
		Pesticide and other residues			
0.0002*	PCBs: daily dietary intake	PCBs, 0.2 μg (U.S. average)	1.7	(9.6)	*101*
0.0003*	DDE/DDT: daily dietary intake	DDE, 2.2 μg (U.S. average)	(−)	13	*16*
0.0004	EDB: daily dietary intake (from grains and grain products)	Ethylene dibromide, 0.42 μg (U.S. average)	1.5	(5.1)	*102*
		Natural pesticides and dietary toxins			
0.003	Bacon, cooked (100 g)	Dimethylnitrosamine, 0.3 μg	(0.2)	0.2	*40*
0.006		Diethylnitrosamine, 0.1 μg	0.02	(+)	
0.003	Sake (250 ml)	Urethane, 43 μg	(41)	22	*24*
0.03	Comfrey herb tea, 1 cup	Symphytine, 38 μg (750 μg of pyrrolizidine alkaloids)	1.9	(?)	*103*
0.03	Peanut butter (32 g; one sandwich)	Aflatoxin, 64 ng (U.S. average, 2 ppb)	0.003	(+)	*18*
0.06	Dried squid, broiled in gas oven (54 g)	Dimethylnitrosamine, 7.9 μg	(0.2)	0.2	*37*
0.07	Brown mustard (5 g)	Allyl isothiocyanate, 4.6 mg	96	(−)	*47*
0.1	Basil (1 g of dried leaf)	Estragole, 3.8 mg	(?)	52	*48*
0.1	Mushroom, one raw (15 g) (*Agaricus bisporus*)	Mixture of hydrazines, and so forth	(?)	20,300	*104*
0.2	Natural root beer (12 ounces; 354 ml) (now banned)	Safrole, 6.6 mg	(436)	56	*105*
0.008	Beer, before 1979 (12 ounces; 354 ml)	Dimethylnitrosamine, 1 μg	(0.2)	0.2	*38*
2.8*	Beer (12 ounces; 354 ml)	Ethyl alcohol, 18 ml	9110	(?)	*23*
4.7*	Wine (250 ml)	Ethyl alcohol, 30 ml	9110	(?)	*23*
6.2	Comfrey-pepsin tablets (nine daily)	Comfrey root, 2700 mg	626	(?)	*103*
1.3	Comfrey-pepsin tablets (nine daily)	Symphytine, 1.8 mg	1.9	(?)	
		Food additives			
0.0002	AF-2: daily dietary intake before banning	AF-2 (furylfuramide), 4.8 μg	29	(131)	*44*
0.06*	Diet Cola (12 ounces; 354 ml)	Saccharin, 95 mg	2143	(−)	*106*
		Drugs			
[0.3]	Phenacetin pill (average dose)	Phenacetin, 300 mg	1246	(2137)	*51*
[5.6]	Metronidazole (therapeutic dose)	Metronidazole, 2000 mg	(542)	506	*107*
[14]	Isoniazid pill (prophylactic dose)	Isoniazid, 300 mg	(150)	30	*108*
16*	Phenobarbital, one sleeping pill	Phenobarbital, 60 mg	(+)	5.5	*50*
17*	Clofibrate (average daily dose)	Clofibrate, 2000 mg	169	(?)	*52*
		Occupational exposure			
5.8	Formaldehyde: Workers' average daily intake	Formaldehyde, 6.1 mg	1.5	(44)	*109*
140	EDB: Workers' daily intake (high exposure)	Ethylene dibromide, 150 mg	1.5	(5.1)	*55*

*Asterisks indicate HERP from carcinogens thought to be nongenotoxic.

ATTACHMENT B

TESTIMONY FOR AMERICAN INDUSTRIAL HEALTH COUNCIL OSHA HEARINGS BY PROF. RICHARD WILSON ON SEPTEMBER 25, 1978

Key statements in Prof. Wilson's testimony on relative risk:

1. "Associated with a linear no threshold theory is usually the statement that at low doses we should measure a long term average exposure to calculate the carcinogenic risk. Fluctuations about this average, while they might affect the actual risk if a threshold is assumed, will not affect the risk if the linear NO threshold is used. This (linear, no threshold) theory remains a conservative upper bound to the risk even in the presence of exposure fluctuations" (emphasis added - pg. 2);

2. Quote from the Advisory Committee on Biological Effects of Ionizing Radiation, National Academy of Sciences, November 1972: "...whether we regard a risk as acceptable or not depends on how avoidable it is, and to the extent not avoidable, how it compares with the risks of alternative options and those normally accepted by society" (pg. 5);

3. "...I derive a number that for every $36 million spent on construction one life will be lost" (pg. 48);

4. "I suggest that if the upper limit to the risk comes out less than 1 in 100,000 per year of exposure (10^{-5}/yr) the question (of reducing remaining risks) can (currently) be ignored by OSHA" (pg. 25);

5. "I suggest a figure for the appropriate amount industry should pay for reducing a risk (is) $10 per person per year for a risk of 10^{-5} per person per year. This corresponds to a cost of $1,000,000 for every calculated hypothetical life saved" (pp. 32-33); and

6. "... the Commissioner of FDA (U.S. Food and Drug Administration) (in February 1977) recommended a lifetime risk of 10^{-6} as acceptable -- which is a yearly risk of 1.5×10^{-8}. At first sight this proposal seems inconsistent with mine. However, his procedure for calculating risk, the Mantel-Bryan extrapolation procedure, is less conservative in most cases than the simpler more easily justified procedure here. The extra factor of conservatism is about the factor of difference. My proposal would give the same result as that of FDA's commissioner in all applications of interest" (pg. 63).

TABLE II

Risks in Sports[42, 43, 44, 45, 46, 47, 48]

		Deaths 1975	Risk/yr.
Football	Averaged over Participants		4×10^{-5}
Automobile racing			1.2×10^{-3}
Horse racing			1.3×10^{-3}
Motorcycle racing			1.8×10^{-3}
Power boating			1.7×10^{-4}
Boxing (amateur)	40 hrs/yr engaged in sports		2×10^{-5}
Skiing			3×10^{-5}
Canoeing			4×10^{-4}
Rock climbing (U.S.)			10^{-3}
Sunbathing, mountain climbing (skin cancer risk/curable)		300,000 cases	5×10^{-3}
Fishing (drowning)	Averaged over fishing licenses	343	1.0×10^{-5}
Drowning (all recreational causes) all over U.S.		4110	1.9×10^{-5}
Bicycling (assuming 1 person per bicycle		1000	10^{-5}

[42] B.G. Ferris, New Eng. J. Med., 268, 430 (1963).

[43] F.D. Sowby, Health Phys., 11, 879 (1965).

[44] C. Starr, Science, 165, 1232 (1969).

[45] K.S. Clarke, J. Am. Med. Assoc., 197, 894 (1966).

[46] Statistical Bulletin, Metropolitan Life Insurance Co., May 1977.

[47] Accident Facts, 1976 edition.

[48] Statistical Abstract of the U.S.

TABLE III

Commonplace and Therefore Accepted Risks of Death (non-cancerous)

		No. of Deaths in 1974	Risk/Year
Motor Vehicle (in 1975)	Total	46,000	2.2×10^{-4}
	Pedestrian (certainly involuntary)	8,600	4×10^{-5}
Home Accidents (1975)		25,500	1.2×10^{-5}
Alcohol—cirrhosis of the liver (1974)			1.6×10^{-4}
Alcohol—cirrhosis of the liver (moderate drinker)			4×10^{-5}
Air travel: one transcontinental trip/year			3×10^{-6}
jet flying professor			10^{-4}
Accidental poisoning—solids and liquids		1,274	6×10^{-6}
gases and vapors		1,518	7×10^{-6}
Inhalation and ingestion of objects		2,991	1.4×10^{-5}
Electrocution		1,157	5×10^{-6}
Falls		16,339	7.7×10^{-5}
Tornados	Average over several years	160	5×10^{-7}
Hurricanes	Average over several years	118	4×10^{-7}
Lightning	Average over several years	90	4×10^{-7}
Air pollution (total U.S.) estimate (sulphates)		30,000	1.5×10^{-4}
Air pollution (benzo (a) pyrene) urban U.S.—cancer risk			3×10^{-5}
Vaccination for small pox (per occasion)			3×10^{-6}
Living for one year downstream of a dam (calculated)			5×10^{-5}

Sources: Accident Facts, 1976 Edition
Statistical Abstract of the U.S.
Alcohol—detailed discussion in appendix
Air travel—detailed discussion in appendix
Air pollution—detailed discussion in appendix
Dam failure—UCLA report, UCLA-ENG-7423, Payyaswamy, et. al., March 1974

TABLE IV

Commonplace Risks of Daily Life (Cancer Risks)

	Risk/year
Cosmic ray risks	
One transcontinental flight/year	5×10^{-7}
Airline pilot 50 hrs./mo. @ 35,000 feet	5×10^{-5}
Frequent airline passenger	1.5×10^{-5}
Living in Denver compared to N.Y.	10^{-5}
One summer (4 months) camping at 15,000 feet	10^{-5}
Other radiation risks	
Average U.S. diagnostic medical x-rays	10^{-5}
Increase in risk from living in a brick building (with radioactive bricks) compared to wood	5×10^{-6}
Natural background at sea level	1.5×10^{-5}
Eating and drinking	
One diet soda/day (saccharin)	10^{-5}
Average U.S. saccharin consumption	2×10^{-6}
Four tablespoons peanut butter/day (aflatoxin)	4×10^{-5}
One pint milk per day (aflatoxin)	10^{-5}
Miami or New Orlean drinking water	1.2×10^{-6}
1/2 lb. charcoal broiled steak once a week (cancer risk only; heart attack, etc. additional)	4×10^{-7}
Alcohol—averaged over smokers and non-smokers	5×10^{-5}
Alcohol—light drinker (1 beer/day)	2×10^{-5}
Tobacco	
Smoker, cancer only	1.2×10^{-3}
Smoker, all effects (including heart disease)	3×10^{-3}
Person in room with smoker	10^{-5}
Miscellaneous	
Taking contraceptive pills regularly	2×10^{-5}

Sources: See Appendix I

TABLE V

Current Occupational Risks

	Number of Fatalities (in 1975 unless stated)	Risk/yr. (per man)
Acceptable at 1 ppm, hypothetical risk		10^{-4}
Mining & Quarrying (accident only)	500	6×10^{-4}
Coal mining - accident (average 1970-74)	180	1.3×10^{-3}
- black lung disease (1969)	1135	8×10^{-3}
Agriculture - total	2100	6×10^{-4}
tractor driver (1 driver/tractor)		1.3×10^{-4}
Trade	1200	6×10^{-4}
Manufacturing	1500	8×10^{-5}
Service	1800	9×10^{-5}
Government	1100	1.1×10^{-4}
Transportation & Utilities	1600	3.3×10^{-4}
Airline Pilot		3×10^{-4}
Truck driver (1 driver/truck)	400	10^{-4}
Jet flying consultant & professor		10^{-4}
Steel worker (accident only) (1969-71)	66	2.8×10^{-4}
Railroad worker (1974) (all accidents excluding grade crossing)	688	1.3×10^{-3}
Fire fighters (1971-72 average)		8×10^{-4}

Source: Accident facts, 1976 Edition, p.23,87.
National Safety Council, 444 N. Michigan Ave., Chicago, Ill., 60611
Also, (coal mining black lung, rail worker, steel worker)
W. Baldewicz, et al UCLA-ENG-7485 Nov. 1974)
Airline pilot - see appendix
Statistical Abstract of the U.S., 1976 Ed. Table 1200

BORAX RESEARCH

November 30, 1989

Mr. Robert Barham, Chief
Toxic Air Contaminant Identification Branch
Air Resources Board
1102 Q Street
P. O. Box 2815
Sacramento, CA 95812

Attn: Inorganic Arsenic

Dear Mr. Barham:

Enclosed are the United States Borax & Chemical Corporation and U. S. Borax Research Corporation's (U.S. Borax) comments on the draft report on inorganic arsenic which were prepared by our consultant, Dr. I. Harding-Barlow. It is our opinion that thirty days is too short a time to adequately review and comment on such an extensive document.

These comments are directed towards the Executive Summary and to Part B, Health Effects of Arsenic Compounds. Supporting our comments on Part B are two sections consisting of Appendix A, addressing the smelter data, and References, used in our discussion but not quoted by DHS/ARB.

We suggest some wording changes in the Executive Summary to clarify and more accurately describe the contents of Part B.

In general, we have found the draft report to be incomplete and in need of reworking. Key data are omitted, and some conclusions need reviewing. These are identified in our attached Summary of Findings on the Executive Summary and Part B - Health Effects.

The Risk Assessment, Section 11, needs review and re-examination on four major points:

A) Re-evaluation of the "practical" threshold concept, due to EPA's change in position.

B) Re-evaluation of the exposure data for workers employed prior to 1945.

C) Re-evaluation of this Risk Assessment in light of the proposed TOTAL Risk Assessment involving all routes of exposure (DHS and ARB), and

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D) Re-evaluation of the interaction of arsenic and sulfur dioxide.

Appendix B (Initiation and Promotion) and Appendix E (Smoking) need peer review by top-flight specialists in those areas in order to be accepted by the scientific community.

The staff of the Air Resources Board suggests that "there is not sufficient available scientific evidence at this time to support the identification of an exposure level below which carcinogenic effects would not have some probability of occurring; the DHS staff therefore recommends that inorganic arsenic be treated as having no identified threshold" (Executive Summary, page 1). U.S. Borax believes that the Air Resources Board can and should establish a reasonable tolerance/"practical" threshold level which is based upon the evidence presented in our comments on the essentiality, detoxification mechanism, metabolism, confounding factors, and smelter data.

U.S. Borax strongly suggests the Air Resources Board and Department of Health Services staff review and rewrite the draft report with the help of the U.S. Borax document dated March 1, 1989 titled, "An Analysis of the Potential of Arsenic as a Carcinogen and Reproductive Toxicant."

In addition, we especially urge the Air Resources Board and Department of Health Services to convene a Roundtable-Workshop of interested scientists to discuss the problems noted in Section 11 and other issues such as a reasonable tolerance/practical threshold.

Thank you for the opportunity to review and comment on the draft documents. If you require additional information on any of our comments, please contact me at 714-490-6000.

Sincerely,

Philip L. Strong, Ph. D.
Manager, Product Safety

/jb

Attachments:
1) Comments on the Executive Summary
2) Summary of Findings on Executive Summary and Part B - Health Effects
3) Comments on Part B
4) Appendix A - Smelter Data
5) References used in the discussion but not quoted by DHS/ARB

COMMENTS ON THE EXECUTIVE SUMMARY

Page 3, Paragraph 3:
What evidence is there for stating that arsenic trioxide is "likely to be the most carcinogenic form"?

If arsenic trioxide is the most carcinogenic form, should it not have its own Risk Assessment and ALL other arsenicals a separate one, or even be declared non-carcinogenic?

Hood (1983) is INCORRECTLY QUOTED as stating arsenic (+5) is "more teratogenic" than arsenic (+3).

Page 5, Paragraph 2:
How recent is the estimate 6ug per pack of cigarettes? It seems high for present U.S. conditions of tobacco growing. Also what assumptions were made concerning inhalation?

Page 5, Paragraph 4:
It would seem more appropriate to say "A number of" rather than "Numerous".

Page 5, Paragraph 4:
It would seem appropriate to say "do not totally explain the association" rather than "does not explain the strong association". It is assumed that "low doses" applies to arsenic levels. The level of "low" needs to be stated. Whereas the data are strong enough to show an interaction between smoking and smelter exposure, it is questionable to "over-extrapolate" to three levels of smoking.

Page 5, Paragraph 6:
Arsenic induces chromosomal aberrations and elevated levels of sister chromatid exchanges; it MAY inhibit DNA repair; it does not cause base-pair substitution or frame-shift mutations. ALL ELSE IS SPECULATION, NOT FACT.

SUMMARY OF FINDINGS ON EXECUTIVE SUMMARY AND PART B - HEALTH EFFECTS

1. Executive Summary, certain sections need rewording.
2. Section 1 (Summary) sections needs to be reworked.
3. Section 2 (Metabolism) is incomplete and key data are omitted.
4. Section 3 (Essentiality) is incomplete and key data are omitted.
5. Section 5 (Toxicity) is incomplete.
6. Section 6 (Reproductive Toxicology) is incomplete, key data are omitted, some conclusions need reviewing and there is a major mis-quote.
7. Section 7 (Genotoxicity) is incomplete, key data are omitted and conclusions are drawn beyond the strength of the data.
8. Section 8 (Animal Experiments) needs some review.
9. Section 9 (Epidemiology) is incomplete and key data are omitted.
10. Section 10 (Mechanisms of Carcinogenicity) needs some review.
11. Section 11 (Risk Assessment) needs review and re-examination on four major points:
    a) Re-evaluation of the "practical" threshold concept due to EPA's change in position.
    b) Re-evaluation of the exposure data for workers employed prior to 1945.
    c) Re-evaluation of this Risk Assessment in light of the proposed TOTAL Risk Assessment involving all routes of exposure (DHS and ARB), and
    d) Re-evaluation of the interaction of arsenic and sulfur dioxide.
12. Appendix B (Initiation vs. Promotion) not main stream science, hence needs top-flight specialist peer review in order to be given wide acceptance.
13. Appendix E (Smoking) not main stream science, hence needs top-flight specialist peer review in order to be given wide acceptance.

COMMENTS ON PART B

Page 1-1, Paragraph 3:
Adverse reproductive effects "as the most sensitive noncarcinogenic endpoints" have not been proven. As stated in this paragraph, reproductive toxicity was observed among the controls. Nagymajtenyi et al. (1985) found that ONLY the highest dose had caused statistically significant chromosomal and fetotoxic effects. The number of cells with aberrations increased from 6/200 in the control group (OugAs(+3)/m3) to 10/200, 13/200 and 24/200 in the low (200ugAs(+3)/m3), medium (2200ugAs(+3)/m3) and high (21600ugAs(+3)/m3) dose groups, respectively.

Other data available would seem to indicate that adverse affects would only take place at the upper end of the range 50-500ugAs/m3, therefore too much is being made of the 50ugAs/m3 value.

Page 1-2, Paragraph 1:
It should be noted that these particular smelter workers were also exposed to LEAD.

Page 1-2, Paragraph 3:
This paragraph DOES NOT REFLECT THE CONCLUSIONS Section 7, stated on page 7-7. "Arsenic is genotoxic", is far too positive and general. The statement, "Arsenic compounds inhibit DNA repair" needs a qualifier such as "may under certain circumstances inhibit DNA repair." The data for the statement "inactivates genes" needs to be rechecked for accuracy.

It should also be noted that the EPA Arsenic Risk Assessment Forum Document (1986/87) stated:
"...unlike the majority of clastogenic agents, arsenic does not appear to directly damage DNA except, perhaps, at highly cytotoxic doses..."

Page 1-3, Paragraph 3:
It should be noted that in the U.S., two smelters (Tacoma and Anaconda) give "strong associations", Garfield now gives a "weak association" and six others give weak or negative associations (Enterline et al., 1986 and 1987b). In the insecticide manufacturing industry, both the DOW and ALLIED studies have problems which tend to weaken the association between arsenic exposure and carcinogenic risk. One of the BIG PROBLEMS in ALL the studies are UNDER ESTIMATES OF EXPOSURE and hence OVERESTIMATE OF RISK.

Page 1-3, Paragraph 4:
There needs to be a NEW UP-TO-DATE listing of SMRs, including ALL NEW DATA, using EPA (1984) and adding 3 out of about 11 possible studies is inappropriate.

Page 1-4, Paragraphs 2 and 3:
In Paragraph 3, the two statements "Confounding from smoking was minimal" and "did not vary by level of arsenic exposure" DO NOT LEAD TO THE STATEMENTS in Paragraph 4, "Interaction....greater than additive and at low doses may be as high as multiplicative."

Page 1-4, Paragraph 4:
The evidence for human carcinogenicity due to inhaled arsenic has been considered to be "strong" because of:

(1) The high relative risk (mortality ratios) seen in occupational studies:
What is not noted is that the workers were exposed to many confounding factors and the interactions of these factors has not been assessed.

(2) The high statistical significance of these findings:
The quality of the data and how it was used has not been assessed.

(3) The evidence of a dose-response effect using different indices of exposure and different measures of response:
The quality of the data and how it was used has not been assessed.

(4) The demonstration of increased risks due to arsenic, including a dose-related effect among nonsmokers:
Some of the data for the Ronnskarsverken smelter is of particular interest and is given again below, since it strongly seems to indicate that the effects of arsenic can be VERY strongly enhanced by more than a single co-factor (Pershagen et al. (1981).

SMRs for Smokers and Non-smokers Exposed to Arsenic and/or Sulfur Dioxide

Exposure	Standardized Rate Ratios Non-Smokers	Smokers
No arsenic	1.0	4.9
High arsenic	1.2	14.7
High sulfur dioxide	1.8	6.5
High (arsenic + sulfur dioxide)	4.4	22.0

(5) The consistency of the arsenic-related effect among cohorts which are geographically dispersed (several states of the U.S., Japan and Sweden):
One troubling fact is the apparent non-consistency of percentage of histological types of lung cancer observed.

(6) The consistency of the arsenic-related effect from at least 2 types of exposures, namely smelters and insecticide manufacturing:
This may be true if only the positive data is considered, rather than both the positive and the negative data.

(7) The failure of potential confounding to explain the observed effect:
To date only smoking and sulfur dioxide have been considered. All possible co-factors and interactions need to be considered. Just 2 co-factors not usually considered will be noted here:

(a). Aromatic Hydrocarbons:
In copper smelting, at least two operations - anode refining and electric furnace smelting - may have produced aromatic hydrocarbons. During the fire refining of blister copper in anode furnaces, unburned hydrocarbons and soot were often visibly emitted. Coal was also sometimes used during fire refining in ways which could potentially produce hazardous emissions. The operation of electric furnaces sometimes involves the evaporation of sizable amounts of carbon paste and pitch from the electrodes.

(b). Additives:
A number of additives, such as pine oil and other chemicals, can become airborne during roasting or drying. Sulfuric acid plants might also cause problems of exposure due to chemicals used in acid production, such as dimethylaniline.

Page 1-5, Paragraph 3:
EPA Science Advisory Board in September 1989 recommended that EPA develop a revised risk assessment based on estimates of the delivered dose of non-detoxified arsenic to target tissues and consider the potential reduction in cancer risk due to detoxication (Pesticide and Toxic Chemical News, pp. 24, November 1, 1989). This is for oral dosage, but since the ARB in a few months will be considering combined (total) routes of administation for arsenic, it is inappropriate to neglect the concept of detoxification, whether or not it is called a threshold or not.

Page 1-6, Paragraph 1:
If there is a detoxification mechanism which becomes saturated is it logical to do a risk assessment based on cumulative lifetime exposure? Also it becomes inappropriate to use a linear non-threshold multiplicative model and extrapolate it to ambient exposures which are well within the power of the body to detoxify.

Page 1-6, Paragraphs 2 and 3:
The epidemiological data just does not justify four smoking categories, see for example, Page 1-4, Paragraph 2.

Page 1-8, Paragraph 1:
Should be Tacoma, Washington rather than Montana.

Page 1-13, Paragraph 2:
Why are only ingeston or injection mentioned? Somewhere the extent of "unmethylated" As(+3) and As(5) for various methods of administration should be compared.

Page 1-12, Paragraph 4:
This proposed mechanism for arsenic carcinogenesis does not seem to fit the Risk Assessment model chosen. In light of the recommendation by the SAB to EPA, it would seem appropriate to discuss methods to logically derive a practical threshold based on detoxification mechanism(s) and other available experimental data.

Page 2-1, Section 2.1:
There has been at least two determinations of the amount of arsenic absorbed by inhalation. In NRCC (1977) it states "A large fraction (50-80%) of the toxic arsenic species in small (less or equal to 0.1 to 0.5 u) particles deposited in the lungs is extracted into the blood and soft tissues (Bogorich, 1975). The extraction efficiency for larger (equal or over 1 u in diameter) arsenic-bearing particles, once they are cleared from the upper respiratory tract and reach the stomach, is much lower, i.e. 5-15% (Bogorich, 1975)." Pershagen and Vahter (1979) noted that in smelters, inhaled arsenic and that brought to the gastrointestinal tract by mucociliary clearance lead to approximately 80% absorption.

The amount of arsenic absorbed following oral ingestion is usually greater than 80%, being close to 100% from liquids and over 80% from solid foods. An appropriate summary table is given on pages 51-53, Thorne, Jackson and Smith (1986).

Pages 2-2, Paragraph 1:
It might be more appropriate to say "absorption of arsenic appears to PARALLEL water solubility."

It seems inappropriate to describe intratracheal instillation as "forced breathing of liquid solutions."

Page 2-2, Paragraph 2:
It is stated "Urinary studies do not quantify the inhalation absorption of arsenic since it is excreted by several routes and correlation between arsenic intake and urinary levels is poor (Smith et al., 1977 and Pinto et al., 1977)." If this statement is not qualified or explained or expanded, it WILL NULLIFY AND

INVALIDATE THE KEY RISK ASSESSMENT USING ENTERLINE'S DATA, which are based to a large extent on the extrapolation of urinary levels to air exposure. An estimate of extent of the extrapolated data versus measured air exposures may be gauged from Osborne (1984).

Page 2-2, Paragraph 3:
It is inappropriate to use 1974 FDA data when later FDA data is available, see for example, that for 1980-82, Gartell et al. (1986 a and b).

Page 2-3, Paragraph 1:
For regulatory purposes, the standard amount of air breathed per day is normally taken to be 20m3/day NOT 18m3/day.

Page 2-3, Paragraph 2:
The sentences "Inhalation of ambient arsenic may be more toxic than ingestion of an equivalent amount of dietary arsenic. Airborne arsenic cannot be methylated (i.e. detoxified) before it reaches the lung tissue, whereas orally ingested arsenic ordinarily passes first through the liver." need to be reconsidered. By no means does all airborne arsenic reach the lung and depending on particle size, much may be swallowed and ingested. Also orally administered arsenic will be subject to several physical and metabolic steps prior to reaching the liver. In order to compare the toxicity of oral and inhaled arsenic, at a minimum, amounts of arsenic absorbed need to be compared. True comparative data on the "arsenic methylation" capacity of the various tissues is presently sadly lacking.

Page 2-3, Paragraph 3:
This paragraph is confusing, since findings for total arsenic are mixed in with incomplete descriptions of what happens for As(+3) and As(+5). It would be useful, where possible, if original references rather than review articles were used. As a general rule arsenic retention is modified primarily by dose level, species and the physical and chemical form of the arsenical which influences its rate of metabolism and hence degree of body retention. The metabolism of both As(+3) and As(+5) with the various blood elements needs to be described since it is an important element in the overall metabolism of arsenic. One of the main references for this is Marafante et al. (1985), which is cited two sentences later.

The statement, "As(+3) is taken up by liver cells", seems to be from in vitro experiments and this should be stated. Lerman et al. (1983) studied the methylation of As(+3) and As(+5) in hepatocyte cultures and found that dimethylarsinic acid was formed when As(+3), but not As(+5), was added to the culture medium. No metabolism of arsenate was seen, nor was the arsenate taken up by the liver cells. Marafante et al. (1985) stated that As(+5)

could be concentrated in the kidney OR RAPIDLY CONVERTED TO TRIVALENT ARSENIC IN THE BLOOD, this latter should be added. It should also be noted that accumulation in tissues is significantly higher after the administration of As(+3) than after As(+5), see Vahter (1983).

Page 2-4, Paragraph 2:
For completeness a statement on the effects of valence and solubility should be made.

Page 2-4, Paragraph 3:
A statement needs to be made that the levels of arsenic used were very high. Also note needs to be taken of the detoxification mechanisms that take over, see Hood et al. (1987 and 1988).

Page 2-5, Paragraph 1:
The paragraph on detoxification is incomplete and hence will leave a wrong impression on the detoxification mechanism with most readers.

In mammals, in vivo, As(+5) is usually rapidly reduced to As(+3) prior to methylation and excretion (Vahter and Envall, 1983). Marafante and Vahter (1984) deduced that reduction of As(+5) to As(+3) is an initial and independent reaction in the biotransformation of As(+5) and probably occurs in the BLOOD. Methylation, as a key detoxification pathway is at least partially enzymically controlled and occurs via As(+3) to monomethylarsonic acid (MMA) and subsequently to dimethylarsinic acid (DMA). The formation of dimethylarsinic acid (DMA) appears to be the rate-limiting step (Buchet and Lauwerys, 1985). The methylated forms of arsenic (monomethylarsonic acid and dimethylarsinic acid) are more rapidly excreted than inorganic As(+5) and As(+3) (Vahter, 1983 and Vahter et al., 1984). Dimethylarsinic acid (DMA) is the major metabolite in humans, but only a secondary metabolite in other mammals. Monomethylarsonic acid can be partially methylated to dimethylarsinic acid, but neither form is significantly demethylated to inorganic arsenic. Furthermore, any decreased methylating capacity caused by chemical inhibition, dietary deprivation, or genetic disposition appears to lead to decreased excretion of dimethylarsinic acid (DMA) in the urine, with retention of arsenic in the lungs, skin, liver and liver microsomes. Methylation is dose dependent, the percentage of dimethylarsinic acid (DMA) in the urine decreasing with increasing inorganic arsenic dose level, whereas the amount of retained arsenic increases.

The liver and to a lesser extent also the kidney and the gastrointestinal tract appear to be the major sites of methylative metabolism (Klaassen, 1974 and Vahter and Marafante, 1985). As stated above true comparative data on the "arsenic methylation" capacity of the various tissues is presently sadly lacking.

Page 2-5, Paragraph 2:
The paragraph on the saturation of the methylation detoxification mechanism is seriously incomplete and hence will leave an inaccurate impression with its readers.

Valentine et al. (1979) showed that following a CHRONIC intake of 200-250 ugAs/day there appeared to be a biological threshold for limiting detoxification.

Buchet et al. (1981a, 1981b and 1982) in acute studies, showed that the methylating capacity in humans starts to slow at 250 ug As/day and appears to reach a "plateau" at 500-600 ugAs/day (Buchet et al. 1981a, 1981b and 1982). At about 600 ugAs/day the absolute amount of monomethylarsonic acid (MMA) begins to plateau and the saturation of methylation occurs between doses of 500 and 1,000 ug/day in people of adequate methylating capacity. Whereas the work done by Vahter on chronically exposed animals (cited by EPA, 1986/87) would seem to indicate that adaption can take place leading to even higher levels at which saturation occurs.

Foa et al. (1984) measured blood and urinary metabolites of arsenic (As203) in 40 glass workers exposed to high levels of arsenic in the AIR and in 148 control subjects drawn from the general population. Each group contained subjects with clearly reduced methylation capacity. It was also found that methylating capacity may adapt in proportion to exposure, but that full methylation capacity for high exposures takes several months to build up and that any accommodation the body may make to very high arsenic levels is rapidly lost.

Thus there are not only acute human data as stated on Page 2-5, Paragraph 1, but also human and animal chronic oral and human inhalation back-up data. In addition, SATURATION COULD EASILY HAVE TAKEN PLACE IN THE OCCUPATIONAL SETTINGS ON WHICH THE RISK ASSESSMENTS ARE BEING PERFORMED.

Page 2-6, Paragraph 1:
Work by Vahter has indicated that As(+3) can be oxidized to As(+5) in hamster lungs (cited by EPA, 1986/87). This needs to be stated on Page 2-6, Paragraph 1.

Although the Crecelius (1977) data may be analytically excellent, the use of ONLY ONE SUBJECT is usually looked upon AS PRELIMINARY DATA ONLY. This needs to be stated on Page 2-6, Paragraph 1.

Page 2-6, Paragraph 3 and Page 2-7, Paragraphs 1 and 2:
This section on elimination is seriously incomplete and should be expanded.

Urinary excretion tends to be the primary means of arsenic elimination in most animals. Whether arsenic elimination occurs

mainly via the urine or feces, appears to depend more on the route of administration and species, than on the nature of the arsenical (NRCC, 1977).

Odanaka et al. (1980) found that 48 hours after giving 5 mgAs (+5)/kg to rats, mice and hamsters, urinary excretion of total arsenic accounted for 17.2, 48.5 and 43.8% and fecal elimination for 33.0, 48.8 and 44.1% of the dose in the species, respectively.

Several studies have compared the rates of excretion of trivalent arsenic and pentavalent arsenic (Vahter and Norin 1980, Vahter 1981, Marafante et al. 1985). Vahter (1981) reported that in mice, both for As(+3) and As(+5), dimethylarsinic acid (DMA) was the major urinary metabolite. Arsenic (+3) was methylated to a greater extent than arsenic (+5), but there was higher whole-body retention for As(+3). Thus, differences in urinary excretion rates appeared to relate to the relative degrees of methylation of the inorganic arsenic, with rapid formation of dimethylarsinic acid (DMA) enhancing the urinary excretion. For both As(+3) and As(+5), retention increased with increasing dose, approximately paralleling a decrease in methylation (in percentage of the dose).

Mappes (1977) gave a single oral dose of As(+3) to a human and found maximal renal excretion at 3 hours and about 25% of the dose appeared in the urine after 24 hours. Pomroy et al. (1980) felt that excretion occurred in three phases - 65.9%, with a half-life of 2.09 days, another 30.4%, with a half-life of 9.5 days and the third 3.7%, with a half-life of 38.4 days. Whereas, as stated on Page 2-7, Paragraph 1, EPA (1984) estimated the clearance of arsenic in man and dogs to fit a three-compartment model with half-life times of 1, 5 and 35 hours (EPA, 1984 and Charbonneau et al., 1978).

Biliary transport of arsenic has been reported for a number of species. Arsenic enters the feces via the bile in rabbits, guinea pigs and chimpanzees (Hunter et al., 1942). Fecal arsenic levels for rabbits given As(+3) intraperitoneally were 10% of the dose after 4 days (Bertolero et al., 1981). As stated on Page 2-7, Paragraph 1, in hamsters, given As(+5) by intraperitoneal injection, little arsenic was found in the bile, whereas for As(+3) about 5% of the dose was found in the bile within 24 hours (Cikrt et al., 1980). Although biliary excretion may be significant and highly variable between species, it will not contribute extensively to elimination, because of reabsorption from the intestines (Klaassen, 1974 and Cikrt et al., 1980).

Arsenic is also excreted in the saliva (Goodman and Gilman, 1941). Daily excretion of arsenic in human hair and nails has been estimated to be 0.3ug and 0.2ug, respectively (Snyder et al., 1975). Profuse sweating may eliminate 2 ugAs/hour and

desquamation may also account for small quantities of arsenic (Vahter, 1983).

Page 3-1, Paragraphs 1 and 2:
These paragraphs on the proposed specific receptor site for the essentiality of arsenic and physiological role are seriously incomplete and hence leaves an erroneous and inaccurate impression with its readers.

Four laboratories (Schwartz, Nielsen, Anke and Schroeder) have reported that dietary arsenic deprivation adversely affected the health of mice, rats, chicks, minipigs and goats. This in itself would not seem significant until it is realized that only 5 laboratories world-wide HAVE EVER HAD THE CAPABILITY TO PERFORM "DEPRIVATION" EXPERIMENTS. Forth's laboratory has never worked on arsenic. Also since each of these laboratories have only worked on two species, it is amazing that the health effects from arsenic deprivation have been noted in ALL five species tested. Judging from the past history of other essential trace elements it would seem better than 95% certain that arsenic will turn out to be essential in humans. Why are not more experiments performed on essentiality? At present there are only three "deprivation" laboratories (Nielsen, Anke and Forth - Schroeder and Schwartz are dead) and the cost of each experiment is very, very high.

Following preliminary work by Schroeder and Balassa (1966) on rats and mice, Nielsen et al. (1975) showed that arsenic was probably essential in rats. Then signs of arsenic deficiency were also seen in minipigs and goats by Anke et al. (1976, 1978 and 1980). Since, arsenic metabolism in rats differs from all other species, Nielsen used chickens in his later experiments on arsenic nutrition and metabolism. From this data it was apparent that arsenic was also an essential nutrient for growing chicks (Nielsen and Shuler, 1978).

Many of the signs of arsenic deprivation seen in these chicks were similar to those seen in zinc deficiency. Signs of arsenic deprivation were more obvious and appeared sooner when high levels of arginine, a zinc antagonist (Colemen et al., 1971), was added to the diet. Further studies by Nielsen et al. were designed, to ascertain whether, arsenic was necessary for the utilization of zinc. It was found that even though the chicks might receive adequate zinc in the diet, LACK of arsenic in the diet prevented efficient utilization of that zinc.

Studies by Nielsen and co-workers, showed that signs of arsenic deprivation also included increased hepatic levels of manganese. Apparently, the arginine, manganese and zinc status of animals markedly influenced the signs of arsenic deprivation. Findings

by Nielsen and co-workers suggest that arsenic may be interrelated with zinc, manganese and/or arginine metabolism. Since a four of these nutrients are affected by, or affect, arginase activity, this seemed a likely locus for their interactions (Uthus et al., 1983 and 1985).

Signs of arsenic deprivation in rats included impairment of fertility and growth. Anke et al. (1987) reported the appearance ultrastructural changes in the mitochondria of cardiac tissue from goats fed an arsenic deficient diet (0.035 ppb). Deficien was found to impair conception and increased the number of abor tions. Arsenic deficiency also depresed growth, particularly during fetal development and after weaning.

Page 3-1, Paragraph 3:
This paragraph claims that because Liebscher and Smith (1968) showed that arsenic was log-normally distributed in human tissues, it must not be an essential element. This was not true, since essential elements such as chromium or manganese, with fairly limited metabolic functions, in a particular organ, are log-normally distributed. Log-normality is also found for most essential elements in organs with a large array of cellular types and functions. Both these statements can be easily prove by taking any raw set of trace element data for 50+ samples eac of kidneys, lungs etc. and plotting normal and log-normal distributions. In fact log-normal distributions are far more common than normal ones in biological and geochemical materials and were in fairly general use prior to the advent of comput rs which made non-parametric statistics easily utilizable in th 1960's. In general, if median values or geometric means gave more realistic estimates of data than did arithmetric means, then log-normal distributions gave a better gaussian pictorial assessment than did a normal distribution. There was nothing magical about log-normal distributions and non-essentiality or normal distributions and essentiality. It should also be noted that Liebscher and Smith's (1968) proposed distinction never found approval with the top trace element workers of the 1960s such as Schroeder, Tipton and Cotzias.

For completeness this section should note that Nielsen and coworkers cautiously estimated a human requirement of 30 to 40 ugAs/day based on the apparent adequacy for chicks of the diet containing 45 ng/g arsenic (Uthus et al., 1983). The current American diet may not always meet this presumed requirement.

Page 4-1, Paragraph 1:
Approximate levels of arsenic causing irritation etc. should be stated so that the reader obtains a feeling of how close to amb ent levels these effects occur. In general, no such effects we noted in workers exposed to 200ug/m3 in air (ACGIH, 1986). A

ready reference for this type of data would be the ATSDR/EPA (1987) document.

Page 4-1, Paragraph 2:
Although Vallee et al. (1960) estimated the average fatal dose of arsenic trioxide for humans to be 125 mg (about 1.4 mgAs/kg body weight), it should be noted that the notorious arsenic eaters of Styria were known to eat almost half a gram of arsenious oxide once or twice a week. Thus the difference in sensitivity between animals and man may not be true.

Page 4-3, Paragraph 2:
Some estimates of NOELs should be obtained from the ATSDR/EPA (1987) document.

Page 5-1, Paragraph 1:
The reference Lagervist et al. (1986) should be inserted at the end of sentence 2.

Page 5-1, Paragraph 2:
The following should be added for completeness after sentence 1, "Exposure to 46 ugAs/m3 as arsenic trioxide produced central nervous system inhibition, decreased levels of sulfhydryl groups, inhibition of cholinesterase activity and increased levels of blood pyruvate (Rozenshtein, 1970)."

Page 5-2, Paragraph 1:
The following two studies need to be added to this paragraph:
Arsenic trioxide at 1500 ug/m3 for 252 hours caused no changes in the behavior of 15 white rats, but neurologic functioning was disrupted (Kamil'dzhanov, 1982).

Chronic exposure to doses of up to 10 mg/kg/day (given by injection once a week for 18 months) did not produce any evidence of neuropathy in rats (Schaumburg, 1980). This exposure level (an average of around 1.4 mg/kg/day) would almost certainly be expected to produce neuropathy, if not lethality, in humans. This study leads further evidence to the view that rats are not appropriate models for arsenic toxicity in humans.

Page 5-2, Paragraph 2:
The last sentence needs a reference.

Page 5-4, Paragraph 1:
The following three experiments need to be added:
Rabbits given oral doses of arsenates, 1.4-9.3 mg/day for 50-250 days, developed cirrhosis and necrosis, as well as bile duct proliferation (Von Glahn et al., 1938).

Dietary arsenite or arsenate at levels of 125-250 mg/kg and 250-400 mg/kg, respectively, led to hepatic fibrosis and bile duct enlargement in rats (Byron et al., 1967).

Fowler et al. (1977) studied structure and function of liver mitochondria and hepatocytes in male rats given 20, 40 or 85 mg/l arsenic as arsenate in drinking water for 6 weeks. Significant depression of growth rate occurred only at the 85 mg/l dose level. Mitochondria in hepatocytes from animals at the upper two dose levels showed extensive swelling. Mitochrondrial respiratory function (for specified substrate conditions) exhibited a dose-related depression at 20 mg/l and 40 mg/l arsenate.

At the bottom of this animal data section two additional data sets need to be added:

DERMAL EFFECTS
Ishinishi et al. (1976) gave young rats arsenic trioxide solution intragastrically and observed that high doses, 7.6 mg/kg/day, caused severe skin changes, which included ulcers, scarring of epidermis, hyperkeratosis and acanthosis, as well as hair bulb enlargement and hyperplasia. However, matched animals given 2 mg/kg/day of arsenic trioxide, had none of the above pathological changes. Osato (1977) intubated suckling Wistar-King rats for 40 days with 10 mg/kg arsenic trioxide (7.6 mg As/kg) and produced hyperkeratoacanthosis of the epidermis and intracellular edema of the prickle cells of the stratum apinosum.

RENAL EFFECTS
Brown et al. (1976) gave rats 40, 85 or 125 mg As/l as sodium arsenate in their drinking water for 6 weeks. The kidney ultrastructure changes did not extend beyond the mitochondria of the proximal tubules. At all the dose levels tested, these mitochondria were swollen and there was an increase in dense autophagic lysosome-like bodies. This was not found in the controls.

Page 5-5, Paragraph 2:
At the end of this section two more experiments are worthy of note:
In a study by Southwick et al. (1981), in Millard County, Utah, no significant differences in nerve conduction velocity (NCV) measurements were noted between a population consuming water with high (200 ug/l) or low (20 ug/l) levels of inorganic arsenic.

Peripheral neutritis has been noted in patients exposed to doses of 3 to 10 mg/day for periods ranging from several weeks (Mizuta et al., 1956) up to several years (Silver and Wainman, 1952).

Page 5-5, Paragraph 5:
The data given on Blackfoot disease is seriously incomplete which

leads to the erroneous conclusion that arsenic causes it, rather than it may or may not be a contributing cause.

Yeh and How (1963), Tseng et al. (1968), Tseng (1977), Chen et al. (1988) and others have conducted epidemiological and demographic studies in the endemic Blackfoot disease region. The area in the early 1960s was one of extreme poverty. Much of the food consisted of sweet potato chips which were moldy for at least part of the year. The water was drawn in metal buckets from the village well tank, which was often encrusted with green and red algae. The vegetables most often consisted of wild grasses. It should be noted that fat and vitamin deficiencies were reported in this endemic area. In addition, in these communities, spontaneous amputation of limbs apparently occurred quite frequently.

Lu et al., (1975, 1977a and 1977b) reported that in addition to arsenic, fluorescent compounds were present in water samples from the endemic area. One of these fluorescent compounds was identified as an alkaline hydrolysate of ergotamine, probably lysergic acid or related compound, whereas another produced abnormalties in developing chick embryos. Lu and Liu (1986) had noted that the fluorescent substance (containing inorganic arsenic) isolated from the artesian well water induced Blackfoot disease compatible lesions in experimental mice.

Thus, it is not surprising that researchers have questioned whether arsenic is THE CAUSE of Blackfoot disease. In 1969, Kuo and Chen (1969) showed that the disease rate was not correlated with the arsenic content of the village well water, see below. It has been questioned whether these villagers obtained all their water from the village well. It seems probable with a very high degree of certainty that they did. It has also been stated that because Tseng ignored these findings in 1977 that they were wrong. However, Tseng ignored ALL data except his own, even the data obtained by the US Naval Medical Research Unit (NAMRU-3), which was extensively written up in the 1960s, mainly with Blackwell as the chief author.

Prevalence of Blackfoot Disease Versus Arsenic Levels in Well Water

Village	Prevalence Rate Blackfoot Disease per 1000 Population	Arsenic Content ug NTUH*	NAMRU-3
Beautiful Village	26.05	695	840
North Door Village	22.28	381	381
Village No. 3	18.57	675	
Red Eggplant Village	11.01	848	800
Village No. 5	9.60	528	
Fu-zone Village	1.81	836	800

* = Kuo and Chen's analysis
\# = Blackwell's analysis for the NAMRU-3 unit, cited by Kuo and Chen

Yu (1984) and Yu et al. (1984) noted that vascular diseases were not observed in a number of studies, where oral arsenic exposure was elevated and proposed that the occurrence of vascular lesions in Taiwan might be related to the presence of a fluorescent arsenic-containing compound of unknown structure which was present in water from the Blackfoot endemic area. Ko (1986) noted that the incidence of Blackfoot disease increased in Taiwan after steps were taken to reduce arsenic exposure through groundwater and, therefore, concluded that arsenic might not be the factor causing this disease.

Chen et al. (1988) studied 241 Blackfoot disease patients, including 169 with spontaneous or surgical amputations, who had developed the disease after the beginning of 1968 and 759 age-sex-residence-matched healthy community controls from 4 districts in the endemic area of south-west Taiwan. Some of the variables considered are given below.

Comparison of Variables in Matched Healthy Controls and Blackfoot Disease Patients

	No. Control	No. Patients	Odd Rat
Artesian Well Water Consumption			
Zero Years	224	26	1.0
1-29 Years	239	89	3.2
Over 30 Years	296	126	3.6

	No. Control	No. Patients	Odds Ratio
"Artesian" Poisoning			
No	629	160	1.00
Yes	130	81	2.43#
Familial History of Blackfoot Disease			
No	743	227	1.00
Yes	16	14	3.06#
Staple Food in 1960			
Sweet Potatoes	177	70	2.21*
Vegetables Consumed (days/week) in 1960			
Under 7	258	108	1.58*
Eggs Consumed (days/week) in 1960			
Less than 1	393	141	3.12#
Meat Consumed (days/week) in 1960			
Less than 1	498	182	2.85#
Occupational Exposure to Sunshine			
6 hours/day or over	624	215	1.79#

* = p less than 0.05 # = p less than 0.01

It should be noted that the diet as described in Chen et al.'s (1988) paper seems to have been better in retrospect than what was described in reports dated 1960 and 1961. Chen et al. (1988) wrote that after adjusting for "arsenic poisoning" the consumption of artesian well water was still highly correlated with Blackfoot disease. Chen et al. (1988) also commented that after adjusting for artesian well water consumption, arsenic poisoning and under-nourishment, the familial tendency for developing Blackfoot disease still existed.

Therefore even if arsenic is a factor in the development of Blackfoot disease it is certainly NOT THE CAUSE.

Page 5-7, Paragraph 2:
The transverse lines should be given their correct name, which are Mees' lines.

Page 5-7, Paragraph 4:
If the "beer" poisoning incident is discussed, the level of arsenic found in the beer should be stated - it is known!

Page 5-8, Paragraph 1:
Although specific concentrations causing irritant effects are lacking, it is known that some arsenicals cause greater irritation than others.

Page 6-1, Paragraph 2:
It is unclear why the following data has been omitted in this paragraph:
Silaev and Lemeshevskaya (1980) showed that exposure of rats to 4.96 mg/m3 of cesium arsenate caused changes in the sperm cells of the male and preimplantation fetal deaths and reduced life of progeny in pregnant females. Whereas, at a level of 330 ug/m3, the males showed intensified cell division of spermatogenic epithelium but no disruption of the spermatozoids.

It is very important to note that Nagymajtenyi et al. (1985) exposed mice on the 9th through 12th day of gestation for 4 hours/day to either 0.26, 2.9 or 28.5 mg/m3 of arsenic trioxide. On the 18th day of gestation it was found that ONLY the highest dose had caused statistically significant chromosomal and fetotoxic effects. In order to obtain a NOEL, this experiment would have to be repeated since chromosomal damage ALSO occurred in the controls. The number of cells with aberrations increased from 6/200 in the control group to 10/200, 13/200 and 24/200 in the low, medium and high dose groups, respectively.

Page 6-3, Section 6.2:
It is unclear why the following two sets of data have been omitted:
Hood et al. (1987) administered 40 mg/kg sodium arsenate to pregnant mice by gavage or 20 mg/kg sodium arsenate by intraperitoneal injection. Levels in placenta and fetus followed a similar time course of accumulation and clearance in both instances, reaching maximum values around 1 to 2 hours after exposure, and then declining to near control levels within 24 hours. The levels (expressed as ugAs/ug tissue) were about 2 to 3 times higher in placenta than in the fetus, again in both instances. During the first several hours, most of the fetal arsenic was inorganic, but dimethylarsinic acid became the predominant form within 4 to 6 hours.

Goeneches et al. (1983) fed pregnant mice doses between 25-175 mgAs(+3)/kg diet/day (given as arsenic trioxide) for 18 days. Only at diet levels of above 93 mgAs(+3)/kg feed/day was arsenic detected in the fetus and amniotic fluid and also only above this level was fetal mortality above normal levels. The LD50s for the embryos and mothers were 153 and 268 mgAs(+3)/kg diet/day, respectively.

Page 6-3, Section 6.2.1:
It is unclear why the following articles using the rat were not reviewed. They need to be abstracted/reviewed either in this section or Appendix G:
Kojima (1974)
Kimmel and Fowler (1977)
Nadeyenko et al. (1978)

Page 6-4, Section 6.2.2:
It is unclear why the following articles using the hamster were not reviewed. They need to be abstracted/reviewed either in this section or Appendix G:
Ferm and Carpenter (1968)
Holmberg and Ferm (1969)
Ferm et al. (1971)
Carpenter (1987)

Page 6-4, Paragraph 3:
It is unclear FROM A METABOLIC POINT OF VIEW why the experiment by Ferm and Hanlon (1985) should "closely approximate" air pollution. It simply is not logical, particularly since for arsenic, route is so critical in establishing reproductive damage levels, see for example Hood (1983). In addition, if it is assumed that a 60 kg person inhales 20 m3 of air per day and absorbs 50% the arsenic in the air (more reasonable assumptions), this would correspond to an ambient air concentration of 30.6 mgAs/m3 not 17 mgAs/m3.

Page 6-5, Section 6.2.3:
It is unclear why the following articles using the mouse were not reviewed. They need to be abstracted/reviewed either in this section or Appendix G:
Hood (1972)
Hood and Bishop (1972)
Matsumoto et al. (1973 a and b and 1974)
Thacker et al. (1977)
Hood et al. (1977, 1978 and 1988)

Page 6-5, Paragraph 2:
Hood (1983) DID NOT STATE THAT As(+5) WAS MORE POTENT THAN As(+3), his data clearly show that As(+3) was more toxic than As(+5). A higher dose level to produce an affect, means LESS toxic not more. The next sentence also does not make sense unless equivalent dose levels, by the SAME route of administration are compared and this was not done.

Page 6-6, Paragraph 1:
Routes of administration are critical for any arsenical reproductive damage assessment, see for example, Hood (1983). The work by Willhite (1981) is i.v. and Morrisay and Mottet (1983) i.p. and the work of Hood has clearly shown that this CANNOT be used for ORAL risk assessments and by analogy INHALATION. From the available data the following may be concluded, that by oral/gavage administation:

a. Doses of sodium arsenite below 20 mg/kg/day do not appear to cause reproductive and developmental damage.
b. Doses of sodium arsenate below 100 mg/kg/day do not appear to cause reproductive and developmental damage. (Lethality may occur in humans at about 0.6 mgAs/kg/day).

Page 7-1, Section 7.0:
This section is rather badly out of date and incomplete and hence needs to be updated using IARC (1987) and other sources. Difference in effects due to As(+3) versus As(+5) should be noted and effects on DNA should be discussed in a separate section.

Page 7-1, Section 7.1:
Under E. coli the following papers need to be considered, perhaps in a table:
Hemmerly and Demerec (1955)
Fiscor and Lo Piccolo (1972)
Rossman et al. (1975 and 1977)
Tkeshelashivili et al. (1980)
McCarroll et al. (1981)
Nunoshiba and Nishioka (1987)

Under B. subtilis:
Kada et al. (1980)

And under S. typhimurium:
Moore (1976)
Lofroth and Ames (1978)
Tiedemann and Einbrodt (1982)
Marzin and Phi (1985)

Page 7-2, Section 7.1.1:
This section needs to be expanded or dealt with under a section on effects of DNA.

Page 7-3, Section 7.2:
Under S. cerevisiae the following papers need to be considered, perhaps in a table:
Fukunga et al. (1982)
Dai et al. (1988)

A section on D. melanogaster needs to be added:
Walker and Bradley (1969)
Dugatova et al. (1980)

Page 7-3, Section 7.3:
This section needs to be divided up and the data summarized in tables with the results put in the main text. The following papers need to be considered:

Under NON-HUMAN MAMMALIAN CELLS - general effects due to arsenic:
Larramendy et al. (1981)
Lee et al. (1985 a and b, 1986 a and b)
Okui and Fujiwara (1986)
Under the MICRONUCLEUS TEST:
DeBrabander et al. (1976)
Pashin et al. (1984)

DeKnudt et al. (1986)
Under DOMINANT LETHAL MUTATIONS:
DeKnudt et al. (1986)
Sram and Bencko (1974)
Sram (1976)
Hodge (1977)
Gencik et al. (1978)
Pashin et al. (1984)
Under NON-HUMAN CHROMOSOMAL EFFECTS the following papers need consideration besides Wan et al. (1982) and Nagymajtenyi et al. (1985):
Sram (1976)
Gencik (1978)
Poma et al. (1981)
Larramendy et al. (1981)
Ohno et al. (1982)
Andersen (1983)
Lee et al. (1985a and b, 1986a, b and c)
Jan et al. (1986)
Huang et al. (1987)

Page 7-4, Paragraph 2:
The data by Oberly et al. (1982) will require review, since in the presence of metabolic activation the results were negative.

Page 7-5, Section 7.3.1:
Under human cells the following papers need consideration in addition to Zanzoni and Jung (1980), Wen et al. (1981), Nordenson et al. (1978 and 1981) and Nordenson and Beckman (1982):

Under HUMAN CHROMOSOMAL EFFECTS:
Oppenheimer and Fishbein (1965)
Petres and Hundeider (1968)
Petres et al. (1970 and 1977)
Petes and Berger (1972)
Paton and Allison (1972)
Happle and Hoehn (1973)
Burgdorf et al. (1977)
Beckman et al. (1977 and 1979)
Gencik (1978)
Ogawa et al. (1978)
Ogawa (1979)
Nordenson et al. (1979)
Lu et al. (1980)
Larramendy et al. (1981)
Nakamuro and Sayato (1981)
Chuang et al. (1981)
Wan et al. (1982)
Andersen (1983)
Crossen (1983)
Sweins (1983)

Vig (1984)
Lee et al. (1986a)
Huang et al. (1987)

As stated above there should be an additional section on the effects of arsenic on DNA and this should include, in addition to the articles discussed in the present Section 7 on genotoxicity, a review of the following papers:
Sibatani (1959)
Jung et al. (1969)
Jung and Trachsel (1970)
Grunicke et al. (1973)
Basmadshijew and Dawidkowa (1974)
Casto (1977)
Petres et al. (1977)
Fornace and Little (1979)
Fong et al. (1980)
Tkeshelashivili et al. (1980)
Nakamuro and Sayato (1981)
McLean et al. (1982)
Sina et al. (1983)
Okui and Fujiwara (1986)
Nunoshiba and Nishioka (1987)

In addition, the data developed by Lee et al. (1985a and b, 1986a, b and c and 1988) should be summarized, not just the one paper referred to on Page 7-6, Section 7.3.2. The last paper is of particular importance.

Page 7-6, Section 7.4:
This section should be expanded to include a summary of the following papers:
Gainer and Pry (1972)
Gainer (1972)
Blakley et al. (1980)
Kerkvliet et al. (1980)
McCabe et al. (1983)
Aranyi et al. (1985)

Page 7-7, Section 7.5:
This section is badly incomplete and below is given a summary of some of the main findings which come out of an indepth review of the mutagenic testing experiments:

(1) Arsenic does not appear to induce point mutations.
(2) Many arsenic compounds induce chromosomal abnormalities in mammalian cells, but have not been shown to cause base-sequence mutations in the absence of chromosomal abnormalities. Synergism has been reported between arsenite and UV light in producing chromosome aberrations and cytotoxicity (Lee et al., 1985b).
(3) Arsenic causes chromosomal breakage (clastogenicity) in a

dose-dependent manner in a variety of cultured cell types, including human ones. Arsenite is an order of magnitude more potent than arsenate.

(4) Such chromosome breaks could lead to stable chromosome aberrations, which require a minimum of two hits with a loss or exchange of genetic material, events that would be compatible with nonlinear kinetics and, therefore, a sublinear dose-response relationship.

(5) Arsenicals increase the frequency of sister chromatid exchanges (SEC) in cultured cells, including human ones.

(6) Arsenicals, at relatively high levels (0.05-0.10M), tested positive (in the Rec assay) for damage in cellular DNA. It should be noted that a chemical need not produce mutations to be considered positive in the Rec assay, since the DNA damage can be lethal rather than mutagenic.

(7) Arsenic has not been shown to decrease the fidelity of DNA synthesis and it does not increase misincorporation of bases into DNA (Zakour et al., 1981).

(8) Arsenic can inhibit and/or prolong the period for excision repair and can slow DNA replication and synthesis (Rossman, 1981 and others).

(9) Arsenic may act as an enchancer of gene amplification.

(10) Very low levels of arsenicals can increase the rate of mitogenesis, whereas higher ones inhibit it.

(11) Arsenic compounds have been shown to potentiate the genotoxid effects of UV light in mammalian cells, as well as in bacteria.

(12) Marczynski (1988) has suggested that the action of arsenic may be to improve the semiconductor properties of DNA by switching on and off of genetic information in gene expression at the electronic level.

Page 8-2, Paragraph 2:
Glaser's laboratory is one of the top, it not the top laboratory in the world at the present time, for animal inhalation studies on metals and similar substances. The methodology used is state-of-the-art.

The dose levels were 60 ugAs(+3) and 200 ugAs(+3)/m3 breathed for 22-24 hours per day every day for 18 months, these levels when pro rated for 8 hour working shifts are DEFINITELY IN THE RANGE EQUIVALENT TO HIGH LEVEL EXPOSURES SEEN IN SMELTER WORKERS. In addition, this type of exposure is certainly more realistic than Berteau et al.'s 40 min/day and 20 min/day exposures. The comment on the use of rats is valid and to a lesser extent the use of 20 and 40 animals per group. It might be worth enquiring from Dr. Glaser whether other experiments on arsenicals, not using rats are in progress.

Page 8-2, Section 8.2:
Any laboratory routinely using intratracheal installations does

not use anesthetized animals and the technique if properly performed is probably less stressful than gavage.

The paper by Ohyama et al. (1988) needs to be reviewed.

The data by Ishinishi and Pershagen needs to be summarized in a table such as the one given below:

Studies by Ishinishi et al. (1983), Pershagen et al. (1984), Pershagen and Bjorklund (1985) and Yamamoto et al. (1987) on Hamsters

Lung Tumors	Adenoma	Carcinoma	Adenoma	Carcinoma
P (1984) As203	2/47 (4%)	3/47 (7%)	0/53	0/53
I (1983) As203	2/20 (10%)	0/20	0/35	0/35
Y (1987) As203	0/17	1/17 (6%)	0/21	1/21 (5%)
P (1985) As2S3	1/28 (4%)	0/28	0/26	0/26
Y (1987) As2s3	1/22 (5%)	0/22	0/21	1/21 (5%)
P (1985) Ca3(AsO4)2	4/35 (11%)	0/35	0/26	0/26
Y (1987) Ca3(AsO4)2	6/25 (22%)	1/25 (4%)	0/21	1/21 (5%)

P (1984) = Pershagen et al. (1984) - carbon, sulfur, saline controls
I (1983) = Ishinisi et al. (1983) - phosphate buffer controls
Y (1987) = Yamamoto et al. (1987) - phosphate buffer controls
P (1985) = Pershagen and Bjorklund (1985) - saline controls

The results are puzzling and before interpretation can be attempted an experiment using at least 3 dose levels should be performed to see if the effects observed are dose-related or not. There is also a great need for further experimentation to compare at either 2 or 3 dose levels the effect of using various arsenical compounds.

There needs to be an additional section, Section 8.5, considering arsenic at low doses as a possible ANTICANCER agent. The following papers give some evidence that this MAY be a possibility:
Baroni et al. (1963)
Boutwell (1963)
Kanisawa and Schroeder (1967 and 1969)
Kroes et al. (1974
Schrauzer and Ismael (1974)
Schrauzer (1977)
Schrauzer et al. (1976 and 1978)
Kerkvliet et al. (1980)
Blakley (1987a and b)
Ip and Ganther (1988)

Page 9-1, Paragraph 1:
It is stated that "only those studies involving exposure via inhalation are considered", then the next 4 paragraphs are oral administration.

Page 9-1, Paragraph 2:
In Neubauer (1947) there are zero cases using arsenicals for anemia and zero cases using arsenicals for rheumatism. Also some of his cases appear to have received organic arsenicals.

Page 9-1, Paragraph 3:
The skin cancer cases from Poland are questionable.

Page 9-2, Paragraph 4:
Table 9-1 (since it is on computer) should be reorganized and updated so that:

(a). Data from essentially the same cohorts are brought together and

(b). The table is updated; there is hardly a major cohort that has not been updated. There is even additional data, both old and new, on "environmental" exposures, such as Baker et al. (1977), Mattson and Guidotti (1980), Greaves et al. (1981), Hartwell et al. (1983), Cordier et al. (1983), Brown et al. (1984), Binder et al. (1987) and Frost et al. (1987). The German vintner studies have also been updated, see for example, Luchtrath (1983). The updates on the Washington State, Dow, Garfield, Anaconda, Tacoma and Ronnskarverken studies are given in Appendix A, Sections A-F and are to some extent also discussed below.

Page 9-3, Paragraph 1:
The updates on the Dow, Garfield, Anaconda, Tacoma and Ronnskarverken studies, see Appendix A, Sections A-F need to be included in Table 9-2.

Page 9-3, Paragraph 2:
As pointed out, many of the "recent studies" have been overlooked.

Page 9-3, Section 9.1:
Some of the key data for the various study plants, omitted in this report, are given in Appendix A, Sections A-F.

As stated above, in the U.S., two smelters (Tacoma and Anaconda) give "strong associations", Garfield now gives a "weak association" and six others give weak or negative associations (Enterline et al., 1986 and 1987b). In the insecticide manufacturing industry, both the DOW and ALLIED studies have problems which tend to weaken the associations between exposure to arsenic and cancer risk.

Page 9-4, Paragraphs 2 and 3:
Both papers by Enterline and Marsh (1982) and Enterline et al. (1987a) use an extrapolation of urinary data to air exposure, BUT DHS APPARENTLY DOES NOT APPROVE OF THIS EXTRAPOLATION, see Page 2-2, Paragraph 3. IF THIS IS SO THE TACOMA DATA SHOULD NOT BE USED FOR RISK ASSESSMENT!

Osborne's data needs to be considered along with Enterline's data, see Appendix A, Section A for further discussion.

Page 9-5, Paragraphs 2 and 3:
What is not stated is that Lee-Feldstein ONLY HAD THREE EXPOSURE AVERAGE MEASUREMENTS, which she applied to ALL cohorts, regardless of whether it was prior to 1925 or after 1948. Higgins did a bit better, since he had 826 measurements dating back to 1943. Hence his exposure data needs to be considered along with Lee-Felstein's data, see also Appendix A, Section B.

Page 9-6, Paragraph 2:
In addition to Lee-Feldstein's data, that by Pershagen et al. (1981) for non-smokers, given below, would seem to indicate at least an additive effect.

SMRs for Non-smokers Exposed to Arsenic and/or Sulfur Dioxide

Exposure	Standardized Rate Ratios Non-Smokers
No arsenic	1.0
High arsenic	1.2
High sulfur dioxide	1.8
High (arsenic + sulfur dioxide)	4.4

The data for Ott et al. (1974) had asbestos and vinyl chloride as confounding factors, whereas Mabuchi et al. (1979) also had the probability of other confounding factors.

Page 9-6, Paragraph 3:
Morris's data were exactly three average values, which leads to semiquantitative exposure estimates at best, NOT "quantitative" ones.

Page 9-8, Paragraph 3:
For an update on the Garfield Smelter see Appendix A, Section C. Rencher's data must be viewed with caution, since his follow-up period was very short.

Page 9-9, Paragraphs 2 and 3:
For updates on the Ronnskarverken smelter see Appendix A, Section D.

Page 9-10, Paragraph 2:
For an update on the Dow plant (Ott et al. study) see Appendix A, Section E.

Page 9-10, Paragraph 3:
Confounding factors should not be overlooked in insecticide manufacturing.

Page 9-11, Paragraph 2:
Table 9-2 needs to be updated using the articles mentioned Appendix A, Sections A-F.

Page 9-13, Paragraph 2:
Why were the data given above (under Page 9-6, Paragraph 2) for the interaction of arsenic and sulfur dioxide discounted, whereas those found by Pershagen for arsenic and smoking were considered of great significance (Table A-4)?

Page 9-19, Section 9.4:
(4) The similarity in smoking habits for workers with different levels of arsenic exposure (Welch et al., 1982):
All this means is that the general community had homogeneous smoking habits.
(5) The demonstration of an arsenic-related dose-response for nonsmokers and smokers separately (Welch et al., 1982):
It is not stated whether the analysis of the whole Anaconda cohort also showed this, it well may not.
(9) The geographical dispersion just means smelter workers get cancer.

Page 10-1, Section 10.1:
These two mechanisms are the traditional explanation of SOME of the toxic effects of arsenic ONCE THE DETOXIFICATION MECHANISMS "SLOW." Hence:
(1). What evidence is there that these are CARCINOGENIC mechanisms, they certainly are not recognized in the main stream of the scientific community,
(2). If by chance they were to be the CARCINOGENIC mechanisms, there would have to be some type of threshold since they are "toxicity mechanisms," obeying the normal "laws" of toxicology and
(3). In addition, it is stated in Paragraph 3, "The clinical significance of most of these inhibitions is uncertain."

Page 10-2, Paragraph 1:
Why should arsenolysis be important in teratogenesis?

Page 10-2, Paragraph 2:
Pentavalent arsenic is NOT more potent than trivalent arsenic, this WAS A MIS-READING OF HOOD'S (1983) ARTICLE. Each route of administration needs to be compared separately. For example, by the oral route As(+3) is 5 times as toxic as As(+5).

Page 10-3, Paragraph 1:
Please state the reference(s) for, "Both sulfhydryl group binding and arsenolysis have been proposed as mechanisms for genotoxic effects of arsenic", the subject does not seem to be discussed in Chapter 7.

The article by Oberly et al. (1982) needs to be re-reviewed, since in the presence of metabolic activation the results were negative.

In addition, to the article by Jan et al. (1986), those by Lee et al. (1985a and b, 1986a, b and c and 1988) need to be reviewed. This section is incomplete as it stands.

At least some of this section needs to be placed in Chapter 7.

Page 10-3, Paragraph 3:
It should be noted that the healthy worker effect normally applied to a much greater extent at high and very high exposure levels. Alice Hamilton wrote of smelter workers in the first two decades of this century, that it was luck that the average time of empolyment was so short, because otherwise they would cause a major health problem.

Page 10-4, Paragraph 2:
It should be remembered that it is HIGHLY probably that the Anaconda "LOW" levels were grossly underestimated, particularly those hired before 1950.

Page 10-4, Paragraph 3:
The size of the low-dose-level cohorts is NOT always so small. Please recheck the data after updating it.

Page 10-4, Paragraph 4:
By examining the data presented by Enterline et al. (1986 and 1987b) and re-examining the up-dated epidemiological and other data, a threshold value can probably be deduced.

Page 10-4, Section 10.4.2:
It would be appreciated if DHS would reconsider its position in light of EPA's SAB recommendation. It should be noted that IARC's opinion is dated 1983 and much has happened since then. Most of the EEC nations have very different rating systems to that espoused by IARC.

Page 10-5, Paragraph 3:
Does the statement in sentence 3 mean that DHS discounts ALL bioassays not conforming to the NTP protocol? There are a number of other protocols which have wide acceptance in the scientific community.

Page 10-6, Paragraph 2 and Page 10-7, Paragraph 1:
Will this argument be applied by DHS to other substances such as cadmium or ONLY to arsenic?

Page 10-8, Paragraph 2:
Could DHS please cite an instance where a chemical is an initiator and hence probably also what use to be called a "complete" or "strong" carcinogen, that is not a carcinogen in animals. Also what experiments suggest, not even prove, that there is an arsenical metabolite which qualitatively appears in humans but not animals?

Page 10-8, Paragraphs 3 and 4:
The mechanisms suggested in these paragraphs would ALL also produce tumors in animals.

Page 10-9, Paragraph 2:
Attempting to tie latency to arsenic as an initiator is not main stream science and hence would need to be backed-up with references by top-flight pathologists such as Francis J. C. Roe or others of his standing.

Page 11-1, Paragraph 1:
A clear distinction needs to be made concerning semi-quantitative data versus quantitative data. For example, Lee-Feldstein's data is semi-quantitative being based upon 3 average measurements.

A clear dose relationship was often not observed and the reasons for this need to be considered. Often even "negative" data can be instructive.

It should be remembered that smelter workers, at high exposure levels, swallowed large quantities of arsenic.

If TOTAL Risk Assessments are to be commonly used by the ARB and DHS they should be discussed in this document and in addition the problem of a threshold or detoxification level assumes even greater importance.

Page 11-2, Paragraph 1:
Both Lee-Feldstein's and Higgin's data have draw-backs, but both sets need to be considered. Perhaps Lee-Feldstein's data tapes might be useable with Higgin's more complete exposure measurements.

Page 11-2, Paragraph 2:
Why not fit models to Osborne's data as well as Enterline's?

Page 11-3, Paragraph 3:
(1) The use of detailed quantitative exposure estimates based on individual work histories in combination with industrial

hygiene surveys going back sometimes to 1938:
What has not been considered is the quality of the data and its relationship to what the workers were in reality exposed to. The data by Lee-Feldstein are semi-quantitative and for the Anaconda smelter Higgins' exposure data are of higher quality. For the Tacoma plant, Osborne's data are probably more realistic than Enterline's for early exposures, their later data are the same.

(2) Over 200,000 person-years (PY) of follow-up for 8044 workers (Higgins et al., 1985) and over 70,000 PY for 2802 workers (Enterline et al., 1987a):
All this means is that one has a large cohort and a long follow-up period. This does not alleviate the difficulty of estimating exposure levels.

(3) The demonstration of a clear dose-response relationship of respiratory cancer mortality to cumulative arsenic exposure:
What has not been assessed are the high exposures often for many years, prior to "entry into the cohort" for a relatively large number of workers.

(4) The similarity in smoking habits for workers with different levels of arsenic exposure (Welch et al., 1982):
All this means is that the general community had homogeneous smoking habits.

(5) The demonstration of an arsenic-related dose-response for nonsmokers and smokers separately (Welch et al., 1982):
It is not stated whether the analysis of the whole Anaconda cohort also showed this.

(6) The finding of no change in the standardized mortality ratios (SMRs) when workers in the Anaconda plant exposed to asbestos were removed from the analysis (Welch et al., 1982 and Higgins et al., 1985):
What is not stated is why they were not removed as a matter of cause.

(7) The finding of an arsenic effect independent of sulfur dioxide exposure at the Tacoma plant (Enterline and Marsh, 1982) and at the Anaconda plant (Lubin et al., 1981):
Whate is not discussed is how and more particularly why the data from the Tacoma and Anaconda smelters differ from that given above for the Ronnskarsverken smelter.

Page 11-4, Paragraph 4:
The data presented here were used by Higgins BUT NOT BY Lee-Feldstein.

Page 11-5, Paragraph 2:
Osborne's data are probably more realistic than Enterline's for early exposures, their later data are the same.

Page 11-6, Paragraph 1:
It would appear smoking is being used as an "interaction" substance, it is suggested that the same be done for sulfur dioxide.

III.

Department of Health Services Staff Responses to Summarized Comments on the Draft Part B and the Executive Summary

Page 11-6, Paragraph 2:

a. The accuracy of the exposure assessment for workers in the cohort:
What has not been assessed are the high exposures often for many years, prior to "entry into the cohort" for a relatively large number of workers. In addition, what has not been considered is the quality of the data and its relationship to what the workers were in reality exposed to. In a recent report by Harper (1988) on the Great Greenhill Arsenic Works in England which functioned until 1925 three short descriptive passages are worthy of note when extrapolating conditions in smelters during the 1940s and the 1920s:
   1. "The furnace operators complained of the affects of "SMEECH", that is the escape of gases containing arsenic and sulfur under certain wind conditions."
   2. "Fuller's earth was used to counteract the irritation caused by the eczema that appeared in the folds of the neck or around the nostrils" and
   3. "The men complained that after having been engaged in removing the arsenic soot from the flues if the mouth is wiped out with a clean handkerchief a black deposit of soot is removed."

b. The accuracy of the measures of cancer mortality:
There is a need to know more about the mechanisms by which arsenic produces lung cancer. Is it related to cumulative exposure or elevated dose or bioavailability? Is there a threshold?

c. The potential effects of confounding factors:
When respiratory cancer has been linked with arsenic in smelters, copper, sulfur and other compounds are always present at high levels. The interactions of arsenic with these substances and these substances with each other are of importance, but are difficult to measure and also to quantify.

d. Demographic characteristics of the cohort, which differ from those of the general population:
The smelter workers in the risk assessment studies are white males exposed to high levels of dusts and chemicals and the factors in extrapolating the finding to the general population at ambient levels are not fully understood.

Page 11-19, Paragraph 2:
The Risk Assessment is basically ALREADY USING URINARY MEASUREMENTS RATHER THAN AIR CONCENTRATIONS. So the third sentence is difficult to understand. Enterline's data just converts the urinary data into air measurements at the beginning of the calculations. What is suggested is that urinary measurements be retained until the final step.

Page 11-30, Paragraph 3:
Since arsenic is known to have detoxification mechanisms and in ALL the cohorts, exposure measurements were greatly underestimated for large numbers of the workers, it is NOT AT ALL CERTAIN THAT THE RESULT UNDERESTIMATES THE RISK.

Page 11-36, Note *:
It should be noted that for many of the smelter workers this was not true. First, the earlier workers were exposed 10 or 12 hours per day and a lot more than 250 days per year. And second, most of the workers were exposed to environmental levels which were much higher than 2 ng/m3.

Appendix B:
Attempting to tie length of latency to initiation or promotion is not main stream science and hence would need to be backed-up with articles by or peer review by Francis J. C. Roe or Sir Richard Doll or others of their standing.

Appendix E:
Attempting to tie arsenic Risk Assessment to THREE levels of smoking would seem to be extreme. It is suggested that the smoking sections be sent for review to Peter N. Lee, a top flight epidemiologist, who specializes in interpreting epidemiological data involving smoking.

APPENDIX A.

A. TACOMA

The most important point in Risk Assessment are the validity and accuracy of exposure data, this was difficult to obtain prior to 1950 and nearly impossible before 1935. The best anyone can do is to obtain an estimate LEVEL before 1950 and a GUESTIMATE prior to 1935. These LEVELS and GUESTIMATES need to be tied to dates of major process changes and big changes in general working conditions. This is why an understanding of process changes and working condition are SO IMPORTANT.

From the data below for the Tacoma plant it can be seen that roughly the data for after 1961 are 10x lower than that between 1951-1960, which in turn are 10x lower than that in the 1940s. From plant history it is GUESTIMATED that the 1940s level was again 10x lower than that prior to 1936, which in turn was 10x lower than that prior to 1916, which in turn was 10x lower than that prior to 1916.

Average Air Arsenic Measurements 1947-1974

Year	ugAs/m3	Year	ugAs/m3
1947	15,290	1956	1,540
1948	39,870	1957	150
1950	21,820	1960	1,660
1951	2,670	1963	170
1952	2,080	1968	720
1953	5,220	1971	170
1954	630	1973	640
1955	1,650	1974	610

Source - Hoerger (1981).

The main studies done on the Tacoma plant are those by Pinto and Bennett (1963), Milhan and Strong (1974), Pinto and Enterline (1975), Pinto et al., 1976, 1977 and 1978), Enterline and Marsh (1980 and 1982), Osborne (1984) and Enterline et al. (1987a).

1. The Osborne 1984) Study:

The Osborne (1984) study is key, because these data are what the CALIFORNIA RISK ASSESSMENT IS BASED UPON. She recalculated the exposure estimates and improved them by incorporating newly available historical air sampling dating from 1938 and urinary measurements starting in 1948. Exposures were estimated for each department and each year or group of years. Departmental urinary arsenic values were reported as GEOMETRIC MEANS from individual workers (these data covered the periods 1948-1952 and 1973-1975).

Using departments where both types of measurements were available, a URINARY-TO-AIR conversion was estimated. Next, this conversion was applied to departments which lacked air data. Augmenting these data with air measurements from 1938 onwards (which were themselves weighted to reflect work-time spent at each sampling site), the exposures for each year in each of the fifteen departments with measurements starting in 1938 or 1948 were derived by linear regression. These regression lines had similar slopes and therefore the MEDIAN percent decline was used to extrapolate back in time for those departments lacking data between 1938 and the 1970s. For all departments, PRE-1938 EXPOSURES WERE ASSUMED EQUAL TO 1938 ESTIMATES. Individual work histories were used to calculate exposures for each worker. Some key data from Osborne's thesis are given below:

Arsenic in Air ug/m3 (Measured or Calculated) in Three Departments

	Cottrell		Arsenic Plant		Roaster-Furnace	
Measurement	Air	Urine	Air	Urine	Air	Urine
1938	2840		8110		1120	
1947	1980		1480		280	
1948	-	2366	5880	3325	-	5172
1949		2834		1405		1984
1950	-	1100	5360	5368	-	8079
1951	-	-	1180	4480	-	6839
1952	-	2444	720	2501	-	1304
1953	-	1480	1100	1926	-	5327
1954	-	-	370	353	-	-
1955	-	-	430	323	-	-
1956	-	202	1140	1109	-	410
1957	-	3610	150	554	-	1149
1960	-	-	6560	149	-	-
1970		263		3306		-
1971	-	124	80	291	-	299
1972		539		1530		775
1973	-	642	360	768	-	502
1974	100	586	1120	1568	-	314
1975		574		766		235
1976	1130	203	430	235	80	68

It will be noted that much of the data is extrapolated from urinary data.

Number of Workers by Age and Year of Hire

AGE AT HIRE#	YEAR OF HIRE				
	Before 1930	1930-39	1940-49	1950-63	TOTAL
Total	516	687	1127	472	2802
Mean age at hire	29.4	29.0	29.8	28.8	29.4
Mean age on entry to follow-up	48.5	33.4	31.3	30.2	34.8

= Enterline and Marsh (1982)

Two things need to be noted:
(1) The age at hire remains fairly constant at 29 years and
(2) 18.4% of the workers were employed before 1930 and a further 24.5% before 1939 (for a total of 42.9%), which means three things
    (a) They would have been exposed to even higher levels of arsenic than measured in 1938,
    (b) There are enough of them to strongly influence any Risk Assessment and
    (c) In MOST studies their employment (exposure x years) prior to a certain year were either set at ZERO or set at an unrealistically low level.

Average Arithmetic Means for Departments Classed as Very High and High 1930-1965

	DEPARTMENT	AVERAGE ug/m3	RANGE ug/m3
VERY HIGH	Roaster-Furnace	9933	17133-1424
	Arsenic	8594	17450-2195
HIGH	Cottrell	4027	7270-715
	Steel-Riggers-Welder	3287	5659-218
	Electric	1974	3211-181
	Carpenter-Paint shop	1721	2939-36
	Repair-Maintenance	1665	2939-36
	Yard-Engine-Crane	1123	1995-18
	Reverberatory-Mudmill-Slag shot	1010	2175-109
	Converter-Flues-Blast	963	1995-18
	Pipe	631	

Estimated Air Arsenic ug/m3 (Geometric Means)

	Before 1931	1940	1950	1960	1970
Cottrell	4008	3631	1675	472	382
Arsenic Plant	9620	9147	1481	1210	1210
Roaster-Furnace	9445	9426	3985	788	1785

The above two Tables are given to show how exposure figures can be manipulated by using arithmetic and geometric means (assuming normal or log-normal distributions).

Ceiling Exposures (Arithmetic Means) and Lung Cancer Mortality

CATEGORY (mg/m3)	AT RISK	PERSON-YEARS	OBS	EXP	SMR#
LOW - Below 0.08	338	8558	11	7.87	139.8
MED - 0.08-0.5	50	1316	2	1.18	169.5
HIGH - 0.5-4.0	1696	42714	55	30.81	178.5**
VERY HIGH - 4.0+	718	17877	36	12.65	284.6**

** = p less than 0.01
# = Expected deaths based on Washington State white males.

Average Geometric Mean Intensity of Exposure (TWA) and Lung Cancer Rates

TWA (mg/m3	AT RISK	PERSON-YEARS	OBS	EXP	SMR#
Below 0.08	799	18890.6	24	13.69	175.3*
0.08-0.5	797	20477.8	27	13.55	199.2**
0.5-4.0	1048	26985.1	42	21.62	194.2**
4.0+	158	4111.4	11	3.64	302.2**

* - p less than 0.02
** - p less than 0.01
# - Expected deaths based on Washington State white males.

Again the above two Tables are given to show how exposure figures can be manipulated by using arithmetic and geometric means (assuming normal or log-normal distributions), as well as ceiling and mean exposure data. This becomes of importance in assessing final Risk Assessment data.

Comparison of Tacoma and Anaconda Air Arsenic ug/m3

TACOMA	Max	Aver*	ANACONDA	AVER**
Cottrell	7270	4027	Cottrell	13003
Arsenic Plant	17450	8594	Arsenic Refinery	7470
Roaster-Furnace	17133	9933	Arsenic Roaster	20226

* = 1938-65 Arithmetic Average
** = 1943-65 Arithmetic Average

The above table shows that the Anaconda exposures were MUCH higher than those at Tacoma, even allowing for the difference in dates, which if anything should lower the Anaconda averages.

In summary, Osborne (1984) noted that when cancer excess was measured using a time weighted average exposure, all categories of exposure were significantly elevated. While an increasing trend over categories was observed, significant differences among categories were not noted.

She also noted that when a 30-day ceiling arsenic level was used as an index of exposure, it resulted in all categories showing an excess of respiratory cancer deaths. However, LOW and MEDIUM categories were not significant, whereas significant excesses in the HIGH and VERY HIGH categories were observed. (It was possible that the SMRs in the LOW and MEDIUM categories failed to reach significance due to the small number of persons in these categories).

Osborne (1984) also reported that in every category the cumulative exposure SMRs were elevated, however, a strong dose-response relationship was not observed. It should be noted that in the life table approach a worker is counted in each cumulative exposure category through which he passes and progresses to a higher conditional on having been counted in each of the lower catgeories. In the 1977 study on retirees from the Tacoma smelter, years at risk were contributed to only one category, the category the worker was in at the time of retirement. Since retirees tended to have longer employments than other workers (Pinto and Bennett, 1963), the higher cumulative exposure categories would receive more years at risk than the lower categories. With more person-years in the higher categories, one would expect a weighting of events in the higher categories.

It should in addition be noted that in this 1984 report some workers hired before 1930 with a mean exposure at the start or follow-up of 19 years, did not contribute person-years to all lower categories. This was also true of the 1930-1939 year of hire group, whereas those hired after 1939 were represented in all exposure categories in computing cumulative exposure.

Another difference between the earlier methods and this 1984 analysis was that in the earlier studies a single non-decreasing exposure value was assigned to each department, whereas in the 1984 report time dependent values were assigned. Thus the 1984 cumulative exposure method would cover a wider range and distribute person-years at risk over a wider range and causing the slope of the dose-response curve to be more shallow than that of the earlier studies.

2. Enterline et al. (1987a) Study:
This study by Enterline et al. (1987a) used the same approach as described in Osborne's thesis and much of the data appears to be the same.

These authors stated that this report differs from earlier published ones in that:

a. A decline in arsenic exposure levels that occurred during the period 1938 to 1948 were incorporated into the exposure estimates,

b. The relation between air and urinary arsenic levels was estimated,

c. The data set representing urinary arsenic were converted to probable air levels,

d. A somewhat different data set was used for urinary arsenic and

e. Dose-response relationships were expressed in terms of air arsenic levels.

It should be noted that in this study the following exposure assumptions were made:

a. Urinary-to-air relationships were used from some departments to estimate air exposures in departments where only urinary data were available,

b. The application of 1938 exposure estimated to the years 1926-1938 and

c. Linear interpolation and extrapolation to estimate air concentrations in years lacking data between 1938 and 1970.

Key data from the Enterline et al. (1987a) article are given below:

Estimated Air Arsenic ug/m3 for Selected Departments

Department	1940	1945	1950	1955	1960	1965	1970	1975
Cottrell	2118	1866	1613	1362	1110	857	604	353
Arsenic	2911	2544	2178	1812	1446	1079	713	346
Roaster-Furnace	2349	2062	1776	1489	1203	917	629	343
Riggers-Welders	1308	1157	1006	854	702	550	399	247
Repair Shop	1404	1216	1030	843	656	470	282	96
Mason	1093	960	826	694	561	429	296	163

This particular table should be compared with Osborne's data, given above. It will readily be noted that the exposure data for the earlier years is much lower, in fact far too low when working conditions are considered.

Further data from Enterline et al. (1987a) are given in the Tables below:

Various Statistics Versus 4 Exposure Levels Measured as Urinary Arsenic

Urinary Arsenic in ug/l	Under 250	250-499	500-749	750+
No. of Men	137	58	46	54
Average year of hire	1937	1944	1945	1943
Ave. year urine taken	1952	1952	1952	1952
Arith. Mean urine ugAs/l	114	356	606	1179
Geom. Mean urine ugAs/l	96	349	602	1119
No. Respiratory Cancers	6	2	4	7
SMR for Respiratory Cancer	181	263	494#	801*

= p less than 0.05
* = p less than 0.01

SMRs Versus Duration and Level of Exposure
DURATION OF EXPOSURE IN YEARS

DURATION OF EXPOSURE IN YEARS	LEVEL OF EXPOSURE: 213ugAs/m3 (under 400) Obs.	SMR	564ugAs/m3 (400-799) Obs.	SMR	1487ugAs/m3 (800+) Obs.	SMR	TOTAL Obs.	SMR
Under 10 yrs	17	151	9	200	14	266*	40	190*
10-19 yrs	9	292*	7	417*	2	158	18	299*
20-29 yrs	12	305*	7	556*	7	609*	26	409*
30+ yrs	9	239#	4	328	7	609*	20	326*
TOTAL	47	213*	27	312*	30	341*	104	263*

Obs. = Observed deaths, # = p less than 0.05,
* = p less than 0.01

Time-Weighted Exposure (TWE) Versus SMRs for Lung Cancer

Time-Weighted Exposure (TWE) ugAs/m3-yrs	Observed Deaths	Entry into Study: Mean TWE	SMR	Follow-up starting Termination: Mean TWE	Employment SMR
under 750	9	424.5	136	401.0	144
750-1999	15	1370.1	170	1316.9	206#
2000-3999	19	2955.0	184#	2944.3	243*
4000-7999	21	5784.5	205*	5731.9	288*
8000-19999	23	11412.0	221*	12554.9	332*
20000-44999	13	29558.2	264*	28614.0	409
45000+	4	57375.0	339	59166.7	477#

= p less than 0.05
* = p less than 0.01

Enterline et al. (1987a) fitted models which allowed for nonlinearities in the data and found a curve that was concave-downward (decreasing slope with increasing dose) provided the best fit between cumulative exposure based on air concentrations and lung cancer mortality. This relationship yielded an extremely steep slope at low doses. A linear relationship was obtained when exposure was expressed in urinary measurements.

In earlier studies duration of exposure appeared not to have a marked effect on respiratory cancer SMRs. In this study, however, the affects of duration of exposure appeared to vary with air arsenic concentration and were smallest in the lowest level of exposure category and largest in the highest level of exposure category. Thus, the contribution of duration of exposure seemed dependent on exposure level.

It should be recognized that, for example, by choosing Enterline et al. (1987a) figures rather than Osborne's the risk assessment numbers can be changed substantially. It should also be realized that by computing data by decades makes little sense if massive reconstruction of the facilities did not coincide with these dates. In addition, workers were exposed for all of their working lives, not just from an arbitrary starting date on.

B. ANACONDA

Several studies have been omitted and other have only been mentioned in passing. Some of the key data and/or comments that need consideration are given below.

1. Lubin et al. (1981) Study:

Their data showed no clear trends by exposure group for any cause of death, although there was an increased risk from respiratory cancer in workers with "high" and "medium" arsenic exposure for any length of employment. Elevated risks were only associated with "low" exposure to arsenic, when the workers had been employed longer than 25 years. Their data on the cofounding factor sulfur dioxide is given below.

Relative Risk of Death 1964-1977 by Years of Employment

HEAVY/MEDIUM EXPOSURE		Years of Employment				
SO_2	As	0-9	10-14	15-24	25+	TOTAL
Yes	Yes	0.98	1.72	2.98	1.98	1.42
Yes	No	0.61	1.13	5.34	1.02	0.90
No	Yes	4.15	1.52	0.56	1.84	2.30
No	No	1.00	1.00	1.00	1.00	1.00

2. Higgins et al. (1981) Study:

Smoking histories were obtained for 86% of those considered. Estimates of the total lifetime exposure were made from the industrial hygiene information collected in three surveys conducted by the State of Montana in 1943, 1958 and 1965 and the data collected from 1943 to 1958 by the Industrial Hygiene Department of the Anaconda Company.

Smokers had a slightly higher SMR than non-smokers only in the "heavily" exposed group, however, the total number of respiratory cancer deaths was very small.

3. Welch et al. (1982) Study:
These authors noted that 436 out of the 1800 workers were potentially exposed to asbestos. Smoking did not appear to be as important as arsenic exposure. The findings relative to smoking contrast with those reported by Pershagen et al. (1981), who found evidence of an interaction between cigarette smoking and arsenic exposure in a case-control study of Swedish copper smelter workers. These authors also noted that smoking was of more importance than arsenic exposure.

4. Higgins (1982) Study:
A number of criticisms have been made of this study:

a. The extent to which respirator usage was an effective protective measure is unknown, although respirators may not have been used until after 1964.
b. Exposure values were probably underestimated from 1884 to 1938, were reasonable for 1938 to 1964 and were overestimated for the period after 1964.
c. Whereas classification of workers according to exposure levels, irrespective of duration, may be a plausible measure of exposure and may correlate better with respiratory cancer than cumulative exposure, the fact that the authors drew these conclusions on small sample sizes has been questions.
d. By analyzing risk according to ceiling category, a significant number of workers in the low and medium TWA categories were placed in high ciling categories, 21% and 60%, respectively, resulting in small sample sizes in the two lower exposure categories.
e. The linear dose-response model cannot detect the risk of lung cancer mortality using these small sample sizes.

5. Lee-Feldstein (1983a and b, 1986 and 1988) Studies:
These four reports need to be considered together because they are different facets of the same study. Only key points from the 1988 study and a couple of other facts will be given. The Table below shows that if the three cohorts were mixed, the death rates would not parallel cumulative exposure too well.

Cumulative Exposure Versus Observed Respiratory Cancer Deaths

Cohort	Exposure	Cumulative Exposure* (ug/m3-years)	Observed Deaths	Observed / Expected Deaths x 100
	H	36064	13	520
25+ years	M	18560	49	700
	L	9280	51	313
15-25	H	22250	9	692
	M	11600	13	325
	L	5800	16	186
less than	H	5973	11	458
15 years	M	3074	31	333

* = Exposure is given in ug/m3-years, estimated as (air concentration) X (duration). Air levels are ONLY ROUGH ESTIMATES.

It should be noted that the excess in respiratory cancer mortality was seven to eight times that expected among men first employed prior to 1925 who were heavily or moderately exposed to arsenic, but it dropped to about four times that expected among men heavily exposed and first employed in 1925-1947.

In her 1988 study Lee-Feldstein explored in a follow-up period of 1938-1977, the relationship between lung cancer mortality and various measures of exposure in a matched case control study on the copper smelter employees. Four measures of exposure were calculated. The maximum arsenic exposure was calculated using the relative scale of "heavy," "medium" or "light." The cumulative arithmetic arsenic exposure averages were calculated using Morris' (1975) data and values of 61.99mg/m3, 7.03mg/m3 and 0.38mg/m3 for "heavy," "medium" amd "light" areas of exposure, respectively. The cumulative geometric arsenic exposure averages were calculated again using Morris' (1975) data and values of 21.65mg/m3, 0.26mg/m3 and 0.19mg/m3 for "heavy," "medium" and "light" areas of exposure, respectively. The time weighted average exposure measures were based on arithmetic means.

In men employed prior to 1925, three measures of exposure, maximum arsenic exposure, cumulative arsenic exposure and time weighted average exposure, all appeared to be good predictors of respiratory cancers. Whereas for men first employed between 1925-1947, time weighted average exposure, appeared to be the best predictor of lung cancers. No arsenic exposure measure was a significant predictor for the men first employed between 1948-1955, the short follow-up time to 1977 may be the reason. No particular advantage was found in lagging exposures.

6. Higgins et al. (1986 and 1988) Studies:
These studies need to be taken into serious consideration since they cover basically the same cohort as Lee-Feldstein and much more data are given. Hence what you have are TWO TOP NOTCH EPIDEMIOLOGISTS looking at the same cohort and publishing on it - this seldom happens!

The aims of Higgins et al. (1986) study (as stated by the authors) were:
a. To extend the period of follow-up to January 1, 1981.
b. To determine whether the results obtained for the 1,800-man sample were borne out for the entire cohort.
c. To determine if there was an excess of respiratory cancer among men whose arsenic exposures were estimated to have been low or medium (below 100ug/m3 and below 500ug/m3, respectively).
d. To evaluate in more detail the effects of age, cohort of hire, latency and duration of exposure, on respiratory cancer mortality.

Three arsenic exposure estimates were initially made:
a. Weighted average exposure concentration (WAEC), which was the same as that used previously in an earlier study by Higgins (1982) for a sample of 1800 men from this same cohort,
b. Revised exposure indices, in which the concentrations estimated for certain departments were changed and
c. No exposure factor estimates, which used department average levels of arsenic, calculated without any exposure factor.

Departments with similar arsenic concentrations were combined int four broad categories of exposure: low (below 100ug/m3), medium (100-499ug/m3), high (500-4,999ug/m3) and very high (above 5,000ug/m3).

Men in this smelter cohort were hired between 1884 and 1956, a time span of 72 years. Of the 8,044 men, 1,392 (17%) were hired between 1884 and 1923, 1,307 (16%) between 1924 and 1937 and 5,435 (68%) between 1938 and 1956. No men were hired after 1956. Men hired before 1924 entered the cohort at an average age of 50 years, men hired from 1924 to 1937 entered at an average age of 31 years and men hired from 1938 to 1956 entered at an average age of 32 years.

Three indices of individual arsenic exposure were developed:
a. Time-Weighted Average (TWA) was based on a man's estimated average arsenic exposure.
b. Thirty-day ceiling was determined by the highest arsenic category (low, medium, high or very high) in which a man had spent at least 30 days.
c. Cumulative lifetime exposure (ug/m3-yr) was calculated by summing each man's arsenic exposure from the date he was hired until 1978.

The authors stated that the arsenic exposures assigned to individual men were certainly tentative and should be considered as broad indicators of exposure. The reasons for this statement become obvious when the figures and tables presented in Higgins et al. (1988) are examined. Exposure data could have been underestimated by a factor of 4 or better. This becomes important when considering the data presented by Jarup et al. (1989) which indicates that exposure rather than cumulative exposure is of importance, when considering lung cancer risks. Thus it is important to note that Higgins et al. (1986) did state that the actual concentrations in the exposure estimates should be treated with reserve, as should the exposure-response relationships derived from them. Uncertainty as to the validity of the exposure estimates in the Anaconda smelter is because:

a. Exposure measurements made from 1943-1965 were applied to both earlier and later years,
b. Department-based data was applied to individual workers,
c. Average measurements were used to represent job sites with very wide ranges of exposure measurements,
d. The use of time exposure factors determined during one period were used for both earlier and later periods,
e. The "unmeasured" job sites were assumed to involve "light" exposures only,
f. Applying the highest level of cumulative exposure reached by and individual to all the years of the worker's follow-up.

Arsenic air concentrations, though not measured before 1938, were certainly higher then than during later time periods. They were likely to have been much higher before 1923-1924 when selective flotation was introduced. Levels were no doubt also considerably reduced during the early 1940s as a result of the improvements brought about by the installation of new converters. Over the years the SMRs for respiratory cancer showed a pronounced downward trend, with those hired during earlier periods having much higher overall SMRs.

The risk of respiratory cancer was strongly influenced by cohort of hire. Men hired before 1938 had almost twice the risk of those hired from 1938 to 1956. The slope of the dose-response curves also differed by cohort of hire. In men hired before 1938 there was a pronounced increasing trend in lung cancer mortality with increasing arsenic exposure. This was expected, since arsenic concentrations in the early days of the smelter were probably many times greater than those measured from 1943 to 1965. Exposure/response relationships also differed strikingly between those hired before 1938 and those hired from 1938 to 1956. Men hired in the earlier period had a much steeper curve of increasing exposure than men hired in the later period. Indeed, the men hired from 1938 to 1965 had a relatively flat exposure/response curve. Thus in men hired from 1938 to 1956, the trend in lung cancer mortality with increasing cumulative arsenic exposure was

small - from a SMR of 149 in the lowest to an SMR of 198 in the highest arsenic exposure category. The method of calculating exposures, using concentrations based on measurements made from 1943 to 1965 for estimating exposures during the entire study period, may have contributed to the flatness of the dose-response curve for this group of men.

There is no doubt that arsenic concentrations from 1966 to 1981 were lower than those measured between 1943 and 1965. There was also a decline in the concentrations between 1943 and 1965. Higgins et al. (1986) analyses ignored these trends. Consequently, exposures during the later years were over-estimated, resulting in some men being categorized in a higher exposure group than they should have been. To the extent that respiratory cancer is related to arsenic dosage this would tend to bias the SMRs in the higher categories downwards and thus flatten the dose-response curve. This flattening of the dose-response curve is more likely to have affected men hired later.

The mortality for respiratory cancer was significantly elevated for all age groups under 55 but the SMRs decreased consistently with increasing age. Much of this decline appears to be due to the confounding factor of age at hire with cohort of hire. When age at hire was considered for each hiring cohort there was little trend in the SMRs for respiratory cancer by age at hire. If anything there was a slight increase in SMRs in those hired at older ages after 1924.

Latency depended strongly on cohort of hire. The mean latency of those hired before 1938 was 42.5 years, whereas that for the men hired from 1938 to 1956 was 24.1 years. This probably reflected the survivorship status of those in the earlier cohort of hire. The cohort hired from 1938 to 1956, on the other hand, was complete. The latency of 24.1 years for this group was thus a true estimate. The 42.5 years for the earlier cohort was probably a measure of the degree of selection through survival.

Duration of exposure, or number of years worked, did not have a clear relationship to respiratory cancer mortality. Among the entire cohort, there was no apparent pattern of respiratory cancer mortality by number of years worked within various cumulative arsenic categories. There was a slight tendency for the SMRs for respiratory cancer to be higher for greater numbers of years worked among those hired before 1938, but not among those hired after 1938. Thus, duration of exposure does not appear to be strongly related to lung cancer mortality for this cohort.

Higgins et al. (1986) reanalysis confirmed the exposure-response relationship between arsenic exposure and excess respiratory cancer risk, regardless of the method used to estimate department arsenic exposure. Men in the highest arsenic exposure categories

had an approximately four-to-six fold excess, whereas those in the medium and high categories had an approximately two-to-three fold excess and those in the low exposure category had a risk about 50% greater than expected. These results were consistent for arsenic exposures categorized by TWA, 30-day ceiling and cumulative methods.

The only men for whom no significant excess of respiratory cancer was observed, were those who had never worked in departments where a maximum concentration of 400ug/m3 had been measured. However, there were only 535 such men and Higgins et al. (1986) did not believe that they formed a sound basis for an arsenic safety threshold. The authors also stated that analysis of mortality in the whole cohort did not support the conclusion reached earlier on the basis of the 1,800 men sample that there was no elevated risk of lung cancer in those men in the lowest exposure groups, but whether it was reasonable to expect to be able to detect a group with below average risk given the incomplete data on exposure within the plant or before or after working there and the absence of smoking histories is debatable.

With regard to the absence of smoking histories, Higgins et al. (1986) stated, "This could clearly influence their risk of respiratory cancer such that an SMR of 100 might not be an appropriate expectation. Relatively heavy smoking might explain the lack of a healthy worker effect, which has been a consistent observation in this cohort."

C. GARFIELD

Milby and Hine (1974) examined the death records of 1,910 employees, who had worked for at least 10 years between 1950 and 1972, in the mine or in the concentrator or in the smelter. No excess of cancers of any type, including respiratory cancers were found when the above cohort was compared with state or U. S. averages. In this cohort, the proportion of lung cancers to total cancers was 21% which was lower than found in other studies. The study has been criticized because:

1. Deaths in the mines, the concentrators and the smelter were considered as a single cohort.
2. The study included persons with little exposure to arsenic.
3. Workers who left the complex before retirement, were only sometimes included in the study.
4. An insensitive technique, namely, proportionality mortality was used.

Rencher et al. (1977 and 1979) examined 965 records of deaths which had taken place between 1959 and 1969. They divided the deaths into four categories - smelter workers, mine workers, concentrator workers and others. There was no indication of the number persons who had been employed in more than one category.

The respiratory cancer death rate was 7.0% for smelter workers, 2.2% for both miners and concentrator workers, whereas that for the state was 2.7%. When age adjusted death rates were compared, the figures were as follows: smelter workers 10.1, miners 2.1 and state averages 2.2. No statistical test of significance was made, since some approximations were required in calculating the rates. The respiratory cancer deaths as a percentage of total deaths for smokers and non-smokder in the smelter workers were 9.2 and 3.3, in the miners 3.3 and 0.7 and in the concentrator workers 3.3 and 0.8, respectively.

In order to calculate total exposure, hourly average concentrations were obtained for sulfur dioxide, sulfuric acid mist, arsenic, lead and copper in each of twelve working areas in the smelter. The average cumulative exposure indices were categorized for respiratory cancer, non-cancer respiratory and non-respiratory deaths and are given below:

Average Cumulative Pollutant Exposure Indices for Respiratory and Non-respiratory Deaths

	SO_2	H_2SO_4	As	Pb	Cu
Respiratory Cancer Deaths	9482	2902	1105	1545	5159
Non-cancer Respiratory Deaths	3654	1283	38.5	78.6	3386
Non-respiratory Deaths	4909	1649	93.4	93.4	4322

It will be readily seen that all indices were substantially higher for respiratory cancer and the differences were statistically significant for sulfur dioxide, arsenic and lead. It is not known if there was a dose-response relationship, but the results do indicate that either the deceased were employed long periods of time or had worked in highly exposed areas. Of the 17 persons who had died of respiratory cancer, all but one had worked in at least one of the four areas with the highest average exposure levels for the five pollutants measured. The average duration of employment for these 17 workers was 29 years.

Further data on this smelter, called Plant 3 were gather by Enterline et al. (1986 and 1987b). They analyzed the mortality experience, through 1980 to 6078 white workers, who had worked at least 3 years between January 1, 1946 and December 31, 1976 in these smelters. The main data taken from both papers are given below.

Numerical Statistics on Cohort of White Male Smelter Workers

No. of Workers	Total	Alive	Dead	Unknown
Garfield Smelter	2288	1681	590	17

Respiratory System Cancers by Cumulative and Average Exposure to Arsenic

	Observed Cancers	SMR U. S.*	SMR State#	Cumulative Exposure ug/m3-yr	Average Exposure ug/m3
Garfield Smelter	50	117	221##	462	43

* = U. S. data used for comparison
\# = State data used for comparison
= p less than 0.01

SMRs for Respiratory System Cancers (No. Cancers Observed)

	Duration of Employment in years				
Smelter	Under 10	10-19	20-29	30+	TOTAL
Garfield Smelter	22 (1)	253 (21)	101 (14)	88 (14)	117 (50)

Respiratory System Cancers by Increasing Cumulative Exposures to Arsenic

Cumulative Exposure ugAs/m3-yrs	Under 100 SMR (Obs)	100-249 SMR (Obs)	250-499 SMR (Obs)	500+ SMR (Obs)	Total SMR (Obs)
Garfield Smelter	123 (4)	60 (2)	90 (5)	141 (32)	123 (43)

In Enterline et al.'s (1986) data (see above) it would appear that arsenic only becomes a significant risk above 500ugAs/m3-yrs, whereas in their (1987b) paper (see below) arsenic appears to be a significant risk at under half this level.

Respiratory Cancers by Cumulative Exposures Lagged for 5 Years				
ugAs/m3-yrs	Under 100	100-249	250-999	1000+
Observed Cancers	12	18	22	18
Relative Risk	0.58	0.85	1.21	1.60

In the Enterline et al. (1987b) study the time period considered was January 1, 1949 through December 31, 1980. The authors stated that, "By using internal controls, a dose-response relationship for lung cancer was observed with exposure to arsenic and sulfur dioxide. When cigarette smoking were included with arsenic and sulfur dioxide exposure data in a nested case-control analysis, only smoking and arsenic were statistically significant factors." However, considering Enterline et al.'s (1986) data it would appear that arsenic only becomes a significant risk following high levels of exposure.

D. RONNSKARSVERKEN SMELTER, SWEDEN

Rehnlund (1978), using proportional mortality, concluded that in his study the increased lung cancer death rate was due to smoking, sulfur dioxide and possibly arsenic in that order.

Axelson et al. (1978) noted a number of interesting facts:

1. There was a fairly high rate of lung cancer amongst smelter workers with no known exposure. (It is not known to which elements and compounds they were exposed).
2. The use of asbestos in the smelter, leading to at least one case of lung cancer plus asbestosis.
3. A case of lung cancer plus pulmonary fibrosis which may or may not have been due to radiation therapy.

These authors noted that on an average 48.6% of the smelter workers were smokers, whereas 83% of the arsenic exposed workers who died of lung cancer were smokers.

The following points are of worthy of note from Wall (1980):

1. Of the 3919 workers, 25% were employed before 1935 and 50% before 1945,
2. The average number of years worked at the smelter was 13.8 years and 19% of the employees worked for less than one year,
3. The observed to expected ratio for smelter workers compared with national Swedish male average, showed an overall excess of 28% in the 65-74 year age group, whereas for the younger age groups, the mortality was similar to or lower than the national average.

Pershagen et al. (1981) examined the interactions between exposure to arsenic and sulfur dioxide in the smelter and smoking as related

to lung cancer mortality among 228 deceased workers using the case-referent technique. The workers were grouped into four categories:

1. High arsenic and high sulfur dioxide exposure - persons who had worked at least 6 months in the gas purifier or roaster departments.
2. High arsenic and lesser amounts of sulfur dioxide than in group 1. - persons who had worked longer than 6 months in the arsenic metal, arsenic refining, arsenic salt, building, electrical, machine, or selenium departments, roaster workers being excluded.
3. Sulfur dioxide levels as high as in group 1., but arsenic levels substantially lower and
4. Control group, low arsenic and low sulfur dioxide - workers in the battery factory, central laboratory, coal crusher, copper foundry, delivery department, electrolysis department, lead smelter, nickel smelter and ore dressing department.

The Standardized Rate Ratios (SRR) for Smoker and Non-Smokers Exposed to High or Low Levels of Arsenic and/or Sulfur Dioxide

Exposure	SRR Non-Smokers	SRR Smokers
No arsenic	1.0	4.9
High sulfur dioxide	1.8	6.5
High arsenic	1.2	14.7
High (arsenic + sulfur dioxide)	4.4	22.0

The data showed a positive dose-response relationship for arsenic, but not for sulfur dioxide exposure among smokers. There appeared to be a positive interaction between arsenic and sulfur dioxide for both smokers and nonsmokers in group 1. There also appeared to be a synergism between arsenic exposure and smoking, the data pointing towards a multiplicative, rather than an additive effect.

In 1989 Jarup et al. published a cause-specific mortality study of 3,916 male smelter workers who had been employed for at least 3 months from 1928 through 1967 and who had been followed through 1981. This study is a follow-up of Wall's (1980) study. Below are given key data for estimated arsenic and sulfur dioxide exposure and lung cancer risks (as expressed by SMRs) experience by these workers.

Arsenic Level by Time Period in Various Areas of the Works

	TIME PERIOD Years I	II	III	ARSENIC LEVELS mg/m³ I	II	III
Sulfur Works	35-43			2.0		
Cu Roaster	-39	40-49	50-	4.0	0.5	0.15
Gas purifier	-39	40-49	50-75	50.0	5.0	1.0
Cu Furnace	-39	40-49	50-	4.0	0.5	0.15
Converter	-39	40-49	50-	2.5	0.4	0.1
As Refining	33-39	40-61	62-77	10.0	1.0	0.1
As & Se Works	33-45	46-69	70-	2.0	0.5	0.05
Machine Shop	-39	40-49	50-	2.5	0.25	0.05
Electric Dept.	-39	40-49	50-	2.5	0.25	0.05
Building Dept.	-39	40-49	50-	2.5	0.25	0.05

SMRs by Arsenic Exposure Level and Year of Hire

Dose Arsenic mg-yrs/m3	YEAR OF HIRE Before 1940 OBS.	SMR#	1940-49 OBS.	SMR#	After 1950 OBS.	SMR#
Below 0.25	3	296	7	379*	4	152
0.25-0.99	3	627**	8	394*	2	190
1.00-4.99	6	191	11	332*	-	-
5.00-14.9	10	324*	5	540*	-	-
15.0-49.9	27	440*	2	876*	-	-
50.0-99.9	6	750*	-	-	-	-
100+	12	1664*	-	-	-	-
TOTAL	67	433*	33	390*	6	134

\# = SMR, 10 year minimum latency, exposure lagged 5 years
** = Significant at the 54% level
* = Significant at the 17% level.

SMRs by Arsenic Exposure Intensity and Years of Duration

Average Intensity mgAs/m3	DURATION OF EXPOSURE IN YEARS: UNDER 10 Yrs. BEFORE 1940 SMR	UNDER 10 Yrs. AFTER 1940 SMR	20-29 Yrs. BEFORE 1940 SMR	20-29 Yrs. AFTER 1940 SMR	30+ Yrs. BEFORE 1940 SMR	30+ Yrs. AFTER 1940 SMR	TOTAL BEFORE 1940 SMR	TOTAL AFTER 1940 SMR
Under 0.1	157	317	250	91	-	181	151	214#
0.1-0.29	642#	358	305	273	655	365	519	332#
0.3+	319	547	540	828	459	-	456	588
TOTAL	358	407	480	205	431	217	433	311

= Significant at the 5% level

SMRs by Cumulative Exposure to Sulfur Dioxide

Cumulative Exposure Index mg-yrs/m3 for Sulfur Dioxide	Observed Lung Cancers	SMR#
Under 0.25	38	369
0.25-14.9	12	348
15.0-29.9	8	406
30.0+	48	391
TOTAL	106	379

= SMR, 10 year minimum latency, exposure lagged 5 years

Jarup et al. (1989) concluded:

1. There was a positive-dose response between cumulative arsenic exposure and lung cancer,
2. However, there was no clear dose-response relationship in the low exposure categories,
3. Arsenic concentration was more important than duration of exposure in the development of lung cancer,
4. There was no evidence of a dose-relationship between estimated exposure to sulfur dioxide and lung cancer and
5. There was no positive dose-response relationship between arsenic exposure and ischemic heart disease or cerebrovascular disease. Also cumulative arsenic exposure was probably not implicated in the development of ischemic heart disease or cerebrovascular disease.

It is important to note that these finding by Jarup et al. (1989) support the concept of a threshold for development of lung cancer following arsenic exposure.

In a paper by Sandstrom et al. (1989), which is another update of Wall (1980), further data on this smelter is given. The cancer incidence in 3710 male smelter workers was analyzed from the years 1958 through 1982. A total of 467 cancer cases were found, of which, 33 had more than one tumor. One hundred and twenty respiratory cancer cases (SMR=232) were found and of these 107 were primary lung cancers. Key results are given below and it will be seen that apparently arsenic exposure is not the full story.

SMRs by Area of Work Exposure

All Men Who Had Ever Worked at:	Lung Cancer Mortality Obs. Cases	SMR	Lung Cancer Incidence Obs. Cases	SMR
Roaster	30	417	35	467
Gas Purifier	22	431	22	415
Nickel Smelter	11	282	12	279
Arsenic Departments	22	286	23	284
Machine Shop	26	371	25(?)	352
Other Departments	25	140	33	172
All Work Sites	95	242	107	255

E. THE DOW INSECTICIDE PLANT STUDY - Ott et al. (1974)
The total number of deaths in the exposed group examined in the proportionate mortality study was 173, whereas the number examined in the retrospective study was variously quoted as 95 or 96. In this latter study, two of the 22 workers with lung cancer had been exposed to asbestos. In addition, it is known that quite a number of the workers had also been exposed to vinyl chloride.

It is difficult to interpret these results, because it is known that 16 of the 28 workers, who had died of respiratory cancer and 138 out of the total cohort of 173, had been exposed to arsenic for less than a year. These short term workers, showed no increase in the ratio of observed to expected deaths with increase in dosage, the ratio remaining approximately constant at about two. Thus, it seems likely, that only once short term workers and others, who had been exposed to asbestos and/or vinyl chloride are removed from the proportionate mortality and the retrospective studies, can meaningful results be obtained.

There also appears to be no association between degree of exposure and time from first exposure to death, most of the lung cancers occurring 20-40 years after first exposure, regardless of total exposure.

Samuels and Howarth (1975) criticized these studies for three reasons:

(1) The numbers of expected deaths based on the estimated proportional mortality ratio are unreliable, because the estimating equation left 43% of the observed variability in the controls, unexplained. Also, the 90% confidence intervals for the exposed groups, probably would not be consistent with a dose-response relationship,

(2) Both the exposed and the control groups, excluded men who had left the company before retirement and hence the results were subject to bias and

(3) The workers were exposed to many substances besides both trivalent and pentavalent arsenic.

In addition, estimates of dosages were very approximate, because the data used, was itself highly variable; for example, in 1952 in one area, the air sampling ranged from 1.7 to 40.8mgAs/m3 and in another 0.2-7.5mgAs/m3, whereas in 1943, the total range was given as 0.18-19.0mgAs/m3. It was also noted that, the job categories in Group 1 (8 hour TWA of 5.0mgAs/m3) and in Group 2 (8 hour TWA of 3.0mgAs/m3) were in very dusty areas and that concentrations of lead would have been very high too. The exposure estimates for Groups 3 (8 hour TWA of 1.0mgAs/m3) and 4 (8 hour TWA of 0.1mgAs/m3) were subjective, because actual measurements did not exist. Finally, Ott et al. (1974) constructed their dose response curve, using a breathing volume of 4m3/8 hours, rather than the generally accepted 10m3 per 8 hours, hence their cumulative exposures were probably low by a factor of 2.5.

Waxweiler (1981) quoted the following ratios for observed to expected rates, for respiratory cancer, at this particular plant: arsenical exposure 3.27 and arsenic and vinyl chloride exposure 5.0.

Sobel et al. (1988) published an update of the Ott et al. (1974) study through 1982 of 611 employees who had been exposed to arsenic between 1919 and 1956. In the update, an additional 9 respiratory cancers were observed subsequent to 1973, versus 7.8 expected. In all, 35 men had died of respiratory cancer versus 15.6 expected, giving a ratio of 2.25. The effects of smoking were not assessed. Sobel et al. (1988) noted that one man had died from a teratoma of the testis (exposed to arsenic for 16 months), whereas another had died of a carcinoma of the penis (exposed to arsenic for 36 years). The Ott et al. (1974) study reported an excess of lymphatic and hematopoietic cancers. One of the lymphatic cancers on recoding proved to be malignant skin melanoma. Thus, on recoding, there were 4 lymphatic and hematopoietic cancers, versus 2.7 expected. Further data are given in the four Tables below.

Status as of December 31, 1982 of persons exposed January 1, 1940 or after

Still Working	38 Men
Retired	222 Men
Deceased	214 Men
Left the Company, But Living	135 Men
Unknown	2 Men
TOTAL	611 Men

Correlation of First Exposure with Observed to Expected Death Ratios

Period of 1st Exposure	Persons-yrs	Observed	Obs./Exp.
Before 1930	3766*	19	3.58
1930-1939	3249*	8	2.42
1940-1949	9176	6	1.26
1950-1956	4103	2	0.91

* = Under estimated, since only exposure after 1940 counted.

Ratio of Observed to Expected Deaths (Observed)

	Duration of Exposure in Yrs.*			
Yrs Since Termination	Under 1	1-4	5+	TOTAL
Under 15	0	0	30.00 (3)	4.29 (3)
15-24	2.35 (4)	8.00 (4)	3.33 (1)	3.60 (9)
25-34	2.22 (8)	2.00 (3)	1.67 (1)	2.10 (12)
35-44	1.30 (3)	0.63 (1)	0	0.89 (4)
45+	3.53 (6)	2.50 (1)	0	3.33 (7)
TOTAL	2.14 (21)	2.20 (9)	3.13 (5)	2.24 (35)

* = May be under estimated, since only exposure after 1940 counted.

Data After Two Follow-up Periods 1940-1973 and 1974-1982

Follow-up Interval	1940-1973#	1974-1982
Number of Persons	611	471
Person-yrs	16305	3951
Obs./Exp. Lung Cancer Deaths	3.33	1.16

= Corrected for incomplete follow-up in Ott et al. (1974)

F. WASHINGTON STATE STUDIES - Follow-up of the Nelson et al. (1973) Study:
Wicklund et al. (1988) in a case control study, evaluated all white male orchardists in the State of Washington, who died between 1968 and 1980 from respiratory cancer. These authors state that, "The cause of excess mortality from respiratory cancer among Washington State orchardists remains unknown." A summary of the data presented are given below.

Odds Ratios for Causes of Lung Cander Deaths in a Case Control Study of Orchardists

Exposure Variable	Cases	Controls	Odds Ratio#
Lead Arsenate Only	9	11	0.79
DDT Only	33	29	0.91
Lead Arsenate + DDT	89	89	1.12
Neither	23	23	1.00

= Adjusted for smoking

REFERENCES USED IN THE DISCUSSION BUT NOT QUOTED BY DHS/ARB

ACGIH; Committee on Threshold Limit Values: Documentation of Threshold Limit Values and Biological Exposure Indices, 5th ed. (Cincinnati, OH, American Conference of Governmental Industrial Hygienists, 1986).

Andersen, O.; Effects of coal combustion products and metal compounds on sister chromatid exchange (SCE) in a macrophage cell line. Environ. Hlth. Perspect. 47: 239-53 (1983).

Anke, M., Groppel, B., Gruen, M., Hennig, A. and Meissner, D.; The influence of arsenic deficiency on growth, reproduction, life expectancy and health of goats. 3rd Spurenelem. Symp. Arsen pp 25-32 (Jena, 1980).

Anke, M., Grun, M. and Partschefeld, M.; The essentiality of arsenic for animals. Trace Subst. Environ. Hlth. 10: 403-9 (1976a).

Anke, M., Grun, M., Partschefeld, M., Groppel, B. and Hennig. A.; Essentiality and function of arsenic. 3rd Intern. Symp. Trace Elem. Metabol. Man Anim. pp 248-52 (1978).

Anke, M., Krause, U. and Groppel, B.; The effect of arsenic deficiency on growth, reproduction, life expectancy and disease symptoms in animals. Trace Subst. Environ. Hlth. 21: 533-50 (1987).

Aranyi, C., Bradoff, J. N., O'Shea, W. J., Graham, J. A. and Miller, F. J.; Effects of arsenic trioxide inhalation exposure on pulmonary antibacterial defenses in mice. J. Toxicol. Environ. Hlth. 15: 163-72 (1985).

Axelson, O., Dahlgren, E., Jansson, C. D. and Rehnlund, S. O.; Arsenic exposure and mortality: a case referent study from a Swedish copper smelter. Brit. J. Indust. Med. 35: 8-15 (1978).

Baker, E. L., Hayes, C. G., Landrigan, P. J., et al.; A nationwide survey of heavy metal absorption in children living near primary copper, lead and zinc smelters. Amer. J. Epidemiol. 106: 261-73 (1977).

Basmadshijewa, K. and Dawidkowa, K.; Biochemical and morphological changes in albino mice which were treated with arsenic trioxide. Z. Ges. Hyg. Ihre Grenzgebiete 20: 586-8 (1974).

Beckman, G., Beckman, L. and Nordenson, I.; Chromosome aberrations in workers exposed to arsenic. Environ. Hlth. Perspect. 19: 145-6 (1977).

Beckman, G., Beckman, L., Nordenson, I. and Nordstrom, S.; Chromosomal aberrations in workers exposed to arsenic. In: Genetic Damage in Man Caused by Environmental Agents, Berg, K., ed., pp 205-11 (Academic Press, 1979).

Bertolero, F., Pozzi, G., Sabbioni, E. and Saffiotti, U.; Cellular uptake and metabolic reduction of pentavalent to trivalent arsenic as determinants of cytotoxicity and morphological transformation. Carcinogenesis 8: 803-8 (1987).

Bertolero, J., Marafante, E., Edel Rade, J. et al.; Biotransformation and intracellular binding of arsenic in tissues of rabbits after intraperitoneal administration of 74As labeled arsenite. Toxicology 20: 35-44 (1981).

Binder, S., Forney, D., Kaye, W. and Paschal, D.; Arsenic exposure in children living near a former copper smelter. Bull. Environ. Contam. Toxicol. 39: 114-21 (1987).

Blakley, B. R.; The effect of arsenic on urethane induced adenoma formation in Swiss mice. Can. J. Vet. Res. 51: 240-3 (1987a).

Blakley, B. R.; Alterations in urethan-induced adenoma formation in mice exposed to selenium and arsenic. Drug Nut. Interact. 5: 97-102 (1987b).

Blakley, B. R., Sisodia, C. S. and Mukkui, T. K.; The effect of methylmercury, tetraethyl lead and sodium arsenite on the humoral immune response in mice. Toxicol Appl. Pharmacol. 52: 245-54 (1980).

Brown, L. M., Pottern, L. M. and Blot, W. J.; Lung cancer in relation to environmental pollutants emitted from industrial sources. Environ. Res. 34: 250-61 (1984).

Brown, M. M., Rhyne, B. C., Goyer, R. A. and Fowler, B. A.; Intracellular effects of chronic arsenic administration of renal proximal tubule cells. J. Toxicol. Environ. Hlth. 1: 505-14 (1976).

Buchet, J. P. and Lauwerys, R.; Study of inorganic arsenic methylation by rat liver, in vitro: relevance for the interpretation of observations in man. Arch. Toxicol. 57: 125-9 (1985).

Buchet, J. P. and Lauwerys, R.; Study of factors influencing the in vivo methylation of inorganic arsenic in rats. Toxicol. Appl. Pharmacol. 91: 65-74 (1987).

Buchet, J. P., Geubel, A., Pauwels, S., Mahieu, P. and Lauwerys, R.; The influence of liver disease on the methylation of arsenite in humans. Arch. Toxicol. 55: 151-4 (1984).

Buchet, J. P., Lauwerys, R., Mahieu, P. and Geubel, A.; Inorganic arsenic metabolism in man. Arch. Toxicol. Suppl. 5: 326-7 (1982).

Buchet, J. P., Lauwerys, R. and Roels, H.; Comparison of the urinary excretion of arsenic metabolites after a single oral dose of sodium arsenite, monomethylarsonate or dimethylarsinate in man. Intern. Arch. Occup. Environ. Hlth. 48: 71-9 (1981a).

Buchet, J. P., Lauwerys, R. and Roels, H.; Urinary excretion of inorganic arsenic and its metabolites after repeated ingestion of sodium meta-arsenite by volunteers. Intern. Arch. Occup. Environ. Hlth. 48: 111-8 (1981b).

Burgdorf, W., Kurvink, K. and Cervenka, J.; Elevated sister chromatid exchange rate in lymphocytes of subjects treated with arsenic. Hum. Genet. 36: 69-72 (1977).

Carpenter, S. J.; Developmental analysis of cephalic axial dysraphic disorders in arsenic-treated hamster embryos. Anat. Embryol. 176: 345-65 (1987).

Casto, B. C.; Letter dated 31 May 1977 to Dr. Bill Waugh, EPA (1977).

Chuang, S. M., How, S. W. and Jean, H. H.; Chromosome study on 42 cases of Blackfoot Disease. J. Formosan Med. Assn. 80: 1210-6 (1981).

Coleman, B. W., Reimann, E. M., Grummer, M. L., et al.; Antagonistic effect of arginine on zinc metabolism in chicks. J. Nut. 101: 1695-1702 (1971).

Cordier, S., Theriault, G. and Iturra, H.; Mortality patterns in a population living near a copper smelter. Environ. Res. 31: 311-22 (1983).

Crossen, P. E.; Arsenic and SCE in human lymphocytes. Mutat. Res. 119: 415-9 (1983).

Dai, H., Wu, K., Lin, B. Y., Kuo, T. T. and Feng, T. Y.; Synergistic effects of sodium arsenite on UV-irradiated Saccaromyces cerevisiae. Bot. Bull. Acad. Sin. 29: 87-91 (1988).

DeBrabander, M., Van de Veire, R., Aerts, F., et al.; A new culture model facilitating rapid quantitative testing of mitotic spindle cell inhabition in mammalian cells. J. Natl. Cancer Inst. 56: 357-63 (1976).

DeKnudt, Gh., Leonard, A., Arany, J. et al.; In vitro studies in male mice on the mutagenic effects of inorganic arsenic. Mutagenesis 1: 33-4 (1986).

Dugatova, G., Podstavkova, S. and Trebaticka, M.; Influence of arsenic on Drosophila melanogaster. II. Test on recessive lethal and other mutations affecting vitality and located in X chromosome and on the occurrence of chromosome aberrations. Acta Facult. Rerum Nat. Univ. Comenianae, Genet. 9: 79-87 (1978), CA 89: 209922 (1978).

Enterline, P. E. and Marsh, G. M.; Mortality studies of smelter workers. Amer. J. Indust. Med. 1: 251-60 (1980).

Enterline, P. E. and Marsh, G. M.; Mortality among workers exposed to arsenic and other substances in a copper smelter. Amer. J. Epidemiol. 116: 895-910 (1982).

Enterline, P. E., Henderson, V. L. and Marsh, G. M.; Exposure to arsenic and respiratory cancer. A reanalysis. Amer. J. Epidemiol. 125: 929-38 (1987a).

Enterline, P. E., Marsh, G. M., Esmen, N. A., Henderson, V. and Ricci, E.; Report on Mortality Among Copper and Zinc Smelter Workers in the United States (Rept. Smelter Environ. Res. Assn., 1986).

Enterline, P. E., Marsh, G. M., Esmen, N. A., et al.; Some effects of cigarrete smoking, arsenic and SO2 on mortality among US copper smelter workers. J. Occup. Med. 29: 831-8 (1987b).

EPA (U.S. Environmental Protection Agency); Risk Assessment Forum Peer Review Workshop on Arsenic (1986/7).

EPA (U.S. Environmental Protection Agency); Special Report on Ingested Arsenic. EPA 625/3-87/013A (1986/7).

Ferm, V. H. and Carpenter, S. J.; Malformations induced by sodium arsenate. J. Reprod. Fert. 17: 199-201 (1968).

Ferm, V. H., Saxon, A. and Smith, B. M.; The teratogenic profile of sodium arsenate in the golden hamster. Arch. Environ. Hlth. 22: 557-60 (1971).

Fiscor, G. and Lo Piccolo, G. M.; Survey of pesticides for mutagenicity by the bacterial-plate assay method. EMS Newsl. 6: 6-8 (1972).

Foa, V., Colombi, A., Maroni, M., Buratti, M. and Calzaferri, G.; The speciation of the chemical forms of arsenic in the biological monitoring of exposure to inorganic arsenic. Sci. Total Environ. 34: 241-59 (1984).

Fong, K., Lee, F. and Bockrath, R.; Effect of sodium arsenate on single strand DNA break formation and post-replication repair in Escherichia coli following UV irradiation. Mutat. Res. 70: 151-6 (1980).

Fornace, A. J. and Little, J. B.; DNA-protein cross-linking by chemical carcinogens in mammalian cells. Cancer Res. 39: 704-10 (1979).

Fowler, B. A., Woods, J. S. and Schiller, C. M.; Ultrastructural and biochemical effects of prolonged arsenic exposure on liver mitochondria of rats. Environ. Hlth. Perspect. 19: 197-204 (1977).

Frost, F., Harter, L., Milham, S. D., et al.; Lung cancer among women residing close to an arsenic emitting copper smelter. Arch. Environ. Hlth. 42: 148-52 (1987).

Fukunaga, M., Kurachi, Y. and Mizuguchi, Y.; Action of some metal ions on yeast chromosomes. Chem. Pharmacol. Bull. 30: 3017-9 (1982).

Gainer, J.H.; Effects of arsenicals on interferon formation and action. Amer. J. Vet. Res. 33: 2579-86 (1972).

Gainer, J.H. and Pry, T.W.; Effects of arsenicals on viral infections in mice. Amer. J. Vet. Res. 33: 2299-307 (1972).

Gartell, M. J., Craun, J. C., Podrebarac, D. C. and Gunderson, E. L.; Pesticides, selected elements and other chemicals in infants and toddler total diet samples, October 1980 - March 1982. Assn. Off. Anal. Chem. J. 69: 123-45 (1986a).

Gartell, M.J., Craun, J.C., Podrebarac, D.S. and Gunderson, E.L.; Pesticides, selected elements and other chemicals in adult total diet samples, October 1980 - March 1982. Assn. Off. Anal. Chem. J. 69: 146-61 (1986b).

Gencik, A.; Effect of trivalent arsenic on the occurrence of structural chromosomal aberrations in vivo and in vitro. Bratisl. Lek. Listy 69: 269-79 (1978).

Gencik, A.; Szokolayova, J. and Cerey, K.; Dominant lethal test after peroral administration of arsenic. Bratisl. Lek. Listy 67: 179-87 (1977).

Goeneches, S., Fischer, B., Fischer, K. and Koehler, F.; Dose-related incorporation of arsenic into organs in pregnant mice following chronic oral administration of arsenic. Anorg. Stoffe Toxikol. Krim., Symp. 91-9 (1983).

Goodman, L. and Gilman, A.; The Pharmacological Basis of Therapeutics. 1st Ed., pp 1-960 (Macmillan, 1941).

Greaves, W.W., Rom. W.M., Lyon, J.L., et al.; Relationship between lung cancer and distance of residence from non-ferrous smelter stack effluent. Amer. J. Indust. Med. 2: 15-24 (1981).

Grunicke, H., Bock, K., Becker, H., et al., Effect of alkylating antitumor agent on the binding of DNA to protein. Cancer Res. 33: 1048-53 (1973).

Happle, R. and Hoehn, H.; Cytogenetic studies on cultured fibroblast-like cells derived from basal cell carcinoma tissue. Clin. Genet. 4: 17-24 (1973).

Hartwell, T.D., Handy, R.W., Harris, B.S. et al., Heavy metal exposure in populations living around zinc and copper smelters. Arch. Environ. Hlth. 38: 284-95 (1983).

Hemmerly, J. and Demerec, M.; Tests of chemicals for mutagenicity. Cancer Res. 15 (Suppl. 3): 69-75 (1955).

Higgins, I., Arsenic and respiratory cancer among a sample of Anaconda smelter workers. Report submitted to OSHA in the comments of the Kennecott Minerals Company on the inorganic arsenic rulemaking (Exhibit 203-5, 1982).

Higgins, I., Welch, K., Oh, M. et al.; Influence of arsenic exposu and smoking on lung cancer among smelter workers: A pilot study. Amer. J. Indust. Med. 2: 33-42 (1981).

Higgins, I.T.T., Welch, K.B., Oh, J.S. and Burchfiel, C.; Mortality of Anaconda smelter workers in relation to arsenic and other exposures. (Report to the Anaconda Company, 1982).

Higgins, I.T.T., Welch, K.B., Oh, M.S., et al.; Arsenic exposure and respiratory cancer in a cohort of 8044 Anaconda smelter workers: A 43-year follow-up study. (Final report to the Chemical Manufacturers' Association and the Smelters Environmental Research Association, 1986).

Higgins, I., Welch, K. and Oh, M.; Measurement of exposure to arsenic in the occupational setting. In: Epidemiology and Health Risk Assessment, Gordis, L., ed. pp 129-38 (Oxford Univ. Press, 1988).

Hodge, H.C.; Estimation of the mutagenicity of arsenic compounds utilizing dominant lethal mutations in mice (SERA Project 76-25, Univ. of California Contract No. SERA-HI-2, 1977).

Hoerger, F.D.; Indicators of exposure trends. Banbury Repts. 9: 435-54 (1981).

Holmberg, R.E. and Ferm, V.H.; Interrelationships of selenium, cadmium and arsenic in mammalian teratogenesis. Arch. Environ. Hlth. 18: 873-77 (1969).

Hood, R.D.; Effects of sodium arsenite on fetal development. Bull. Environ. Contam. Toxicol. 7: 216-22 (1972).

Hood, R.D.; Toxicology of prenatal exposure to arsenic. In: Arsenic: Industrial, Biomedical, Environmental Perspectives, eds., Lederer, W. H. and Fensterheim, R.J., pp 134-50 (1981, Pub. Van Nostrand Reinhold, 1983).

Hood, R.D. and Bishop, S.L.; Teratogenic effects of sodium arsenate in mice. Arch. Environ. Hlth. 24: 62-5 (1972).

Hood, R.D., Thacker, G.T. and Patterson, B.L.; Effects in the mouse and rat of prenatal exposure to arsenic. Environ. Hlth. Perspect. 19: 219-22 (1977).

Hood, R.D., Thacker, G.T., Patterson, B.L. and Szczech, G.M.; Prenatal effects of oral versus intraperitoneal sodium arsenate in mice. J. Environ. Pathol. Toxicol. 1: 857-64 (1978).

Hood, R.D., Vedel, G.C., Zaworotko, M.J., Tatum, F.M. and Meeks, R.G.; Uptake, distribution, and Metabolism of trivalent arsenic in the pregnant mouse. J. Toxicol. Environ. Hlth. 25: 423-34 (1988).

Hood, R.D., Vedel-Macrander, G.C., Zaworotko, M.J., Tatum, F.M. and Meeks, R.G.; Distribution, metabolism and fetal uptake of pentavalent arsenic in pregnant mice following oral or interaperitoneal administration. Teratology 35: 19-25 (1987).

Huang, R.Y., Jan, K.Y. and Lee, T.C.; Post-treatment with sodium arsenite is co-clastogenic in log phase but not in stationary phase. Hum. Genet. 75: 159-62 (1987).

Hunter, F.T., Kip, A.F. and Irvine, J.W. Jr.; Radioactive tracer studies on As injected as $KAsO_2$. I. Excretion and localization in tissues. J. Pharmacol. Exptl. Therap. 76: 207-20 (1942).

IARC; IARC Monographs on the Evaluation of Carcinogenic Risks to Humans - Genetic and Related Effects: An Updating of Selected IARC Monographs from Volumes 1-42. Suppl. 6: 1-696 (1987).

Ip, C. and Ganther, H.; Efficacy of trimethylselenium versus selenite in cancer chemoprevention and its modulation by arsenite. Carcinogenesis 9: 1481-4 (1988).

Ishinishi, N., Osato, K., Kodama, Y. and Kunitake, E.; Skin effects and carcinogenicity of arsenic trioxide: a preliminary experimental study in rats. In: Effects and Dose-Response Relationships of Toxic Metals, Nordberg, G.F., ed., pp 471-9 (Elsevier, 1976).

Jan, K.Y., Huang, R.Y. and Lee, T.C.; Different modes of action of sodium arsenite, 3-aminobenzamide and caffeine on the enhancement of ethyl methanesulfonate clastogenicity. Cytogenet. Cell Genet. 41: 202-8 (1986).

Jarup, L., Pershagen, G. and Wall, S.; Cumulative arsenic exposure and lung cancer in smelter workers: A dose-response study. Amer. J. Indust. Med. 15: 31-41 (1989).

Jung, E.G. and Trachsel, B.; Molekularbiologische untersuchungen zur arsencarcinogenese. Arch. Klin, Expt. Dermatol. 237: 819-26 (1970).

Jung, E.G., Trachsel, B. and Immick, H.; Arsenic as an inhibitor of the enzymes concerned in cellular recovery (dark repair). Germ. Med. Monthly 14: 614-6 (1969).

Kada, T., Hirano, K. and Shirasu, Y.; Screening of environmental chemical mutagens by rec-assay system with Bacillus subtilis. Chem. Mutagens 6: 149-73 (1980).

Kerkvliet, N.I., Steppan, L.B., Koller, L.D. and Exon, J.H.; Immunotoxicology studies of sodium arsenate effects of exposure on tumor growth and cell-mediated tumor immunity. J. Environ. Path. Toxicol. 4(5/6): 65-79 (1980).

Kimmel, C.A. and Fowler, B.A.; Quoted by Hood et al. (1977).

Klaassen, C.D.; Biliary excretion of arsenic in rats, rabbits and dogs. Toxicol. Appl. Pharmacol. 29: 447-57 (1974).

Ko, Y.C.; A critical review of epidemiologic studies on black-foot disease. Sangyo Ika Daigaku Zasshi 8: 339-53 (1986).

Kojima, H.; Developmental pharmacology of arsenite. II. Effect of arsenite on pregnancy nutrition and hard tissue. Nippon Yakurigaku Zasshi 70: 149-63 (1974).

Kroes, R., van Logten, M.J., Berkvens, J.M., et al.; Study on the carcinogenicity of lead arsenate and sodium arsenate and on the possible synergistic effect of diethylnitrosamine. Fd. Cosmet. Toxicol. 12: 671-79 (1974).

Kuo, T.P. and Chen, M.H.; Follow-up study of surgical treatment of endemic spontaneous gangrene in tropical Taiwan. J. Formosan Med. Assn. 68: 275-90 (1969).

Larramendy, M.L., Popescu, C. and DiPaolo, J.A.; Induction by inorganic metal salts of sister chromatid exchanges and chromosome aberrations in human and Syrian hamster cell strains. Environ. Mutagen. 3: 597-606 (1981).

Lee, T.C., Huang, R.Y. and Jan, K.Y.; Sodium arsenite enhances the cytotoxicity, clastogenicity and 6-thioguanine resistant mutagenicity of ultraviolet light in Chinese hamsters. Mutat. Res. 148: 83-9 (1985a).

Lee, T.C., Lee, K.C., Tzeng, Y.J., Huang, R.Y. and Jan, K.Y.; Sodium arsenite potentiates the clastogenicity and mutagenicity of DNA crosslinking agents. Environ. Mutagen. 8: 119-28 (1986a).

Lee, T.C., Oshimura, M. and Barrett, J.C.; Comparison of arsenic induced cell transformation, cytotoxicity, mutation and cytogenic effects in Syrian hamster embryo cells, in culture. Carcinogenesis 6: 1421-6 (1985b).

Lee, T.C., Tanaka, N., Lamb, P.W., Gilmer, T.M. and Barrett, J.C.; Induction of gene amplification by arsenic. Sci. 241: 79-81 (1988).

Lee, T.C., Tzeng, S.F., Chang, W.J., Lin, Y.C. and Jan, K.Y.; Post-treatments with sodium arsenite during G2 enhanced the frequency of chromosomal aberrations induced by S-dependent clastogens. Mutat. Res. 163: 263-9 (1986c).

Lee, T.C., Wang-Wuu,, S., Huang, R.Y., Lee, K.C. and Jan, K.Y.; Differential effects of pre- and post-treatment of sodium arsenite on the genotoxicity of methyl methanesulfonate in Chinese hamster ovary cells. Cancer Res. 46: 1854-7 (1986b).

Lee-Feldstein, A.; Arsenic and respiratory cancer in man: follow-up of an occupational study. In: Arsenic: Industrial, Biomedical and Environmental Perspectives, Lederer, W. and Fensterheim, R., eds., pp 245-54 (Van Nostrand Reinhold, 1983b).

Lee-Feldstein, A.; Cumulative exposure to arsenic and its relationship to respiratory cancer among copper smelter employees. J. Occup. Med. 28: 296-302 (1986).

Lee-Feldstein, A.; Comparison of several measures of exposure to arsenic. Matched case-control study of copper smelter employees. Amer. J. Epidemiol. 129: 112-24 (1988).

Lerman, S.A., Clarkson, T.W. and Gerson, R.J.; Arsenic uptake and metabolism by liver cells is dependent on arsenic oxidation state. Chem.-Biol. Interact. 45: 401-6 (1983).

Lofroth, G. and Ames, B. N.; Mutagenicity of inorganic compounds in Salmonella tryphimurium: arsenic, chromium and selenium. Mutat. Res. 53: 65-6 (1978).

Lu, F. J. and Liu, T. M.; Fluorescent compounds in the drinking water of Blackfoot disease endemic areas: Animal experimental model. J. Formosan Med. Assn. 85: 352-8 (1966).

Lu, F. J., Tsai, S. C. and Chen J. Y.; Studies on natural toxicants occurring in artesian well water of Blackfoot disease endemic areas of Taiwan: Chromosome aberrations in cultured lymphocytes exposed to fluorescent compounds. J. Chin. Biochem. Soc. 9: 49-54 (1980).

Lu, F. J., Tsai, M. H. and Ling K. H.; Studies on fluorescent compound in drinking water of Blackfoot disease in endemic areas. I. The toxic effect of fluorescent compound on the chick embryos. J. Formosan Med. Assn. 76: 58-63 (1977a).

Lu, F. J., Tsai, M. H. and Ling K. H.; Studies on fluorescent compound in drinking water of Blackfoot disease in endemic areas. II. Isolation and identification of fluorescent compounds. J. Formosan Med. Assn. 76: 209-17 (1977b).

Lu, F. J., Yang, C. K. K. and Ling, K. H.; Physico-chemical characteristics of drinking water in Blackfoot disease in endemic areas of Chia-I and Tainan Hsiens. J. Formosan Med. Assn, 74: 596-605 (1975).

Lubin, J. H., Pottern, L. M., Blot, W. J., et al.; Respiratory cancer among copper smelter workers: recent mortality statistics. J. Occup. Med. 23: 779-84 (1981).

Luchtrath, H.; The consequence of chronic arsenic poisoning among Moselle wine growers. J. Cancer Res. Clin. Oncol. 105: 173-82 (1983).

Mappes, R.; Experiments on the excretion of arsenic in urine. Intern. Arch. Occup. Environ. Hlth. 40: 267-72 (1977).

Marafante, E. and Vahter, M.; The effect of methyltransferase inhibition on the metabolism of 74arsenite in mice and rabbits. Chem. Biol. Interact. 50: 49-57 (1984).

Marafante, E. and Vahter, M. and Envall, J.; The role of the methylation in the detoxification of arsenate in the rabbit. Chem.-Biol. Interact. 56: 225-38 (1985).

Marcus, W. L. and Rispin, A. S.; Threshold carcinogenicity using arsenic as an example. Adv. Mod. Environ. Toxicol. 15: 133-58 (1988).

Marczynski, B.; Carcinogenesis as the result of the deficiency of some essential trace elements. Med. Hypotheses 26: 239-49 (1988).

Marzin, D. R. and Phi, H. V.; Study of the mutagenicity of metal derivatives with Salmonella typhimurium TA102. Mutat. Res. 155: 49-51 (1985).

Matsumoto, N., Iijima, S. and Katsunuma, H.; The burden of chemicals on the fetal body and its effect on fetal growth and development. Minzoku Eisei 40: 84-102 (1974).

Matsumoto, N., Okino, T., Katsunuma, H. and Iijima, S.; Effects of sodium arsenite on the growth and development of the fetal mice. Congen. Anom, Curr. Lit. 13: 175-6 (1973a).

Matsumoto, N., Okino, T., Katsunuma, H. and Iijima, S.; Effects of Na-arsenate on the growth and development of fetal mice. Teratology 8: 98 (1973b). (Na-arsenate should be Na-arsenite, see Hood, 1983).

Mattson, M. E. and Guidotti, T. L.; Health risks associated with residence near a primary copper smelter - a preliminary report. Amer. J. Indust. Med. 1: 365-74 (1980).

McCabe, M., Maguire, D. and Nowak, M.; The effects of arsenic compounds on human and bovine lymphocyte mitogenesis in vitro. Environ. Res. 31: 323-31 (1983).

McCarroll, N. E., Piper, C. E. and Keech, B. H.; An Escherichia coli microsuspension assay for detection of DNA damage induced by direct acting agents and promutagens. Environ. Mutagen. 3: 429-44 (1981).

McLean, J. R., McWilliams, R. S., Kaplan, J. G. and Birnboim, H. C.; Rapid detection of DNA strand breaks in human peripheral blood cells and animal organs following treatment with physical and chemical agents. Prog. Mutat. Res. 3: 137-42 (1982).

Milby, T. and Hine C.; A Survey of Mortality due to Respiratory Diseases among Employees at the Kenncott Corporation. Report submitted to Kennecott Copper Corporation (4 October 1974).

Milham, S. Jr. and Strong, T.; Human arsenic exposure in relation to a copper smelter. Environ. Res. 7: 176-82 (1974).

Mizuta, N., Mizuta, M., Ito, F., et al.; An outbreak of acute arsenic poisoning caused by arsenic contaminated soy-sauce (shoyu) A clinical report of 220 cases. Bull. Yamaguchi Med. Sch. 4: 131-50 (1956).

Moore, L. O.; Mutagenicity and carcinogenicity tests with mono-sodium methaneasonate, cacodylic acid and arsenic trioxide by bacteria and cell culture tests (1976), cited by the American Wood Preservers Institute to the EPA 20 May (1981).

Nadeyenko, V. G., Lenchenko, V. G., Genkina, S. B. and Arkhipenko, T. A.; Influence of tungsten, molybdenum, copper and arsenic in intrauterine development of the fetus. Farmakol. Toksikol. 41: 620-3 (1978).

Nakamuro, M. and Sayato, Y.; Comparative studies of chromosomal aberrations induced by trivalent and pentavalent arsenic. Mutat. Res. 88: 73-80 (1981).

Nielsen, F. H. and Shuler, T. R.; Arsenic deprivation studies in chicks. Fed. Proc. 37: 893 (1978).

Nielsen, F. H., Givand, S. H. and Myron D. R.; Evidence of a possible requirement for arsenic by the rat. Fed. Proc. 34: 923 (1975).

Nordenson, I., Salmonsson, S., Brun, E. and Beckman, G.; Chromosome aberrations in psoriatic patients treated with arsenic. Hum. Genet. 48: 1-8 (1979).

NRCC (National Research Council of Canada); Effect of arsenic in the Canadian environment. NRCC Pub. No. 15391: 1-349 (1977) - Bogorich's data is Canadian government data.

Nunoshiba, T. and Nishioka, H.; Sodium arsenite inhibits spontaneous and induced mutations in Escherichia Coli. Mutat. Res. 184: 99-105 (1987).

Odanaka, Y., Matano, O. and Goto, S.; Biomethylation of inorganic arsenic by the rat and some laboratory animals. Bull. Environ. Contamin. Toxicol. 24: 452-9 (1980).

Ogawa, H.; Mutagenicity of various metal compounds studies by the induction of sister chromatid exchanges of human cultured lympho-cytes. Kyoto-furitsu Ika Daigaku Zasshi 88: 505-39 (1979), CA 91: 50844 (1979).

Ogawa, H., Misawa, S., Morita, M., et al.; Sister chromatid ex-changes of human cultured lymphocytes induced by metal compounds. Igaku no Ayumi 107: 584-5 (1978), CA 90: 98233 (1979).

Ohno, H., Hanaoka, F. and Yamada, M.; Inducibility of sister chromatid exchanges by heavy metal ions. Mutat. Res. 104: 141-5 (1982).

Ohyama, S., Ishinishi, N., Hisanaga, A. and Yamamoto, A.; Comparative chronic toxicity, including tumorigenicity of gallium arsenide and arsenic trioxide intratracheally instilled into hamsters. Appl. Organomet. Chem. 2: 333-7 (1988).

Okui, T. and Fujiwara, Y., Inhibition of human excision DNA repair by inorganic arsenic and the co-mutagenic effect in Chinese hamster cells. Mutat. res. 172: 69-76 (1986).

Oppenheim, J. J. and Fishbein, W. N.; Induction of chromosome breaks in cultured normal human leukocytes by potassium arsenite, hydroxyurea and related compounds. Cancer Res. 25: 980-5 (1965).

Osborne, P.; Additional Analysis of Arsenic Exposure in a Copper Smelter and its Possible Relation to Respiratory Cancer Combining Air and Urine Data (Master of Science Thesis, University of Pittsburgh, 1984).

Pashin, Yu. V., Kozachenko, V. I. and Toroptsev, S. N.; Inhibition by arsenic trioxide of the induction of mutations with thiophosphanide in mouse somatic and germ cells. Genetika (Moscow) 20(2): 365-6 (1984).

Paton, G. R. and Allison, A. C.; Chromosome damage in human cell cultures induced by metal salts. Mutat. Res. 16: 332-6 (1972).

Pershagen, G. and Vahter, M.; Arsenic, a Toxicological and Epidemiological Appraisal. Libertryck, Stockholm, Sweden, SNV PM-1128 (1979).

Pershagen, G., Nordberg, G. and Bjorklund, N. E.; Carcinomas of the respiratory tract in hamsters given arsenic trioxide and/or benzo(a)pyrene by the pulmonary route. Environ. Res. 34: 227-41 (1984).

Pershagen, G., Wall, S., Taube, A. and Linnman, L.; On the interaction between occupational arsenic exposure and smoking and its relationship to lung cancer. Scand. J. Work Environ. Hlth. 7: 302-9 (1981).

Petres, J. and Berger, A.; Zum einfluss anorganischen arsens auf die DNA-synthese menschlicher lymphocyten *in vitro*. Arch. Dermatol. Forsch. 242: 343-52 (1972).

Petres, J. and Hundieker, M.; Chromosome pulverization induced *in vitro* in cell cultures by sodium diarsonate. Arch. Klin. Expt. Dermatol. 231: 366-70 (1968).

Petres, J., Baron, D. and Hagedorn, M.; Effects of arsenic cell metabolism and cell proliferation: cytogenetic and biochemical studies. Environ. Hlth. Perspect. 19: 223-27 (1977).

Petres, J., Schmidt-Ullrich, K. and Wolf, U.; Chromosomenaberrationen an menschlichen lymphocyten bei chronischen arsenschader. Dtsch. Med. Wchnschr. 95: 79-80 (1970).

Pinto, S. S. and Bennett, B. M.; Effect of arsenic trioxide exposure on mortality. Arch. Environ. Hlth. 7: 583-91 (1963).

Pinto, S. S. and Enterline, P. E.; OSHA Hearing, Exhibits 29b and 111 (1975/6).

Pinto, S. S. and McGill, C. M.; Arsenic trioxide exposure in industry. Indust. Med. Surg. 22: 281-7 (1953).

Pinto, S. S., Enterline, P. E., Henderson, V. and Varner, M. O.; Mortality experience in relation to a measured arsenic trioxide exposure. Environ. Hlth. Perspect. 19: 127-30 (1977).

Pinto, S. S., Henderson, V. and Enterline, P. E.; Mortality experience of arsenic-exposed workers. Arch. Environ. Hlth. 33: 325-32 (1978).

Pinto, S. S., Varner, M. O., Nelson, J. W., et al.; Arsenic trioxide absorption and excretion in industry. J. Occup. Med. 18: 677-80 (1976).

Poma, K., Degraeve, N., Kirsch-Volders, M., et al.; Cytogenetic analysis of bone marrow cells in spermatogonia of male mice after in vivo treatment with arsenic. Experientia 37: 129-30 (1981).

Pomroy, C., Charbonneau, S. M., McCullough, R. S. and Tam, G. K. H.; Human retention studies with arsenic. Toxicol. Appl. Pharmacol. 53: 550-6 (1980).

Rehnlund, S. O.; Lung cancer at a copper smelter. Boliden. Metall. AB S-932-00 (S. Kelleftehamn, Sweden, 1978).

Rencher, A. C., Carter, M. W. and McKee, D. W.; A retrospective epidemiological study of morbidity at a large western copper smelter. J. Occup. Med. 19: 754-8 (1977).

Rencher, A. C., Carter, M. W. and McKee, D. W.; A retrospective epidemiological study of morbidity at a large western copper smelter. Amer. Indust. Hyg. Assn. J. 40: 695-701 (1979).

Rossman, T. G.; Enhancement of UV-mutagenesis by low concentrations of arsenite in E. coli. Mutat. Res. 91: 207-11 (1981b).

Rossman, T. G., Meyn, M. S. and Troll, W.; Effects of sodium arsenite on the survival of UV-irradiated Escherichia coli: inhibition of a "Rec-A" dependent function. Mutat. Res. 30: 157-62 (1975).

Rossman, T. G., Meyn, M. S. and Troll, W., Effects of arsenite in DNA repair in Escherichia coli. Environ. Hlth. Perspect. 19: 229-33 (1977).

Samuels, S. and Howarth, C.; Respiratory cancer and occupational exposure to arsenicals. Arch. Environ. Hlth. 30: 423 (1975).

Sandstrom, A., Wall, S. and Taube, A.; Cancer incidence and mortality among Swedish smelter workers. Brit. J. Indust. Med. 46: 82-89 (1989).

Schaumburg, H. A.; Failure to Produce Arsenic Neurotoxicity in the Rat. PB80-208505 (1980).

Schrauzer, G. N., White, D. A. and Schneider, C. J.; Cancer mortality correlation studies. IV. Associations with dietary intake and blood levels of certain trace elements, notably selenium antagonists. Bioinorg. Chem. 7: 35-6 (1977).

Schroeder, H. A. and Balassa, J. J.; Abnormal trace metals in man: arsenic. J. Chron. Dis. 19: 85-106 (1966).

Sibatani, A.; In vitro incorporation of 32P into nucleic acids of lymphatic cells. Exptl. Cell Res. 17: 131-43 (1959).

Silaev, A. A. and Lemeshevskaya, E. P.; Experimental data on the gonadotropic effect of cesium arsenate. Gig. Tr. Prof. Zabol. #9: 46-8 (1980).

Silver, A. S. and Wainman, P. L.; Chronic arsenic poisoning following use of an asthma remedy. J. Amer. Med. Assn. 150: 584-5 (1952).

Sina, J. F. , Bean, C. L., Dysart, G. R., et al.; Evaluation of the alkaline elution/rat hepatocyte assay as a predictor of carcinogenic/mutagenic potential. Mutat. Res. 113: 357-91 (1983).

Smith, T. J., Crecelius, E. A. and Reading, J. C.; Airborne arsenic exposure and excretion of methylated arsenic compounds. Environ. Hlth. Perspect. 19: 89-93 (1977a).

Smith, T. J., Peters, J. M., Reading, J. C. and Castle, C. H.; Pulmonary impairment from chronic exposure to sulfur dioxide in a smelter. Amer. Rev. Respir. Dis. 116: 31-9 (1977b).

Snyder, W. S., Cook, M. J., Nasset, E. S., et al.; Report of the Task Group on Reference Man, pp 369-70 (Pergamon Press, 1975).

Sobel, W., Bond, G., Baldwin, C. L. and Ducommun, D. J.; An update of respiratory cancer and occupational exposure to arsenicals. Amer. J. Indust. Med. 13: 263-70 (1988).

Southwick, J. W., Western, A. E., Beck, M. M., et al.; Community Health Associated with Arsenic in Drinking Water in Millard County, Utah. EPA 600/1-81-064 (1981).

Sram, R. J.; Relationship between acute and chronic exposures in mutagenicity studies in mice. Mutat. Res. 41: 25-42 (1976).

Sram, R. J. and Bencko, V.; A contribution for the evaluation of the genetic risk of exposure to arsenic. Cesk. Hyg. 19: 308-15 (1974).

Sweins, A.; Protective effect of selenium against arsenic induced chromosomal damage in cultured human lymphocytes. Hereditas 98: 249-52 (1983).

Thacker, G. T., Patterson, B. L. and Hood, R. D.; Effects of administration route on arsenate teratogenesis in mice. Teratology 15: 30A (1977).

Thorne, M. C., Jackson, D. and Smith, A. D.; Pharmacodynamic Models of Selected Toxic Chemicals in Man, Vol. 1: 30-102 (MTP Press, 1986).

Tiedemann, G. and Einbrodt, H. J.; Mutagenicity of inorganic arsenic compounds. Wiss. Umwelt 3: 170-3 (1982).

Tkeshelashvili, K., Shearman, C. W., Zakour, R. A., et al.; Effects of arsenic selenium and chromium on the fidelity of DNA synthesis. Cancer Res. 40: 2455-6 (1980).

Tseng, W. P., Chu, H. M., How, S. W., et al.; Prevalence of skin cancer in an endemic area of chronic arsenicism in Taiwan. J. Natl. Cancer Inst. 40: 453-63 (1968).

Uthus, E. O., Cornatzer, W. E. and Nielsen, F. H.; The consequences of arsenic deprivation in laboratory animals. In: Arsenic, Industrial, Biomedical, Environmental Perspectives, eds. Lederer, W. H. and Fensterheim, R. J., pp. 173-89 (1981, Pub. Van Nostrand Reinhold, 1983).

Uthus, E. O. and Nielsen, F. H.; Effects in chicks of arsenic, arginine and zinc and their interaction on body weight, plasma uric acid, plasma urea and kidney arginine activity. Biol. Trace Elem. Res. 7: 11-20 (1985).

Vahter, M.; Biotransformation of trivalent and pentavalent inorganic arsenic in mice and rats. Environ. Res. 25: 286-93 (1981).

Vahter, M.; Metabolism of arsenic. In: Biological and Environmental Effects of Arsenic, ed. Fowler, B., pp 171-98 (Elsevier, 1983).

Vahter, M. and Envall, J.; In vivo reduction of arsenic in mice and rabbits. Environ. Res. 32: 14-24 (1983).

Vahter, M. and Marafante, E.; Reduction and binding of arsenate in marmoset monkeys. Arch. Toxicol. 57: 119-24 (1985).

Vahter, M. and Norin, H.; Metabolism of 74As-labeled trivalent and pentavalent inorganic arsenic in mice. Environ. Res. 21: 446-57 (1980).

Vahter, M., Marafante, E. and Dencker, L.; Tissue distribution and retention of 74As-dimethylarsenic acid in mice and rabbits. Arch. Environ. Contam. Toxicol. 13: 259-64 (1984).

Valentine, J. L., Kang, H. and Spivey, G.; Arsenic levels in human blood, urine and hair in response to exposure via drinking water. Environ. Res. 20: 24-32 (1979).

Vig, B. K.; Chromosome Studies on Human Subjects Exposed to Arsenic in Drinking Water. EPA 600/51-84-023 (1984).

Von Glahn, W. C., Flinn, F. B. and Keim, W. F. Jr.; Effect of certain arsenates on the liver. Arch. Pathol. 25: 488-505 (1938).

Walker, G. W. R. and Bradley, A. M.; Interacting effects of sodium monohydrogen-arsenate and selenocystine on crossing over in Drosophila melanogaster. Canad. J. Genet. Cytol. 11: 677-88 (1969).

Wall, S.; Survival and mortality pattern among Swedish smelter workers. Intern. J. Epidemiol. 9: 73-87 (1980).

Wan, B., Christian, R. T. and Soukup, S. W.; Studies of cytogenic effects of sodium arsenicals on mammalian cells in vitro. Environ. Mutagen. 4: 493-8 (1982).

Waxweiler, R. J.; Epidemiologic problems associated with exposure to several agents. Environ. Hlth. Perspect. 42: 51-6 (1981).

Welch, K., Higgins, I., Oh, M. and Burchfiel, C.; Arsenic exposure, smoking and respiratory cancer in copper smelter workers. Arch. Env. Hlth. 37: 325-35 (1982).

Wicklund, K. G., Daling, J. R., Allard, J. and Weiss, N. S.; Respiratory cancer among orchardists in Washington State, 1968 to 1980. J. Occup. Med. 30: 561-4 (1988).

Yamamoto, A., Hisanaga, A. and Ishinishi, N.; Tumorigenicity of inorganic arsenic compounds following intratracheal installations to the lungs of hamsters. Intern. J. Cancer 40: 220-3 (1987).

Yeh, S. and How, S. W.; A pathological study on the Blackfoot disease in Taiwan. Reports Inst. Pathol. Natl. Taiwan Univ. 14: 25-73 (1963).

Yu, H. S.; Blackfoot disease and chronic arsenism in southern Taiwan. Intern. J. Dermatol. 23: 258-60 (1984).

Yu, H. S., Sheu, H. M., Ko, S. S. et al.; Studies on blackfoot disease and chronic arsenism in southern Taiwan: with special reference to skin lesions and fluorescent substances. J. Dermatol. (Tokyo) 11: 361-70 (1984.

II.

Air Resources Board Staff Responses to Summarized Comments on the Draft Part A and the Executive Summary

II.

Air Resources Board Staff Responses to Summarized Comments on the Draft Part A and the Executive Summary

o **CalMat Co, November 28, 1989**

1. **Comment:** The Draft Part C, Section II response related to arsenic emissions from raw material preparation and cement preparation states that arsenic emissions "may be significant because most of them are not equipped with any control devices." Dust emissions from virtually all sources (crushers, screens, grinding mills, storage silos, clinker coolers, conveyor belt transfer points, air slide alleviators, etc.) <u>are</u> controlled by high efficiency baghouses.

Response: While the CalMat facility is equipped with baghouses at most of it's process stations and is recognized by the ARB test engineers as a "pretty clean cement facility," it is not typical of most cement production facilities in California. Dust emissions have not been adequately quantified for most of the process stations at cement production facilities. Fugitive emissions from material transfer points and storage areas are often sources of uncontrolled dust emissions leading to intermittent violations of the particulate matter standards.

2. **Comment:** The emissions range of 0.004-0.76 ton of arsenic should be given in Table II-2 as combined coal combustion and cement production emissions so that cement production emissions remain in perspective with the other sources.

Response: Appendix D and Table II-2 have been modified to show the range of 0.004-0.76 ton of estimated arsenic emissions for coal combustion and cement production for 1985.

o **Chemical Manufacturers Association,** January 18, 1990

1. **Comment:** The Biocides Panel Arsenic Acid Task Force would like the arsenic data generated from EPA-mandated personal air monitoring of workers at wood treatment plants in the final document and the Executive Summary.

Response: The data have not been added to the text of Part A or the Executive Summary because 1) worker exposure studies are helpful tools in ambient air investigations of emission sources but are not directly used to determine ambient

air concentrations of a substance, and 2) the data do not alter the conclusions of the report.

- **Fox, Weinberg & Bennett, November 30, 1989**

1. **Comment:** The ARB has not adequately addressed the comments made on the Preliminary Draft Report which included a request for a complete inventory of all inorganic arsenic sources near the Quemetco secondary lead smelting facility and new modeling of the facility emissions.

Response: Section 39650 (e) of the California Health and Safety Code states "That, while absolute and undisputed scientific evidence may not be available to determine the exact nature and extent of risk from toxic air contaminants, it is necessary to take action to protect public health." This means that the ARB may act to identify toxic air contaminants and to protect public health even in the absence of comprehensive knowledge, modeling, and inventories of all sources of emissions. If inorganic arsenic is identified as a toxic air contaminant, more information will be obtained and used to set priorities for control.

2. **Comment:** The ARB's risk assessment with respect to secondary lead smelters concludes that these emissions are responsible for "6 to 9 excess cancer deaths," when ARB's own modeling and stack test data of the facility show that the emissions will account for less than one-half excess cancer deaths. A revised "hot spot" exposure analysis based on the 1988 stack test and monitoring study should be put in the revised Executive Summary.

Response: The "6 to 9 excess cancer deaths" statement has been taken out of context. The Draft Executive Summary stated that "a one-month monitoring study of a secondary lead smelter in the South Coast Air Basin's City of Industry demonstrated an average inorganic arsenic concentration of 61 ng/m^3. These concentrations were subsequently reduced as a result of the study. If these concentrations had continued unabated for a lifetime (75 years), as many as 6 to 9 excess cancer deaths might have occurred among the 725,000 persons residing nearby."

The DHS has not been requested to do a risk assessment of the facility based on the latest (1988) monitoring study because it does not alter the conclusions of the report that inorganic arsenic qualifies as a toxic air contaminant according to the criteria found in California Health and Safety Code Section 39655.

3. **Comment:** In the Executive Summary, the average concentration of 61 ng/m^3 is based on a 1986 study which is limited and outdated. In fact, a summary of data from a three-month monitoring study (1988) downwind of the Quemetco facility demonstrated area minimum, mean, and maximum concentrations of 1.43 ng/m^3, 11.44 ng/m^3, and 61.52 ng/m^3, respectively. The fact that the area maximum in the 1988 monitoring study is the same as the area mean in the 1986 study conclusively demonstrates that the 1986 study is flawed and must be rejected.

Response: The Part A states that the 1986 ambient air monitoring downwind from the facility was done to verify that the ambient air was being impacted by the secondary lead smelter. The concentrations data generated from this special study, coupled with limited source tests of the facility resulted in two conclusions: the facility was an emitter of inorganic arsenic, and the ambient air downwind of the facility was being impacted by the facility. The ARB has not interpreted this to mean that Quemetco is the only source of arsenic contributing to the monitored concentrations.

The 1988 study does not invalidate the 1986 study because it reported different concentrations data. Monitoring studies are independent of each other and can not be used for invalidation unless the monitors are co-located and sampling is simultaneous.

If inorganic arsenic is identified as a TAC, specific control measures for any facility will not be based on the results of the 1986 study. Numerous factors are taken into account when assessing potential control options, including the availability of more recent data.

4. **Comment:** Page two of the Executive Summary states that secondary lead smelting operations are a "major" source of inorganic arsenic emissions. This has not been demonstrated. The statement should be revised as necessary pending completion of a thorough analysis of inorganic arsenic emissions from all sources in California.

Response: Part A and the Executive Summary have been revised to show secondary lead smelting operations as "smaller" and "other" sources of inorganic arsenic emissions, respectively, rather than "major" sources. This is consistent with the estimated emissions inventory found in Table II-2 of Part A. Also, see response to comment 1.

5. **Comment:** The ARB's 1988 survey of secondary smelters and foundries in California referenced on page A-40 of Part A is not in the Draft Report.

Response: The survey was conducted by staff of the ARB's Technical Support Division for the purpose of quantifying the number of secondary smelters and foundries in California and was referenced in the report.

6. **Comment:** RSR believes that the ARB should delete all reference to the Radian Corporation document entitled Control of Arsenic Emissions from the Secondary Lead Smelting Industry -- Technical Document (May 7, 1985). It may never have been subjected to peer review, and the emission estimates do not include actual emission data from Quemetco. The data obtained from the South Coast Air Quality Management District's (SCAQMD) 1988 downwind monitoring study of the Quemetco facility should be used in its place.

Response: The Radian document referenced in Part A discusses the arsenic content of process lead and the species of arsenic emitted from some facilities smelting lead feedstock contaminated with plastic. The document was used for emission estimates in the Preliminary Draft Report, but not in the Draft Report. Radian Corporation is a private entity and is not required to have peer review of their published documents.

The 1988 SCAQMD stack test data of the Quemetco facility was used in the Draft Report to model the facility emissions and project estimated exposure to the local population. Results of the 1988 SCAQMD ambient air monitoring downwind of the facility have been incorporated into Section I.B of the Final Part A to complement the ARB modeling of the facility.

7. **Comment:** RSR believes that the ARB should quantify the arsenic concentrations in feed materials used in the manufacture of cement. Additionally, all potential sources of arsenic emissions should be identified and quantified.

Response: Please see the response to comment 1.

8. **Comment:** The ARB confused secondary lead smelting operations with metal processing operations in the Preliminary Draft Report. In response to our comments, the ARB claims to address the definitional problem by "clarifying" the distinction between secondary lead smelting operations and other lead processing activities. This clarification is wholly inadequate and misses the point completely because the ARB continues to believe that secondary lead smelting is a "major" source of arsenic emissions. No effort has been made to quantify emissions from secondary lead smelters or all other sources of arsenic emissions.

Response: Please see the responses to comments 1 and 4.

9. **Comment:** Much of the modeling on which the emissions estimates in the preliminary analysis were derived was improperly based on the Industrial Source Complex Short-Term (ISCST) model rather than the Industrial Source Complex Long-Term (ISCLT) model. The ISCST model requires extensive and accurate source-specific data to produce meaningful results.

Response: The ISCST modeling used in the Preliminary Draft Report was replaced in the Draft and SRP-Version Report with more recent (1989) modeling of the facility. The current report utilizes the ISCST model based on source-specific stack test data (1988) from the modeled facility.

o **Gary Friedman, M.D., December 18, 1989**

1. **Comment:** In the Executive Summary, page 5, line 5 from the bottom, insert "among nonsmokers" after "excess cancer deaths" if this is what you mean to say here.

Response: "(A)mong non-smokers" has been added to the text.

2. **Comment:** On page 6 of the Executive Summary, first full paragraph: If smoking trends in California differ from those in the U.S. -- presumably less smoking in California -- why is the California range merely wider, rather than having both the upper and lower bound shifted lower?

Response: The words "Because the smoking trends in California differ from the United States as a whole" have been replaced with "Because the sex-specific patterns of lung cancer and all-cause mortality in California differ from those in the United States as a whole." This change of wording indicates that California's differences are in the percentages of men versus women who smoke, not in the total percentage of the population that smokes.

3. **Comment:** Page 6 of the Executive Summary, last full paragraph, line 5: Insert "as such" after "it."

Response: The text has been changed as suggested.

4. **Comment:** Page A-2 of the Draft Part A, third full paragraph: Were medicinal arsenic exposures considered for the non-atmospheric exposures section? Should drugs be added to Table I-7 Levels of Daily Human Inorganic Arsenic Intake?

Response: Arsenical medicines have not been used in the U.S. since 1945 when penicillin came into general use. The percentage of California's population that might have used arsenical medicines is presumed to be quite small, since their

former uses included treatment for malaria, syphilis, and St. Vitus' Dance.

5. **Comment:** Part A, page A-44: Mono Lake is salty and is not being drained to provide drinking or irrigation water. Rather, the City of Los Angeles is taking water from some of the streams that feed Mono Lake and as a result its level has fallen. Thus, delete "e.g., Mono Lake."

Response: The text has been rewritten to reflect that some lake levels (e.g., Mono Lake) are lowering as a result of the diversion of inflow streams. Arsenic salts are a component of the lake brine and become available for atmospheric entrainment as the exposed lakebed dries.

o **J. H. Baxter and Company, November 28, 1989**

1. **Comment:** The Draft Executive Summary "hot spot" paragraph attributes the high concentrations of arsenic monitored during an agricultural burn to the burning of vine support posts (treated with copper arsenate) with the vine cuttings. Another source of arsenic was not mentioned, namely, the use of inorganic arsenic pesticides used in vineyards for disease control.

Response: The burning of vine cuttings previously treated with arsenical pesticides will result in some arsenic emissions to the atmosphere, however, arsenic concentrations as high as 12,639 ng/m^3 and copper concentrations as high as 2,680 ng/m^3 would not be expected. In this particular case, the technicians operating the sampling monitors saw vineyard workers throwing vine support posts into the vine cuttings fire.

o **PG&E on 27 November, 1989**

1. **Comment:** On May 9, 1988, PG&E submitted comments on the Preliminary Draft Report. These comments were summarized and responded to in the Part C Report, with the exception of the comments found in Attachment E. The cover letter, Attachments A, B, E, and the accompanying references were not included in Part C. We believe that the omission of the comment letter attachments from Part C was accidental. An addendum to Part C containing the omitted material should be issued. The comment period should be extended 30 days from the time the addendum is mailed so that our comments can be considered.

Response: The omission of the PG&E cover letter, attachments, and reference pages from Part C was accidental. The inclusion of comment letter copies in Part C is not required by law but is done as a courtesy to the commentors and the report reader. The comments found in the complete letter were summarized and responded to in Part C by the ARB and the DHS. Therefore, a special addendum was not mailed out, nor was the comment period extended.

Note: Copies of the cover letter, reference pages and Attachments A, B, and E of PG&E's May 9, 1988 comment letter are included with PG&E's comment letter of November 27, 1989 found in this Part C Addendum.

o PG&E on 1 December, 1989 (Suggestions by Dr. Paul Solomon)

1. **Comment:** The Executive Summary section entitled Does Arsenic Exist in More Than One form? should be revised to include "While As(III) may be the most predominant form of arsenic emitted from some high temperature sources, in the ambient atmosphere the As(III)/As(V) ratio in atmospheric particulate matter and in rain water is typically less than one [i.e., As(V) is the predominant form]."

Response: The section has been modified to include the statement that "Conditions in the ambient air favor oxidation, so inorganic arsenic (V) compounds generally predominate in ambient air". This is followed by a statement that As(III) is generally more toxic than As(V), while As(V) is more frequently teratogenic in animal studies than As(III).

2. **Comment:** The Executive Summary section entitled What are the Ambient Concentrations of Inorganic Arsenic in the State? should summarize the 1986 arsenic data used in the October 1989 version of Part A, not 1985 data.

Response: The Executive Summary has been rewritten to summarize the 1986 ambient inorganic arsenic data because a complete year's worth of data is available for most of the 19 arsenic monitoring sites.

3. **Comment:** The Executive Summary section entitled What is the Risk Assessment for Exposure to Inorganic Arsenic? needs to be changed to reflect a risk assessment that has been based on a 1986 statewide population-weighted exposure of 1.5 ng arsenic/m^3. This would lower the risk assessment by about 32 percent.

Response: The DHS has recalculated the risk assessment based on the ARB's 1986 statewide population-weighted exposure estimate of 1.9 ng arsenic/m^3. The lower bound population-weighted exposure estimate for 1986 is 1.5 ng/m^3, while the upper bound estimate is 2.6 ng/m^3. The ARB's population-weighted exposure estimates for the South Coast and San Francisco Bay Area air basins were developed using a method that considers both population density (taken from census tract centroids) and ambient arsenic concentrations relative to that population. For the remaining air basins, it was assumed that the entire air basin population had been exposed to the estimated air basin mean.

The geographic mean concentration for 1986 was 1.5 ng/m^3. It was not used for the risk assessment because it is an average concentration for the 19 monitoring sites and does not consider population density.

4. **Comment:** The Part A summary should discuss the 1986 arsenic data presented in the text of the report, rather than the 1985 data carried over from the Preliminary Draft version.

Response: The 1985 arsenic data discussion has been replaced in the summary by a discussion of the 1986 data. The body of the report has also been rewritten to more clearly emphasize the 1986 data. The 1986 data is used because a full year's worth of data is available for most of the arsenic monitoring sites. The August 1985 through December 1987 arsenic data set is also presented in the report but was not used for developing the population-weighted estimates.

5. **Comment:** According to results presented in Table I-3 (now Table I-2), high peak-to-mean ratios occurred at only two sites, which would not be considered common. High peak-to-mean ratios would be observed near sources; if that is what you are referring to, it should be stated.

Response: The high peak-to-mean ratios at Long Beach (9.1) and Simi Valley (6.0) may have occurred either as a result of strong micro-meteorological influences, intermittent arsenic emissions from unknown sources impacting the monitors, or arsenic emissions from transient sources (e.g., ships in Long Beach Harbor burning residual oil for fuel).

6. **Comment:** Paragraph 4 on page A-3 should be changed to reflect the 1986 data set. For example, the overall geographic mean arsenic concentration for 1986 was 1.5 ng/m^3. The mean statewide population-weighted exposure for 1986 was 1.5 ng/m^3 with a lower

bound of 1.2 ng/m^3 and an upper bound of 2.0 ng/m^3, based on the data in Table I-4 (now Table I-3).

Response: The 1986 population-weighted concentrations are now discussed on page A-3. Also, please see the responses to comments 3 and 4.

7. **Comment:** What do the data suggest on Page A-5, paragraph 2? Should arsenic +3 and +5 speciation be considered in the health risk assessment, since both species appear to be present in the atmosphere?

Response: Paragraph 2, page A-5 describes the results of two studies which show that atmospheric arsenic exists as both As(III) and As(V) in varying ratios. The Solomon study conducted in Tucson, Arizona found that the average As(III)-to-As(V) ratio was 0.31 to 1. The ARB study conducted in the SoCAB's City of Industry found an average As(III)-to-As(V) ratio of 1.2 to 1.

The DHS has addressed the question regarding consideration of valence in the risk assessment in Section III of this Part C Addendum.

8. **Comment:** Can the seasonal trends observed in Figures I-2 to -4 be explained in terms of meteorology or other factors? Do fine particle mass concentrations follow the same trend? In the SoCAB, PM_{10} and fine particles show a summer minimum and a winter maximum.

Response: Figures I-2 to -4 (representing quarterly and monthly means from July 1985 through August 1987) have been removed from the document. They have been replaced with Figure I-4 (a line graph of the August 1985 through December 1987 data set). Text discussion accompanying Figure I-4 describes the seasonal nature of arsenic concentrations following the same general patterns observed with other particulate matter (i.e., high winter peaks). Figures I-5 and -6 also show that there have been summer concentrations atypical of the PM_{10} seasonal trend of summer minimums and winter maximums (e.g., August 1985 where reported concentrations were more typical of winter maximums).

9. **Comment:** The values for the SoCAB population-weighted exposure and overall population-weighted exposure are incorrect if they are the arithmetic mean of the values for each site within the air basin.

Response: For most of the air basins, it was assumed that all of the people within the air basin were exposed to the same estimated air basin mean concentration of arsenic. However, the SoCAB and SFBAAB population-weighted exposure estimates are not identical to

the mean concentrations, as they were developed using a program that considers population density as well as the mean arsenic concentration of the nearest monitoring site. The overall population-weighted exposure estimate is the mean of all population-weighted air basin exposure estimates.

10. **Comment:** The recalculated population-weighted exposure estimates should be reported in Part A and used for the health risk estimate calculations in Part B.

Response: The recalculated population-weighted exposure estimates (please see the response to comment 3) are reported in the current Part A and Executive Summary. They are also used in the current Part B for the risk estimate calculations.

11. **Comment:** What high peak-to-mean ratios are being referred to in paragraph 1 of page A-20? Most are less than 5 in Table I-3 (now Table I-2).

Response: The reference to the peak-to-mean ratios has been removed.

12. **Comment:** What is the point of the first footnote in Table I-7? Andreae observed both As(III) and As(V) in most rainwater samples he collected?

Response: The footnote has been deleted from the table since both valences have been observed in rainwater and drinking water.

13. **Comment:** "Table II-2" was not reproduced on page A-33.

Response: The table number is reproduced in this version of the report.

14. **Comment:** Paragraph 3 on page A-35 presents the results (of the Geysers Air Monitoring Program [GAMP])in a biased worst-case manner. The phrase "is being impacted" is too strong of a statement considering that greater than 95 percent of the data were below the detection limit of 3 ng/m^3. The phrase should be changed to "may be impacted" since it is difficult to draw a definitive conclusion about the impact of the geysers on the surrounding area.

Response: The sentence containing the phrase "is being impacted" has been removed from the text because a corresponding source test of all steam field point sources has not been completed.

Note: The LOD for the ARB arsenic method used for ambient data is 0.4 ng/m^3. The SoCAB annual arsenic average for 1986 was 2.6 ng/m^3, a concentration level below the GAMP LOD of 3 ng/m^3.

15. **Comment:** Sentence 2, paragraph 3, page A-35 is inaccurate. It should be changed to read: "Fine particle arsenic concentrations obtained at two sites located east of the developed steam field have shown maximum 24-hour averages up to 14 ng/m^3 (second high was 6 ng/m^3) during 1983-1984, and 4 ng/m^3 (second high was <3 ng/m^3) during 1986-1987. Maximum coarse particle concentrations were always less than the detection limit of 3 ng/m^3 (GAMP, 1987)."

Response: The previously reported maximum averages (17 ng/m^3 for 1983-1984 and 6 ng/m^3 for 1986-1987) have been changed in the report to 14 and 4 ng/m^3 of fine particulate matter, respectively. The previously reported maximums were the sum of fine and coarse arsenic collected by a size-selecting dichotomous sampler. The fine (<2.5 um) and coarse (>2.5 um and <10 um) arsenic samples had been analyzed separately using a method with a LOD of 3 ng/m^3.

16. **Comment:** Sentence 5, paragraph 3, page A-35 should be deleted because large fluctuations in concentrations can also be due to variable meteorology. Also, there is insufficient data to reach this conclusion, since less than 5 percent of the data were above the detection limit of 3 ng/m^3.

Response: The sentence has been deleted from the text.

17. **Comment:** If the changes in comment 15 are not made, sentence 6 should be moved to follow sentence 2 of paragraph 3. Also, change "as fine particles" to "in the fine particles".

Response: Sentence 6 has been deleted from the text.

18. **Comment:** Sentence 6, paragraph 2, page A-55 (the statement that arsenic trioxide plays the largest role in determining overall arsenic exposure levels) has not been proven for the ambient environment; however, it is probably true for occupational exposures. Current ambient arsenic speciation data referenced in the report indicate that the concentration of As(III) in the atmosphere is on the average equal to or less than As(V).

Response: This sentence has been deleted from the text.

19. **Comment:** Andreae contributes the variation in the As(III)/As(V) ratio to several factors, only one of which was the presence of industrial sources that emit arsenic trioxide. Other factors included sources of As(V) (e.g., ocean spray), the age of the aerosol, and the effective oxidation-reduction potential of the aerosol.

Response: The text has been modified to include these other factors contributing to the variation in the As(III)/As(V) ratio.

The following comments were used to make changes in the text:

20. **Comment:** On page A-1 (Part A), paragraph 5, sentence 3, add the following after sentence 3: "In the air, arsenic can exist as the +3 or +5 oxides, oxyacids, or salts of the oxyacids." Give examples or refer to Table III-1.

21. **Comment:** On Page A-1, paragraph 5, sentence 4-6, delete sentence 5. As_2O_3 sublimes in high temperature sources to form As_4O_6 and in the atmosphere condenses onto existing particles as As_2O_3. This is correctly stated in the next paragraph, sentence 4.

A new paragraph should be started with sentence 4. Sentence 4 and 6 should be changed to: "Arsenic trioxide (as As_4O_6), a species with arsenic in the +3 oxidation state, is the ... and combustion sources (Eatough et. al., 1979). In the air, it can react with water to form a less volatile and more water-soluble oxyacid (e.g., H_3AsO_3) or can be oxidized to arsenic pentoxide (As_2O_5), a species with arsenic in the +5 state. Arsenic pentoxide also is less volatile and more water-soluble than the trioxide form."

22. **Comment:** Add the number of samples to Table I-2.

23. **Comment:** On page A-9, line 17 add "at a given site" after the word "data".

24. **Comment:** Insert "for the period July 1985 - August 1987" after "by month" in paragraph 2, page A-9. The text up to here summarizes only 1986 data.

25. **Comment:** The overall geographic arithmetic mean by sites, based on the data in Table I-2, should be 1.5 ng/m^3, not 2.2 ng/m^3.

26. **Comment:** The last sentence of paragraph 1, page A-20 should be repeated during the discussion of peak-to-mean ratios on page A-13, paragraph 1.

27. **Comment:** Replace the SoCAB annual average of 2.4 ng/m^3 (observed in 1985) with the 1986 SoCAB annual average of 2.6 ng/m^3 in line 3 of the text on page A-21. Also add "observed in 1986" to the end of the sentence.

28. **Comment:** Delete the last sentence of paragraph 2, page A-24.

29. **Comment:** Insert "the detection limit of" after "or below" in sentence 2, paragraph 3, page A-35.

30. **Comment:** Paragraph 4 of page A-51 should have the following added to the end of the paragraph: "However, these levels of arsenic have not been observed in the atmosphere. This is probably because the thermodynamic calculations of Murray et. al. and Pupp et. al. do not consider the reaction of water with As_2O_3 to form the less volatile and more water soluble species oxyacid or the oxidation of As(III) to As(V).

31. **Comment:** Insert "(Eatough et. al., 1979)" at the end of sentence 1, paragraph 1, page A-54.

32. **Comment:** Change "arsenic trioxide" to "As(III)" and "arsenic pentoxide" to "As(V)" on page A-55, paragraph 3, sentence 1. They are assuming to know the species.

33. **Comment:** Insert "near a known high temperature source of arsenic" after "in Los Angeles" in sentence 1, paragraph 3, page A-56.

34. **Comment:** Sentence 3, paragraph 2, page A-56 should be changed so that the results are not biased toward As(III), which was actually at lower concentrations than As(V). It should be changed to read: "Trivalent arsenic was present above the detection limit (approximately 1 ng/m^3) in only half of the samples, whereas, As(V) was present in all samples analyzed. A wide variation also was observed in the relative amounts of trivalent and pentavalent arsenic in the samples."

35. **Comment:** Replace the paper used in Appendix B with the improved version of the paper published in the May 1987 JAPCA. Also, use the higher quality copy of the second paper by Solomon et. al., 1983 that accompanies this set of comments.

o **U.S. Borax Research Corporation, November 30, 1989**

1. **Comment:** How recent is the estimated inhalation of 6 ug arsenic per pack of cigarettes? It seems high for present U.S. conditions of tobacco growing. Also, what assumptions were made concerning inhalation?

Response: Page 9-2 of the EPA document Health Assessment Document for Inorganic Arsenic, Final Report, March 1984, states that assuming "a mass of 1 gram per cigarette and an average tobacco value of 1.5 ppm, this yields 1.5 ug arsenic per cigarette. With 20 percent of this amount in mainstream smoke, the inhaled amount for each pack of cigarettes would be approximately 6 ug arsenic, and of this amount, 40 percent would be deposited in the respiratory tract."

DEPARTMENT OF HEALTH SERVICES
STAFF RESPONSES TO PUBLIC COMMENTS
ON THE OCTOBER 1989 REVISION OF THE
DRAFT REPORT TO THE AIR RESOURCES BOARD
ON INORGANIC ARSENIC

Comments on New or Revised Parts of the Report

Comment: The Executive Summary (page 3) leads readers to believe that all arsenic in the atmosphere is in the most carcinogenic form, As(III). The As(III):As(V) ratio in atmospheric particulate matter is typically less than one (PG&E). What is the evidence that arsenic trioxide (an As(III) compound) is likely to be the most carcinogenic form (U.S. Borax Research Corporation [U.S. Borax])?

Response: The Executive Summary has been modified to indicate that inorganic arsenic (V) compounds are generally more prevalent in ambient air than inorganic arsenic (III) compounds. It is not clear, however, that arsenic trioxide or As(III) is the most carcinogenic form: this is now noted in the Executive Summary.

Comment: In the Executive Summary (page 3, paragraph 3), Hood (1983) is incorrectly quoted as stating that As(V) is more teratogenic than As(III) (U.S. Borax).

Response: This point regarding teratogenicity has been clarified in the Executive Summary. Hood (1983) stated that "valence state influences the relative toxicity of inorganic arsenic. Arsenite [As(III)] is more acutely toxic to both mother and conceptus, but arsenate [As(V)] is more likely to cause malformation of fetuses." (page 134) "Both gross and skeletal malformations are seen more frequently ... following arsenate treatment." (page 137)

Comment: Regarding page 5, paragraph 2 of the Executive Summary, how recent is the estimate of 6 μg of inorganic arsenic per pack of cigarettes? What assumptions regarding inhalation were made (U.S. Borax)?

Response: See the ARB staff responses to comments (ARB staff have indicated that this estimate is from EPA (1984), as cited in Part B).

Comment: Different wording ("a number of" rather than "numerous") would be more appropriate in paragraph 4, page 5, of the Executive Summary (U.S. Borax).

Response: The word "numerous" has been deleted from this passage.

Comment: Regarding page 5, paragraph 5 of the Executive Summary, different wording would be appropriate in discussing the interaction between smoking and arsenic exposure, and the meaning of "low doses" should be stated (U.S. Borax).

Response: The paragraph has been modified to address the concerns raised by the commentor.

Comment: Page 5, paragraph 6 of the Executive Summary should state that arsenic "may" inhibit DNA repair, rather than "inhibits DNA repair" (U.S. Borax)

Response: The passage has been modified in accordance with the suggestion of the commentor.

Comment: The DHS risk estimate is based on 1985 data while the exposure data in Part A have been updated for 1986 data. It would seem reasonable to base the risk assessment on the entire state. In 1986 the (statewide) population-weighted exposure was 1.5 ng/m^3, 32% lower than the urban air basin data used for the DHS estimate. The risk assessment should (also) be based on 1.7 ng/m^3, the population-weighted average for the South Coast Air Basin (SCAB) and the San Francisco Bay Area Air Basin (SFBAAB) in 1986. The risk assessment can be calculated for both the entire state and for the SCAB and SFBAAB, where about 60% of the state's population resides (PG&E).

Response: The DHS document now uses the most up-to-date statewide population-weighted average ambient air concentration available from the Air Resources Board. The data for the urban air basins were used because, at the time the earlier drafts of the document were written, these were the only data available. A separate risk estimate for the South Coast air basin is also provided in the revised document.

Comments on Part C (Comments and Responses), October 1989

Comment: DHS does not appear to address a draft document (by William L. Marcus of the U.S. Environmental Protection Agency's Office of Drinking Water) submitted in the previous comment period (Pacific Gas and Electric Company [PG&E]).

Response: On pages 12 and 13 of the Department's previous responses (Part C, Section III), DHS staff noted that the document in question was (1) an undated preliminary draft that had been circulated for review of its technical merit, and (2) largely concerned with ingestion of arsenic. Staff noted that although the document in question postulated a threshold for adverse health effects from ingestion of arsenic, it recognized a linear nonthreshold carcinogenic potency factor for lung cancer from inhaled arsenic. Staff noted that the threshold discussion in the document in question was not applicable to respiratory cancer produced by inhalation of arsenic. DHS staff consider this response to have been adequate.

Comment: DHS should have summarized a comment differently than it did on page 11 of Part C, Section III (PG&E).

Response: Page 3 of Attachment A of the commentor's submittal stated, "Insoluble arsenic (As(III)) salts are probably more hazardous than the soluble salts because they are retained in the target organ (the lung) whereas the soluble forms can readily enter the bloodstream where they can be taken up by the liver to undergo detoxification by methylation." The DHS summary read, "Insoluble arsenic salts are probably more hazardous than soluble salts because they are retained in the target organ (the lung)

longer...." On page 10 of Part C, Section III, DHS staff noted the commentor's suggestion that Part B estimate risks from As(V) separately from As(III). It was not immediately clear, however, that the commentor had suggested, in Attachment D of its submittal, that separate unit risks be provided for each item in the matrix, insoluble As(III), soluble As(III), soluble As(V), and insoluble As(V). The commentor had stated that insoluble As(III) compounds would appear to be the most hazardous, while insoluble As(V) compounds would appear to be the least hazardous ("because they would be unlikely to ever convert to the hazardous As(III) form"). The commentor now adds that soluble As(III) would pose the second greatest hazard and soluble As(V) the next to lowest hazard.

DHS staff acknowledge that the summary in the previous Part C did not state this comment clearly. Nevertheless, the responses presented there are still valid. Inadequate data exist to assess risks from As(V) separately from As(III) risks. No mechanism has been elucidated for arsenic carcinogenesis. The available data do not clearly establish that soluble salts of either valence present more or less of a lung cancer hazard than corresponding insoluble (or less soluble) salts. Were there adequate relevant data (and measurement capability) to adjust the quantitative risk estimates for factors such as solubility, valence state, bioavailability, and capture or retention in human lung, such adjustments would be considered in the report.

Comments on Old or Unchanged Parts of the Report.

Comment: Speciation is still an important consideration in performing a risk assessment for inorganic arsenic (EnviroMD).

Response: Although As(III) compounds are generally more active than As(V) compounds in assays of genetic toxicity, inadequate data exist to assess cancer risks from As(V) separately from As(III) risks. No mechanism of carcinogenesis by arsenic has been elucidated. As(V) is converted in the body to As(III), although it is unclear whether this occurs in the lung. The comment correctly indicates that the difference in arsenic species composition, between the smelter exposures upon which the risk assessment is based and exposures from ambient air, is still a matter of concern. Potency estimates based on valence might be useful; however, the postulated difference in carcinogenic potency between As(III) and As(V) is unproven and cannot be assessed.

Comment: The document presents data which suggest that cancer risk from inorganic arsenic differs according to factors including route of exposure, pulmonary retention time, and bioavailability. Both drafts ignore the effect of particle size and solubility upon capture and retention in the bronchioles. Both drafts ignore the demonstrated lower toxicity and lower lung retention of As(V) versus As(III). Geothermal drift exposures probably differ from smelter exposures in particle size distribution, relative proportion of As(V), and solubility. Since the risk estimate is based on smelter exposures, it should only be applied to smelter-type exposures, or formulae should be included for adjusting unit risks for differences in As(III):As(V) ratios, bronchial capture of As(III) particles, and pulmonary retention time of captured As(III). Bronchial deposition may be a critical factor as cancer has historically occurred in human bronchioles. Solubility

should also be considered, as it affects pulmonary retention time and cancer risk. Ignoring these factors simplifies the risk estimation and control decision process. But if it forces industries to spend millions of dollars on unnecessary controls, such simplicity is false economy (PG&E).

Response: The Part B risk assessment only considers exposure via inhalation because it has been prepared for the Toxic Air Contaminants Program. The document does not suggest that different risks can be estimated for arsenic exposures characterized by different pulmonary retention times and bioavailabilities. The risk assessment does not consider capture or retention in the bronchioles, or differences in lung retention between As(V) and As(III), because there are not adequate data to do so. DHS staff investigated these issues and did not ignore them; chapter 11 (Section 11.1.2) of Part B has been modified to recognize this. The document certainly does not ignore the lower acute and chronic toxicities of As(V) versus As(III); they are mentioned in the appropriate sections. Inadequate data exist to ascribe a lower carcinogenic potency to As(V), however. No mechanism has been elucidated for arsenic carcinogenesis. Were there adequate relevant data (and measurement capability) to suggest adjustments in the quantitative risk estimates based on factors such as solubility, valence state, bioavailability, and bronchial deposition or retention in human lung, such adjustments would be considered in the report.

DHS staff are aware that the commentor operates one or more geothermal power facilities, and appreciate the commentor's concern over the extrapolation from smelter exposures. Staff and peer reviewers have found the extrapolation to be of scientifically valid based on currently available data. Extrapolation from smelter exposures has been utilized by other regulatory agencies including the U.S. Environmental Protection Agency, and is the method used in a number of journal articles on the subject of inorganic arsenic exposure.

Regarding the concern over the cost of emission controls, it should be noted that the mandate of DHS is to protect public health. In the Toxic Air Contaminants Program, DHS is primarily charged with evaluating the health effects of substances that may be determined to be toxic air contaminants. The Air Resources Board is the agency charged with managing the health risks from emissions of toxic air contaminants.

Comment: Smoking is voluntary and any cancer risk from arsenic due to interaction with smoking should be considered as voluntary. Part B should be expanded to place this risk into perspective with other voluntary risks (e.g., mountain climbing and sunbathing; several other examples of risk comparisons were submitted with this comment). The Executive Summary should note that this risk is voluntary and probably insignificant in relation to the smoking risk itself (PG&E).

Response: The primary Department of Health Services role in the Toxic Air Contaminants Program is that of risk assessor. The Air Resources Board is the risk managing agency. ARB requests health effects assessments from DHS. ARB has not asked the Department to conduct health risk assessments in a voluntary-versus-involuntary framework or in relation to the several risks suggested by the commentator. How useful such information would be to the ARB is unclear. The board is not required to consider such information in

adopting airborne toxic control measures. In addition, public health protection should not be limited to those members of the public who make the healthiest choices in their personal lives. To the disappointment of most public health practitioners, smoking tobacco is still an acceptable personal and cultural choice in many families and communities within California. In public health practice, however, ends do not justify means: awareness that environmental health protection is being provided mainly for nonsmokers might induce some smokers to quit, but this would not justify excluding people who smoke from the level of protection afforded to other members of society (or equivalently, allowing industries to impose greater mortality risks on certain people simply because these members of society (smokers) engage in certain culturally acceptable but risky behavior).

With inorganic arsenic, incremental cancer risk is estimated to be dependent on "background" cancer risk which is in turn dependent on personal behavior choices. It is likely that other cancer risks associated with environmental contaminants follow this pattern. Consider one possibility: a high-fat diet might be thought to significantly elevate a background cancer risk. A commentor might then argue that eating a high-fat diet is voluntary behavior, and that people who eat such a diet should not be considered in control decisions regarding a contaminant (rather than imposing the best available control technology on industry, regulators should protect only those who eat the best available diet). DHS staff would be reluctant to endorse such a suggestion.

Comment: The risk assessment by DHS considers only As(III) because it is based on data from occupational exposures where As(III) is believed to have been the predominant species inhaled. Few data relate As(V) concentrations to carcinogenicity, but more than half of the arsenic observed in the ambient environment is As(V). Therefore, a risk assessment based just on As(III) may be premature and inaccurate (PG&E).

Response: Inadequate data exist to assess cancer risks from As(V) separately from As(III) risks. Sampling data do indicate that there is proportionally more As(V) in the ambient environment than in smelter work areas. As(V) is converted in the body to As(III), although it is unclear whether this occurs in the human lung. Furthermore, insufficient data exist to demonstrate that inhaled As(V) only increases risk after it is converted to As(III).

Comment: Inhaled As(V) is not readily metabolized to As(III) in the lungs. Direct attempts to test the relative potency of As(III) and As(V) suggest that As(V) either causes no effect or is one-tenth as potent as As(III). Therefore, inhaled As(V) cancer risk estimates should be at least 10 times lower than inhaled As(III) cancer risk estimates (PG&E).

Response: This comment is not supported by the available data. The metabolism of As(V) in the human lung has not been adequately assessed. Although As(V) is less potent than As(III) in certain assays of genotoxicity, it should be remembered that inorganic arsenic is an atypical carcinogen: it is carcinogenic by ingestion and inhalation in humans, but its carcinogenicity has not been clearly established in animal models. The DHS document discusses several possible reasons for this discrepancy, including differences between the lung tissue of common laboratory animals and higher primates. No mechanism of arsenic carcinogenesis has been established.

As(V) may be converted to As(III) in the body and insufficient data exist to consider the two valences separately in cancer risk assessment.

Comment: Differences in As(III) to As(V) ratios between the smelter exposures (upon which the risk assessment is based) and ambient exposures in California suggest that the draft document's unit risk for ambient exposure should be reduced by a factor of at least 2 to 4 (PG&E).

Response: This comment appears to be based on the assumption that As(V) is not carcinogenic. As noted in response to the two previous comments, insufficient data exist to demonstrate that inhaled As(V) only increases risk after it is converted to As(III) and insufficient data exist to consider the two valences separately in cancer risk assessment.

Comment: Data from an intratracheal instillation study presented by Rosner and Carter in a 1987 paper demonstrate marked differences in metabolic excretion profiles for As(III) compared to As(V). Thus the bioavailabilities of As(III) and As(V) in the lung are not the same. As(V) was more rapidly cleared from the lung and removed from the body more rapidly than As(III). Thus, lacking evidence to the contrary, it should be assumed that the toxicity and carcinogenic potency of As(III) is greater than that of As(V); this should be factored into the risk assessment (EnviroMD, PG&E).

Response: The DHS health effects document has been modified to mention the report by Rosner and Carter (Rosner MH and Carter DE (1987) Metabolism and excretion of gallium arsenide and arsenic oxides by hamsters following intratracheal instillation. Fundam Appl Toxicol 9:730-737). Nevertheless, this report does not provide sufficient reason to modify the risk assessment for lung cancer due to inorganic arsenic. The experiment reported was in hamsters. Rodent lung tissue, as discussed in Chapter 10 of the DHS document, differs from that of higher primates and humans. Still, the experiment did not investigate transformation of As(V) to As(III) or vice versa in the lung. The method of exposure, intratracheal instillation, is dissimilar to inhalation. The study was designed primarily to compare metabolism and excretion of arsenic compounds, rather than assess their absorption from the lung.

Even if this experiment were directly applicable to human exposure to inorganic arsenic in ambient air, it would not tell us very much about lung clearance of As(V) versus As(III). Although the relative amounts of arsenate (an As(V)-containing ion) and arsenite (an As(III)-containing ion) retained in the lung one day after dosing were statistically significantly different (using a nonstandard mathematical procedure, transformation to the arc sine of the square root of the proportion of the dose retained), the authors of the paper did not find this difference to be important, and DHS staff concur. The experiment was designed primarily to compare the metabolism and excretion after instillation of gallium arsenide (GaAs), a compound whose increasing use in the electronics and semiconductor industry raised concern regarding industrial exposure, with that of the soluble arsenicals sodium arsenate and sodium arsenite (page 730). Rosner and Carter found that "lung arsenic was rapidly cleared after sodium arsenate and arsenite exposure, but GaAs was cleared more slowly...." (page 736) The data presented in their Table 1 (page 733) show that 0.185% of the arsenate dose, 0.329% of the arsenite dose, and 41.78% of the GaAs dose remained in the lung one day after dosing

(narrow ranges of ± one standard deviation were presented). Rosner and Carter wrote, "The solutions of arsenite and arsenate were almost entirely cleared from the lung by the first day; less than 1% ... remained. Large amounts of arsenic were present in the lung after GaAs dosing; more than 40% of the dose still remained ... after 24 hr." (page 732) This study did not demonstrate an important difference in clearance of sodium arsenate versus sodium arsenite from hamster lung.

Comment: Since ingested arsenic exposures far exceed inhaled arsenic exposures, inhaled As(III) and As(V) that enters the bloodstream could be ignored (PG&E).

Response: In contrast to ingested arsenic, inhaled arsenic cannot be detoxified by the liver before it reaches the lung, skin or other target organ for carcinogenesis. Whether or not it enters the bloodstream, inhaled arsenic should not be ignored. The vast body of epidemiologic data showing increased risks of lung cancer due to inhaled arsenic attests to the importance of such exposures.

Comment: Section 2.1 of the draft document asserts without support that approximately 80% of an ingested dose of arsenic is absorbed. This figure depends on solubility and valence state of the arsenic and species of animal, however. Approximately 90% of soluble arsenic (As(III) or As(V)) is absorbed, but suspensions of insoluble arsenic trioxide are only 30-40% absorbed by rodents and not appreciably absorbed by humans (Chemical Manufacturers Association [CMA]).

Response: The DHS document indicates that the discussion in Chapter 2 highlights information from the U.S. Environmental Protection Agency's [EPA] 1984 health assessment document. The passage in question has been changed, however, because the 80% figure was taken to summarize animal studies that the EPA stated "generally confirm" (EPA 1984, p. 4-9) the findings in humans. The EPA's finding that "Greater than 95 percent of inorganic arsenic taken orally by man appears to be absorbed..." (page 4-8) has been reported instead. The commentor does not substantiate its claim regarding human absorption of arsenic trioxide suspensions.

The main purpose of the DHS document is to assess the health effects of inorganic arsenic compounds in ambient air. Thus, further examination of the oral ingestion issue at this time does not appear warranted.

Comment: The evidence for direct myocardial toxicity from arsenic exposure is weak. If there were a strong association, it would have been revealed in the cancer epidemiology studies of arsenic exposure. The peripheral vascular changes that are reported for arsenic exposure should not be taken as evidence of cardiotoxicity (CMA).

Response: Numerous findings of vascular disorders are discussed in the chronic toxicity chapter under the heading "cardiovascular system." A few findings of electrocardiographic abnormalities are noted under that heading (for both humans and animals) as well. Readers may or may not draw the same conclusion as the commentor, that the evidence for adverse effects of arsenic on cardiac muscle is weak. It is not clear that the cancer epidemiology studies of arsenic exposure were designed to assess myocardial toxicity. The

discussion does not imply that the vascular changes should be taken as evidence of direct cardiotoxicity.

Comment: Skin lesions are regarded by clinicians as a hallmark of arsenic intoxication. Whether or not such lesions are "precancerous" is not scientifically established (CMA).

Response: Not all arsenic-induced skin lesions are considered precancerous. Klaassen (1985) notes that some may possibly proceed to cancer and Schoolmeester and White (1980) call Bowen's disease "cutaneous precancerosis" (page 203). The document has been modified to clarify this issue.

Comment: The Pennwalt Corporation has recently completed developmental toxicity studies of arsenic acid in mice and rabbits, and will make the results of this unpublished work available to the Air Resources Board for consideration (CMA). Summaries of these studies are enclosed, but they are proprietary and any use beyond reference in the ARB/DHS report is not allowed (Atochem North America, formerly Pennwalt Corporation).

Response: It is not clear that it would be important for the ARB to consider this information in addition to the extensive database of developmental toxicity studies that already exists and is summarized in the DHS document. In addition, complete reports published in peer-reviewed journals can be given more credence than unpublished summary reports. Considering the proprietary and preliminary nature of the reports, reference to this information was not made in the revised document.

Comment: Both inhalation and ingestion studies form the basis for treating inorganic arsenic as a human carcinogen. The draft document bases its cancer potency estimates on inhalation data only. If only inhalation data are to be considered, then only arsenic trioxide can reliably be considered a carcinogen (CMA).

Response: The health effects document is intended for use in California's Toxic Air Contaminants Program, and the risk assessment is for airborne exposures. That is the reason the risk assessment relies on inhalation data. While arsenic trioxide may have been the predominant form of arsenic in the smelter environments upon which the risk assessment is based, no mechanism has been elucidated for arsenic carcinogenesis, and other arsenic compounds have toxic properties and routes of metabolism similar to those of arsenic trioxide. As is noted in the document, arsenic trioxide is an As(III) compound, and other arsenic compounds are converted to As(III) compounds in the body. Furthermore, the document discusses a mechanism by which As(V) compounds may be carcinogenic without being converted to As(III). The available data do not preclude carcinogenicity of compounds other than arsenic trioxide.

Comment: The draft report is incomplete and in need of reworking. The risk assessment needs review and reexamination on four points (practical threshold, pre-1945 exposure data, routes of exposure, and interaction with sulfur dioxide) (U.S. Borax).

Response: The four points listed by the commentor have been considered by DHS staff and are adequately considered in the document. Specific suggestions made by the commentor are discussed below.

Comment: The draft report should be rewritten with the help of the U.S. Borax document dated March 1, 1989, and entitled "Analysis of the Potential of Arsenic as a Carcinogen and Reproductive Toxicant" (U.S. Borax).

Response: This comment is somewhat unclear: it does not specify how the draft report should be rewritten. The U.S. Borax document contains numerous details that need not be included in the DHS report. The U.S. Borax document does not represent the findings of a governmental agency or an authoritative body. Furthermore, it is not intended as a risk assessment (this is stated in its foreword). The U.S. Borax document has not led DHS staff to change the risk assessment presented in the DHS report. Nevertheless, the extensive bibliography and numerous summaries of research contained in the U.S. Borax document may prove useful to readers, so reference to this document has been made in the DHS report.

Comment: The ARB and DHS should convene a roundtable workshop of interested scientists to discuss the problems noted in the risk assessment section of the draft report and other issues (U.S. Borax).

Response: These issues have been discussed by DHS staff and other scientists at conferences, in journal articles, and in numerous personal communications. In addition, the draft report has already been the subject of two rounds of public comments. DHS staff see no need for a roundtable discussion at this time.

Comment: Regarding page 1-1, paragraph 3 of Part B, it has not been proven that adverse reproductive effects are among the most sensitive noncarcinogenic endpoints. Data indicate that adverse effects would only take place at the upper end of the range 50-100 μg As/m^3 (U.S. Borax).

Response: Adverse reproductive effects (including birth defects) are justifiably listed among the probable most sensitive noncarcinogenic endpoints. As noted in the document (see also Chapter 6 and Appendix G), statistically significant dose-response trends were observed in mice for a range of effects over the dose range noted in the summary. These trends were not simply dominated by findings at the high dose level, as suggested by the commentor. Therefore, DHS staff would not characterize the low dose as a no observable adverse effect level.

It is difficult to precisely establish a threshold for the effects listed. The data from human exposures to 50-500 μg As/m^3, however, clearly suggest that such exposure range may cause or contribute to serious adverse health effects.

Comment: Regarding page 1-2, paragraph 1, worker exposure to lead should also be noted (U.S. Borax).

Response: This summary passage is adequate as it stands. It notes that "conclusive evidence of reproductive toxicity is lacking." The more detailed

discussion in Chapter 6 states that other toxicants were present in the smelter processes, and has been modified to mention lead.

Comment: Regarding page 1-2, paragraph 3, this paragraph does not reflect the conclusions of Chapter 7. The data for the statement "inactivates genes" should be rechecked for accuracy. An EPA statement regarding DNA damage should also be noted (U.S. Borax).

Response: This paragraph has been slightly modified to qualify the finding regarding DNA repair inhibition. Statements regarding sister chromatid exchange and DNA repair have been added to the "conclusions" section of Chapter 7 for better concordance.

The paragraph still states that "one assay in mammalian cells indicates that arsenic can inactivate genes...." This is based on a mouse lymphoma $TK^{+/-}$ assay (Oberly et al. 1982). The $TK^{+/-}$ assay works on a lethal synthesis principle. Unmutated cells ($TK^{+/-}$) are killed by a substance such as trifluorothymidine (TFT), because they unwittingly incorporate it into a DNA synthesis pathway. However, test substances may inactivate the thymidine kinase (TK) locus, and hence this pathway, thereby conferring resistance to TFT on mutated ($TK^{-/-}$) cells. Two mechanisms have been reported for a positive response in this system: gene or point mutation, and chromosomal aberration (Oberly et al. 1982, page 368, citing Clive et al. 1979). Since arsenic has been negative in a number of gene or point mutation assays, and positive in assays of chromosomal aberration, the data indicate that arsenic can inactivate genes by damaging chromosomes.

In the judgement of DHS staff, the EPA statement cited by the commentor need not be included in Part B. The mechanism by which arsenic is clastogenic (i.e, causes DNA damage) is not known.

Comment: Regarding page 1-3, paragraph 3, weak or negative associations observed in some studies should also be noted. There are problems with certain studies of workers in the insecticide manufacturing industry. One problem with all the studies is underestimate of exposure and hence overestimate of risk (U.S. Borax).

Response: Chapter 1 is a summary of Part B. This paragraph is an accurate and adequate summary of conclusions of Chapter 9, which discusses in greater detail the human evidence for the carcinogenicity of arsenic.

Comment: Regarding page 1-3, paragraph 4, a new up-to-date listing of SMRs should be included (U.S. Borax).

Response: As suggested by the commentor, the range of SMRs reported here reflects findings summarized in EPA (1984) and a select few later reports. The commentor suggested that this is inappropriate and stated that 11 later reports should be included. However, these were not listed by the commentor. The new reports included by DHS staff update earlier studies of smelter cohorts used for the risk assessment. The passage at issue has been modified to eliminate the implication that it reflects all the reports that are available.

Comment: The findings in Chapter 1 regarding confounding from smoking do not lead to the findings summarized there regarding interaction with smoking (U.S. Borax).

Response: Confounding and interaction are distinct. There can be interaction in the absence of confounding. As noted in Chapter 1, an interaction between arsenic and smoking has been characterized, but confounding from smoking was minimal in the datasets that show an association between occupational exposure to arsenic and respiratory cancer.

Comment: Certain data are not presented with, and certain assessments or qualifications do not accompany the summary of reasons in Chapter 1 for considering the evidence of human carcinogenicity due to inhaled arsenic to be "strong." The summary of reasons fails to note that (1) workers were exposed to confounding factors and that interactions were not assessed, (2) that quality of the data showing high statistical significance was not assessed, (3) the quality of the data showing dose-response trends was not assessed, (4) data of Pershagen et al. (1981) indicate that the effects of arsenic may be greatly enhanced by a co-factor other than smoking, e.g., sulfur dioxide, (5) the apparent non-consistency of histological types of cancer is a troubling fact, (6) the consistency of the arsenic-related effect may not be true if the negative data are considered along with the positive data, and (7) possible confounding factors other than smoking and sulfur dioxide, including aromatic hydrocarbons and process additives, should be considered. (U.S. Borax).

Response: Chapter 1 is a summary chapter intended to bring together salient points from every chapter. The counterarguments made by the commentor need not be listed in Chapter 1. Most of these issues are discussed in great depth in Chapters 9-11.

(1) Section 9.2 discusses confounding and Section 11.1.2c discusses its effect on the risk assessment. Section 9.3 and Appendix A discuss interaction and Section 11.3.3 discusses risk assessment based on adjusting for interaction with smoking. (2,3) The quality of the data is addressed throughout Chapter 9, and Section 11.1 addresses the data quality issues in great detail as they pertain to the studies relevant to the risk assessment.

(4) The data presented by the commentor from the 1981 article by Pershagen et al. are weak, at best. Among the nonsmokers there was only one lung cancer case in the baseline (no arsenic) group. This means that all of the rate ratios among the nonsmokers are very unstable, and hence the comparisons between exposure groups among the nonsmokers cannot be interpreted. Furthermore, unlike the comparisons between smokers and nonsmokers, the exposure categories for the sulfur dioxide analysis are not very distinct. For instance, the high sulfur dioxide exposure group did not really have low or no arsenic; only substantially lower than the roaster workers. More to the point, several studies (Lubin et al. 1981, Welch et al. 1982, Jarup et al. 1989) found no effect of sulfur dioxide exposure on lung cancer risk. Another study (Enterline et al. 1987b), using a multivariate analysis, found no effect of sulfur dioxide after controlling for arsenic and smoking, except in one model where sulfur dioxide had a significantly protective effect against lung cancer that was less protective in the presence of arsenic. The

issue of interaction with sulfur dioxide is now discussed in Section 9.3 of the document.

(5) The commentor provided no documentation regarding the inconsistency in histological types of lung cancer cases.

(6) Regarding negative studies of smelter workers and insecticide manufacturing, few such studies were found. In fact, the only negative findings in these two industries came from extremely small smelters with very low exposures, for which the statistical power to detect excesses in lung cancer predicted from dose-response data in other smelters ranged from 0.05 to 0.28.

(7) Regarding confounding, it is not possible to consider "all possible co-factors", as suggested by the commentor. Aromatic hydrocarbons and process additives have been added to the list of potential confounders in Chapter 9; however, the data presented by the commentor are insufficient to assess the quantitative importance of these factors as confounders. Other confounders have been discussed (e.g., in Section 9.2, an effect of arsenic found independently of exposures to radon and nonarsenical pesticides). In short, confounding was considered in great detail and found to be an implausible explanation for the association between inhaled arsenic and lung cancer among exposed workers.

Comment: An EPA advisory board recommended in September 1989 that the EPA consider estimates of the delivered dose of non-detoxified arsenic in its risk assessment for oral exposure. Since the ARB will soon be considering combined routes of exposure, the concept of detoxification should not be neglected (U.S. Borax).

Response: DHS staff have not been asked to prepare a risk assessment for oral (ingestion) exposure to arsenic as part of the identification phase of the Toxic Air Contaminants Program. Detoxification is discussed in the health assessment document. Although detoxification mechanisms in internal organs (e.g., the liver) play a role in protecting humans against the toxic effects of inhaled arsenic, it should be remembered that the effect of most concern here, lung (or respiratory system) cancer, occurs where the toxicant first contacts the body. Detoxification at the contact site in humans has not been shown. The document discusses differences between lab animal and human lung tissue as possible explanations for the apparent discrepancy between animal and human data regarding arsenic carcinogenesis.

Comment: Is there a detoxification mechanism which becomes saturated? If so, is a risk assessment based on cumulative lifetime exposure logical? Linear nonthreshold multiplicative models would not be appropriate (U.S. Borax).

Response: It is known that inorganic arsenic is detoxified by methylation in the liver, and that this mechanism can be saturated by very high doses of inorganic arsenic. Data are available associating human exposure levels with rates of lung cancer. It has not been shown that the methylation mechanism was saturated by these exposures. Inadequate data are available to allow consideration of pharmacokinetic parameters in the risk assessment model. In

addition, it should be noted that the tumor of concern occurs in the lung, where the toxicant contacts the body.

Comment: The epidemiological data do not justify four smoking categories (U.S. Borax).

Response: The data described in Appendix F of Part B are sufficient for a four-smoking-category model.

Comment: On page 1-8, paragraph 1, Tacoma, Washington, should be mentioned rather than Montana (U.S. Borax).

Response: The document has been changed accordingly.

Comment: Why are only injection and ingestion mentioned on page 1-12 in reporting unmethylated arsenic in the urine? Other routes of exposure should be compared (U.S. Borax).

Response: Extensive data show that As(III) and As(V) may be found unmethylated in the urine after injection or ingestion. The report of Foa et al. (1984) indicates that this may be true after inhalation as well, so inhalation has been added to this list of exposure routes. A quantitative comparison is not necessary for the purposes of the document, however.

Comment: The proposed mechanisms of carcinogenesis on page 1-12 do not seem to fit the model chosen for the risk assessment. A discussion of methods to derive a practical threshold would be appropriate (U.S. Borax).

Response: The actual mechanism of arsenic carcinogenesis has not been established. Clastogenesis and chromosomal rearrangement were listed in this summary as proposed mechanisms. Whether one hit from arsenic is sufficient for carcinogenesis is unknown; the commentor's concern regarding the risk assessment model may relate to this issue. A single molecule or ion of an arsenic compound might disrupt DNA or a DNA-related enzyme, initiating clastogenesis and the inactivation of a growth-controlling gene. Insufficient data exist to derive a practical threshold for arsenic exposure and lung carcinogenesis.

Comment: At least two determinations of the amount of arsenic absorbed by inhalation have been reported. These suggest that 50-80% of inhaled arsenic is absorbed (U.S. Borax).

Response: The bases for the determinations cited by the commentor are unclear and have not been published in the open literature. From the quote included in the comment, it appears that the 1977 determination from "Canadian government data" may have been based on intratracheal instillation in lab animals. The basis for the approximation in the 1979 Swedish review by Pershagen and Vahter is not clear, and this "Toxicological and Epidemiological Appraisal" was not readily available to DHS staff. Although urinary excretion of arsenic by exposed smelter workers was substantial, DHS staff are not familiar with studies designed to quantify absorption of inhaled arsenic by such workers. The only estimate of human pulmonary absorption of arsenic in the 1984 EPA health assessment document was based in large part on experience with other substances (Piscator 1986a). It should

be noted that the DHS risk assessment is based on measurements or estimates of arsenic levels present in the air, and no quantification of absorption need be made for the risk assessment.

Comment: The amount of arsenic absorbed following ingestion is usually greater than 80%. A summary table is available (U.S. Borax).

Response: The document has been revised on this point.

Comment: It might be more appropriate to say that absorption appears to parallel, rather than depend on, water solubility (U.S. Borax).

Response: The document has been revised to say "parallel."

Comment: The statement on page 2-2, paragraph 2, that the correlation between arsenic inhalation and urinary levels is poor could nullify and invalidate the risk assessment, which is based to a large extent on extrapolation of urinary levels to air exposure. An estimate of this extent may be garnered from a 1984 M.S. thesis by P. Osborne (U.S. Borax).

Response: The paragraph has been revised to note that Osborne (1984) and Enterline et al (1987) developed a correlation from relatively high level exposure data and that this correlation was useful for estimating air levels of arsenic to which smelter workers had been exposed. While such data might be employed to give a lower bound on the absorption of inhaled arsenic by the workers, urinary data could not be employed to assess the absorption of arsenic inhaled by the general population. At ambient levels of airborne arsenic, urinary levels are largely determined by oral (dietary) exposures to arsenic compounds.

Comment: Later data should be used to quantify daily dietary arsenic ingestion (U.S. Borax).

Response: These data (Gartell et al. 1986a,b) have been referenced in the document.

Comment: The standard amount of air breathed per day for regulatory purposes is 20 m^3/day, not 18 m^3/day (U.S. Borax).

Response: A breathing rate of 18 m^3/day is a reasonable estimate; this figure is usually paired with a body weight of 60 kg, and 20 m^3/day is usually paired with 70 kg. The risk assessment in the document does not rely on an assumption regarding breathing rate, however. Therefore, this figure, as cited in the document, is not intended to have regulatory significance.

Comment: Regarding page 2-3, paragraph 2, certain sentences regarding the relative toxicity of inhalation and ingestion should be reconsidered. Not all airborne arsenic reaches the lung and data on the "arsenic methylation" capacity of various tissues are currently sadly lacking (U.S. Borax).

Response: The passage has been modified to address the commentor's concerns.

Comment: Regarding page 2-3, paragraph 3: this paragraph is confusing. Original references rather than review articles should be used. The

influence of metabolism and factors which influence metabolism should be considered. The in vitro nature of the findings regarding liver uptake should be noted, as should data regarding interconversion of As(V) and As(III) and the relative magnitude of accumulation in tissues after administration of the different arsenic species (U.S. Borax).

Response: This paragraph is adequate as it stands. It is intended as part of a general summary rather than a detailed literature review. The primary purpose of Part B, risk assessment, would not be aided by more detail regarding the distribution of arsenic compounds in the body.

There is in vivo evidence for uptake of As(III) by the liver (Marafante et al. 1985).

Comment: Regarding page 2-4, paragraph 2: a statement regarding the effects of valence and solubility should be included here (U.S. Borax).

Response: This paragraph addresses the distribution of arsenic after inhalation. It is not clear that the available data would support generalizations regarding the effects of valence and solubility. Moreover, such a statement is not necessary for the purpose of the document.

Comment: Mention of the doses and the detoxification mechanisms that take over at very high doses should be made in paragraph 3 of page 2-4 (U.S. Borax).

Response: This paragraph is intended to address distribution of arsenic, rather than detoxification. It is intended as part of a general summary rather than a detailed literature review. It is adequate as it stands.

Comment: The paragraphs on detoxification and saturation of methylation (page 2-5) are seriously incomplete and hence will leave inaccurate impressions with readers.

Marafante and Vahter deduced that reduction of As(V) to As(III) probably occurs in the blood. Decreased methylating capacity caused by chemical inhibition, dietary deprivation, or genetic disposition may alter excretion of metabolites. Methylation occurs in the kidney and the gastrointestinal tract as well as in the liver. One study showed that following a chronic intake of 200-250 μg As/day a threshold for limiting detoxification appeared. Work by Buchet et al. should be more fully described. Work in animals by Vahter cited by an EPA Risk Assessment Forum Workshop indicates that adaptation can raise the level at which saturation occurs. A study by Foa et al. of glass workers had similar findings and should be discussed.

The document states that there are only acute human data on saturation of methylation, and this is not so.

In contrast to the statement on page 2-5 of the document, saturation could have occurred in the occupational settings on which the assessment is based (U.S. Borax).

Response: The document has been changed to mention the speculation regarding reduction in the blood (this is from Marafante et al. 1985). However, not

all the findings mentioned by the commentor need be listed in the document. This section is intended as part of a general overview rather than a detailed literature review. For example, the liver is identified as the principal site of methylation, but this does not preclude some methylation in the gastrointestinal tract or kidney. DHS staff have found it unnecessary to mention the study of Foa et al. in this context. Valentine et al. (1979) stated that their data needed substantiation before a statement could be made asserting the safety of 100 micrograms per liter of arsenic in drinking water (page 31).

The document does not imply that only acute human data are applicable to the question of saturation of methylation.

The finding that saturation is not likely at occupational exposure levels has been modified in the revised document. Buchet et al. found saturation at an i.v. dose of 0.5 mg, but did not find saturation at an oral dose of 0.5 mg. This latter dose approximates the middle of the range of airborne concentrations to which smelter workers were exposed (roughly 1000 μg As/m^3, which would correspond to about 6 μg As inhaled per work shift), considering that the workers' inhaled doses were spread out over their work shifts and that absorption to the bloodstream was not likely to have been rapid or 100% complete. It should be noted in this context that the tumor of concern (lung cancer) occurs at the contact site (the lung), and the high end of the dose-response curve does not exhibit an inflection or curvature that would indicate saturation of detoxification. In fact, increasing cumulative exposure is associated with decreasing slope in this range.

Comment: Work by Vahter cited by an EPA Risk Assessment Forum Workshop indicates that As(III) may be oxidized to As(V) in hamster lung; this finding should be included in Section 2.3.2 (U.S. Borax).

Response: Data of Marafante and Vahter (1987) indicate that this may indeed have occurred. This has been mentioned in the document.

Comment: Regarding page 2-6, paragraph 1, it should be noted that the study by Crecelius involved only one subject and data from the use of only one subject is usually looked upon as preliminary (U.S. Borax).

Response: The paragraph has been modified in response to this comment.

Comment: The section on elimination is seriously incomplete. A finding of the Canadian National Research Council should be included. An experiment by Odanaka et al. should be described. Several studies by Vahter, Norin, Marafante, Mappes and colleagues should also be described. A conclusion by Pomroy should also be included. Findings by Hunter, Bertolero and coworkers should be described as well as those by Cikrt et al and Klaassen. Salivary excretion should be mentioned, as well as quantitative estimates of daily arsenic excretion in human hair and nails, and via sweat and desquamation (U.S. Borax).

Response: This section is intended as part of a general summary chapter rather than a detailed literature review. Not all of these reports need be mentioned.. The quantitative estimates suggested by the commentator are unnecessary for purposes of the risk assessment.

Comment: The discussion of essentiality is incomplete and thus misleading. It should be mentioned that only five laboratories have ever had the capability to perform dietary deficiency studies on arsenic. Since arsenic deprivation adversely affected all animal species tested, the probability that arsenic will turn out to be essential for humans is greater than 95%. Specifics of work by Schroder, Balassa, Nielsen, Anke, Shuler, and colleagues should be included, along with an estimate by Nielsen et al. of a human requirement based on work in chicks. Data indicate that lack of arsenic in the diet prevents efficient utilization of zinc by chicks. Arginase activity may be a locus for the interaction of zinc, manganese, arginine, and arsenic. The implied assumption of Liebscher and Smith that only nonessential elements are found in human tissue concentrations that approximate a log-normal distribution is not true because essential elements such as chromium or manganese are log-normally distributed in a particular organ and log-normal distributions are found for most essential elements in organs with varied cell types and functions. Log-normal distributions are common and have been used in statistics for years. Schroeder, Tipton and Cotzias never approved of Liebscher and Smith's distinction (U.S. Borax).

Response: The document notes that studies demonstrating arsenic's essentiality in various species are reviewed elsewhere. Because of the controversy on the point of essentiality in humans, the commentor's impression, that it is 95% certain that such essentiality will eventually be found, is not scientific. The document has been modified to point out the interspecies concordance and lack of negative findings in animal studies. To state that few laboratories have ever been able to perform deprivation experiments would be problematic, however. On one hand, it is not clear that no one else could have performed such an experiment. On the other, experiments that could not be independently replicated might not be called scientific. The commentor's observation regarding the capability of laboratories does not appear in the revised document.

This chapter is not intended as a detailed literature review. DHS staff have considered the relevant evidence, including the commentor's submittal, and have included findings in the document as appropriate. It is noted that there may be some essential elements for which no homeostatic mechanism exists, and that a lognormal distribution would be expected of such an element.

Because the effects or existence of arsenic deficiency in humans have not been established, DHS staff believe it would be premature to report the presumed human requirement cautiously estimated by Nielsen and co-workers. The conclusion of this comment implies that based on this presumed requirement, some individuals might benefit from arsenic supplements added to their diets. DHS staff believe that reporting this estimate in the document could present public health problems. Arsenic is toxic in high doses and is notorious as a poison. Any demand for making arsenic compounds available on "health food" shelves could lead to abuse or an unintended impression of safety. In addition, small doses of arsenic "may lead to an occult edema, particularly facial, which has been mistaken for a healthy weight gain and misinterpreted as a 'tonic' effect of arsenic." (Klaassen 1985, page 1615) Of course, common sense dictates that DHS would not ordinarily use a Toxic Air Contaminants Program document to recommend dietary supplements.

Comment: Regarding the chapter on acute toxicity, NOELs and levels associated with adverse effects should be included. A particular document should be used to obtain these data. In addition, it should be noted that certain "notorious arsenic eaters" were known to eat almost half a gram of arsenious oxide once or twice a week, and that this casts doubt on the finding that humans are more sensitive than animals (U.S. Borax).

Response: Although toxicity data for chronic exposure are more relevant to the Toxic Air Contaminants Program than acute data, DHS staff tried to find dose levels associated with adverse effects listed in this chapter. Few such data were available. The document suggested by the commentor as a source of data is referred to only as ATSDR/EPA (1987) and is not listed in the commentor's reference list under ATSDR or EPA. That the commentor did not provide such data in its otherwise extensive submittal indicates that such data may, indeed, not be readily obtainable.

Comment: Lagervist et al. (1986) should be cited at the end of the second sentence in Chapter 5 (U.S. Borax).

Response: This has been done in the revised document.

Comment: Regarding page 5-1, paragraph 2, a particular elaboration on the work of Rozenshtein should be added (U.S. Borax).

Response: The purpose of this chapter is to present highlights and summarize relevant findings. The highlights presented in this paragraph are adequate for this purpose.

Comment: Regarding page 5-2, paragraph 1, two studies should be added to the discussion (U.S. Borax).

Response: These studies in rats, which (as the commentor points out) are not appropriate models for arsenic toxicity in humans, need not be mentioned in this section.

Comment: Regarding page 5-2, paragraph 2, the last sentence should be referenced (U.S. Borax).

Response: The reference for this sentence has been made more clear.

Comment: Regarding page 5-4, paragraph 1, three additional studies of liver toxicity should be discussed (U.S. Borax).

Response: DHS staff have considered these studies. The paragraph has been modified to condense the statements regarding findings in rats, and include some discussion of the study in rabbits.

Comment: Two additional data sets should be discussed at the end of Section 5.1 (U.S. Borax).

Response: These data have been mentioned in the revised document.

Comment: Two additional experiments are worthy of note at the end of Section 5.2.1 (U.S. Borax).

Response: The document now notes that several reports of chronic As(V) ingestion by humans are reviewed in EPA (1984).

Comment: The discussion of Blackfoot disease in Chapter 5 is incomplete and therefore leads to the erroneous conclusion that arsenic causes it [pages 13-15 of the commentor's "Comments on Part B" contain an extended discussion of this issue] (U.S. Borax).

Response: DHS staff have considered the data suggested by the commentor and modified the document to note that Blackfoot disease was found to be associated with, rather than caused by, arsenic-contaminated water. This note is followed by reservations regarding the finding.

Comment: Regarding page 5-7, paragraph 2, the transverse lines of whiter-than-normal nails should be described as Mees' lines (U.S. Borax).

Response: This has been done in the text of the revised document.

Comment: Regarding page 5-4, paragraph 4, if the beer poisoning incident is discussed, the level of arsenic found in the beer should be stated (U.S. Borax).

Response: The document presents as precise a description of the contamination level as presented in the referenced source (NAS 1977); this description is adequate. The commentor, in its otherwise extensive submittal, did not include or cite a source for this datum.

Comment: Regarding the discussion of irritant effects in humans, some arsenicals cause greater irritation than others (U.S. Borax).

Response: The document has been modified to note not only that data relating specific concentrations with irritant effects are lacking, but that data for specific arsenical compounds are lacking as well.

Comment: The reason why data from an experiment by Silaev and Lemeshevskaya has been omitted from page 6-1, paragraph 2, is unclear (U.S. Borax).

Response: As described by U.S. Borax (1989), this study was in the rat, which is not a good animal model for arsenic toxicity, and it did not establish a NOEL.

Comment: Regarding page 6-1, paragraph 2, certain other details of the experiment by Nagymajtenyi et al. should be presented (U.S. Borax).

Response: More details of this work are presented in Section 6.2.3. This paragraph is adequate as it stands. DHS staff agree with the commentor that this experiment did not establish a NOEL.

Comment: It is unclear why certain data from of Hood et al. and Goeneches et al. have been omitted from Section 6.2 (U.S. Borax).

Response: The study by Hood et al. was not designed to assess reproductive toxicity. Rather, it compared arsenic concentrations in fetuses and maternal tissue after i.p. (intraperitoneal) and p.o. (oral) dosing with As(V). The report of Goeneches et al. was not readily available to the staff of DHS. According to the commentor, however, this experiment was designed to assess incorporation of arsenic into tissue, but reported LD_{50}s for dietary exposure to arsenic trioxide. DHS staff do not believe it is necessary to mention this study in the chapter.

Comment: It is unclear why several articles using the rat, hamster or mouse were not reviewed in Chapter 6 or Appendix G (U.S. Borax).

Response: DHS staff have considered this information and do not believe it is necessary to include descriptions of these studies in the document. The purpose of this chapter is to summarize relevant findings and present highlights, with particular reference to studies of airborne exposure in order to establish LOAELs and NOELs. Many of these reports were available for review by EPA (1984), or were reviewed in Hood (1983). Mention of this has been made in the revised document.

Comment: It is unclear why, considering metabolism, the subcutaneous implant method of administration closely approximates air pollution. Route of exposure is critical for establishing reproductive damage levels. Other assumptions, moreover, would result in the subcutaneous exposure being considered to correspond to 30.6 mg As/m^3 rather than 17 mg As/m^3 (U.S. Borax).

Response: This method provides near-constant rate dosing, similar to ambient air exposure, as opposed to intermittent dosing from injection, gavage, or even dietary exposure. DHS staff believe that the assumptions leading to the 17 mg As/m^3 figure (60 kg body weight, 18 m^3/day inhalation, 100% absorption) are appropriate for the comparison made in the document.

Comment: Hood (1983) did not state that As(V) may be more potent than As(III), as stated in Section 6.3. In the second sentence of that section, dose level and route of exposure should be considered. (U.S. Borax).

Response: This point regarding teratogenicity has been clarified. Hood (1983) stated that "valence state influences the relative toxicity of inorganic arsenic. Arsenite [As(III)] is more acutely toxic to both mother and conceptus, but arsenate [As(V)] is more likely to cause malformation of fetuses." (page 134) "Both gross and skeletal malformations are seen more frequently ... following arsenate treatment." (page 137) A statement regarding dose level and route of exposure has been added to this section.

Comment: Route of exposure is critical for a reproductive damage assessment of arsenic. One cannot generalize from other routes to inhalation. Certain levels of oral/gavage exposure that do not appear to cause reproductive and developmental damage can be stated for sodium arsenite and sodium arsenate; these levels are well above the level at which lethality may occur in humans (U.S. Borax).

Response: A statement regarding route of exposure has been added to Section 6.3. The oral/gavage levels presented by the commentor have not been

included, however. The point of this section's last paragraph is to establish qualitatively that arsenic is teratogenic (and to refute the argument that maternal toxicity may have caused arsenic's teratogenicity).

Comment: Chapter 7 is out of date and incomplete and should be updated using a number of sources [enumerated by the commentator, including a review and reports from work with E. coli, B. subtilis, S. typhimurium, S. cerevisiae, and D. melanogaster]. Differences in the effects of As(III) and As(V) should be noted. Effects on DNA should be discussed in a separate section; Section 7.1.1 should be expanded or transferred to such a section (U.S. Borax).

Response: The purpose of this chapter is to present highlights of research and summarize relevant findings in order to reach conclusions regarding the genotoxic activity of inorganic arsenic. DHS staff have considered the information suggested by the commentor and have referenced some of the reports listed by the commentor in the revised document. Many of the listed reports were considered by DHS staff in preparation of the earlier draft. Many of these reports have been discussed by EPA (1984); highlights of that discussion are included in the DHS document as Table 7.1. DHS staff find no need to expand the document so extensively as suggested by the commentor. Further amplification on the different effects of As(III) and As(V) has been included in the revised document, however. The comment regarding a separate section for effects on DNA is unclear (e.g., this section "should include ... the articles discussed in the present Section [Chapter] 7"), so no such section has been added. The information regarding genotoxicity presented by the commentor has not led DHS staff to alter the risk assessment presented in the document.

Comment: Section 7.3 should be reorganized into new divisions and tables should be included within the text. Several specific papers should be considered under the following headings: non-human mammalian cells, micronucleus test, dominant lethal mutations, non-human chromosomal effects, and human chromosomal effects. There should be an additional section on the effects of arsenic on DNA, with a discussion of several specific papers and additional data. Section 7.4 should be expanded to include a summary of several specific papers (U.S. Borax).

Response: DHS staff do not consider such reorganization and expansion to be necessary (see the response to the previous comment). Chapter 7 is not intended to be an exhaustive literature review. After considering the information suggested by the commentor, DHS staff find that the conclusions presented in the Chapter remain valid.

Comment: The data of Oberly et al. (1982) should be reviewed again, since in the presence of metabolic activation, the results were negative (U.S. Borax)

Response: Oberly et al. (1982) only presented data from a trial with metabolic activation if such activation was necessary to produce a positive result (page 370). This was the case with the As(V) compound tested, sodium arsenate. The As(III) compound, sodium arsenite, was positive without activation, so Oberly et al. did not present data from the trial with activation. The EPA (1984) erroneously reported that this latter trial was negative. Since this trial was, in fact, not reported, mention of it has been deleted from the revised DHS document.

Comment: The "Conclusions" section of Chapter 7 is incomplete; at least 12 main findings [specified by the commentor] should be considered (U.S Borax

Response: The key findings regarding the genotoxicity of arsenic compounds are (1) that they are clastogenic, but (2), in numerous tests, have not bee shown to induce point or frame-shift mutations. These are stated in the "Conclusions" section (Section 7.5), and correspond to the commentor's poi 1 and 3. Point 2, that arsenic induces chromosomal abnormalities, has bee included in Section 7.5. The findings with respect to UV light and chromosome aberrations have not been included there; they would be more relevant to a skin cancer risk assessment. Point 4, which states that sta chromosome aberrations would require a minimum of two hits, was not documented by the commentor and has not been included in Section 7.5. If this were so, it would not necessarily dictate a sublinear dose-response relationship, as arsenic's effect could be upon a background rate of hits. (It should be noted in this context that the epidemiological data suggest that arsenic acts proportionally upon a background rate of lung cancer.) Even so, it is possible to envision how a single hit of an arsenic compour could induce clastogenicity. Point 5, that arsenic induces sister chromat exchanges, has been added to Section 7.5. DHS staff do not find it necess to include point 6, the positive finding at high concentrations in the Rec assay, point 7, regarding the fidelity of DNA synthesis (a negative findi or point 8, regarding excision repair and retardation of DNA replication synthesis, in this section. These are stated elsewhere in the chapter. staff have considered the evidence regarding gene amplification (point 9) is now discussed in Chapter 10. Point 10, regarding mitogenesis, is discussed in Section 7.3. Point 11, regarding UV-light, is discussed in Section 7.4. Point 12, the hypothesis by Marczynski, is now cited in Cha 10.

Comment: Regarding page 8-2, paragraph 2, Glaser's laboratory is preemin in the field of inhalation studies on metals and similar substances. Its methodology is state-of-the-art. The dose levels used in the described s of Glaser and co-workers were in the range equivalent to high level expos experienced by smelter workers (U.S. Borax).

Response: The commentor acknowledged that some of the criticisms raised the document are valid: the rat is not a good animal model for the effec arsenic on humans, and few animals were used in the study. The point regarding dose levels has been clarified in the revised document.

Comment: It seems inappropriate to describe intratracheal instillation forced "breathing" of liquid solutions. Any laboratory routinely using intratracheal instillation does not use anesthetized animals and the technique if properly performed is probably less stressful than gavage.

Response: In intratracheal instillation studies of carcinogenesis, "the animals must be anesthetized with sodium pentobarbital or another suitab anesthetic for the procedure which then calls for another control group. Even with technicians experienced with both anesthetization and intratra administration, the procedure cannot be repeated more often than at week intervals over a period of a few months." (Robens JF, Joiner JJ and Sch RL (1982) Methods in testing for carcinogenicity. In: Principles and Me

of Toxicology, Hayes AW, ed. New York: Raven Press, p. 86) This indicates that the procedure is more stressful than gavage.

The experiment of Rosner and Carter (1987, cited above) used "a modified method of Brain *et al.* (1976)" for intratracheal dosing (page 731). Brain et al. (Brain JD, Knudson DE, Sorokin SP and Davis MA (1976) Pulmonary distribution of particles given by intratracheal instillation or by aerosol inhalation. Environ Res 11:13-33) used anesthetization with sodium methohexital (page 16).

Although the procedure is clearly stressful, the "forced 'breathing'" description has been deleted from the document. Nevertheless, instillation does not accurately model passive breathing (ordinary inhalation). The Brain et al. report described an experiment designed to compare the distribution of particles resulting from intratracheal instillation with that resulting from inhalation (page 14). They reported that "the distribution of intratracheally instilled particles differs considerably from that produced following inhalation of comparable particles." (page 32)

Comment: A 1988 paper by Ohyama et al. should be reviewed (U.S. Borax).

Response: Mention of this paper has been made in the revised document.

Comment: The data of Ishinishi and Pershagen should be summarized in a table. Their results are puzzling and an experiment using at least 3 dose levels should be performed prior to attempting to interpret them (U.S. Borax).

Response: DHS staff believe that the existing discussion of tumorigenicity studies that used intratracheal instillation exposure is adequate. In addition, staff believe that it is reasonable to quote the interpretation by Pershagen (1984) in Part B, whether or not an additional experiment is conducted.

Comment: An additional section should be added, considering arsenic as a possible anticancer agent. Certain [specified] papers give some evidence of this (U.S. Borax).

Response: DHS staff have considered the papers specified by the commentor and have discussed them as appropriated in the document. In general, the evidence for arsenic being an anticancer agent is weak and does not require an additional section in Part B. This is particularly true for evidence regarding inhalation exposure.

Comment: Regarding page 9-1, paragraph 1, the statement that "only those studies involving exposure via inhalation are considered" is contradicted by the following four paragraphs (U.S. Borax).

Response: This statement should have continued "for use in quantitative risk assessment". This has been corrected in the revised document.

Comment: Regarding page 9-1, paragraph 2, Neubauer (1947) did not report cases who had been treated for anemia or rheumatism. Some of the cases reported by Neubauer appear to have received organic arsenicals (U.S. Borax).

Response: Neubauer (1947) reported four cases treated for "anaemia and haemorrhagic diathesis" (page 195). Schoolmeester and White (1980) reported a case of "multiple squamous cell carcinomas" subsequent to treatment with Fowler's solution for rheumatism (page 204). Neubauer (1947) reported that "in nearly all cases *inorganic drugs* were used" (page 196).

Comment: Regarding page 9-1, paragraph 3, the skin cancer cases in Poland are questionable (U.S. Borax).

Response: The association between arsenic in drinking water and skin cancer in an area of Poland was cited, as stated in the document, by Tseng (1977). The commentor's unsupported statement did not provide enough information to lead DHS staff to remove this reference from the document.

Comment: Table 9-1 should be reorganized to group data from essentially the same cohorts together and updated with certain data (U.S. Borax).

Response: In the interest of not "reinventing the wheel," DHS staff used the well-researched table presented by EPA (1984) and added summaries of studies that had been published before completion of the first draft of Part B that was released for public comments. Since that time, other studies have been published and DHS staff have made new entries in the table for several studies. The EPA (1984) portion of the table is still presented intact, so the table has not been reorganized.

Comment: Updates of several occupational studies should be included in Table 9-2 and elsewhere in the document. Some key data have been omitted from the document. [Updates and data are given in Appendix A of the commentor's submittal.] (U.S. Borax).

Response: Table 9-2 was taken from another publication; it was included for information purposes. Given the vast literature on arsenic carcinogenicity, DHS staff do not believe it is necessary to provide a detailed account of every study. Staff have focused on the main findings of recent studies of each cohort and synthesized the critical issues as they relate to quantitative risk assessment. DHS staff did not review the epidemiologic studies of environmentally exposed populations for reasons including the following: (1) the occupational studies had better quality exposure data, (2) environmental exposures generally involve a less clear definition of the exposed population, (3) the power of such studies is usually very low, and (4) the ecologic study design may allow a great deal of uncontrolled confounding.

Comment: Regarding page 9-3, paragraph 2, many of the "recent studies" have been overlooked (U.S. Borax).

Response: The commentor refers to numerous updates that were published after the document was released for first round of public comments (e.g., Jarup et al. 1989, Lee-Feldstein 1989, Sandstrom et al. 1989, Wicklund et al. 1988, Sobel et al. 1988). These have been considered by DHS staff and noted in the revised document. None of the newly published reports deviates in its results from the thrust of the previously published reports. For instance, the 1988 paper by Lee-Feldstein appears to confirm the findings of Welch et

al. (1982) with respect to various indices of exposure. The dose-response data published by Jarup et al. (1989) are consistent with the concave downward curvature observed by Enterline et al. (1987) and the confidence intervals of every data point from the Swedish cohort overlap the best fitting curve reported for the Tacoma cohort. A new report (Jarup et al. 1989b) also appears to confirm the observation that the interaction between smoking and arsenic may be multiplicative at moderate doses, but less than multiplicative at high doses. DHS staff have not found new epidemiologic information which would substantially alter the summary of epidemiologic studies provided in Chapter 9, the discussion of mechanisms in Chapter 10, or the quantitative risk assessment in Chapter 11.

Comment: Regarding Section 9.1, data from two smelters show "strong" associations between exposure to arsenic and cancer risk. The data from another smelter (Garfield) now present a "weak" association, and data from six other smelters present weak or negative associations. Studies of insecticide manufacturers have problems which tend to weaken the associations observed (U.S. Borax).

Response: There are numerous cohorts of smelter and mine workers showing strong associations: Tacoma, Anaconda, Ronnskar, the Japanese smelter, and several Chinese smelters and mines (Wu 1988, Taylor et al. 1989). Two insecticide manufacturing plants also show strong associations. Besides showing strong overall associations, clear dose-response relationships were also observed. The reanalysis of the Garfield smelter and the analysis of seven other smelters by Enterline et al. (1987b) yielded results that were fully consistent with all of the previous data. The magnitude of the standardized mortality ratio (SMR) for the Garfield plant was similar to what was predicted by the equation for the dose-response among the Tacoma smelter workers. Of the remaining seven smelters, one had arsenic levels that were too low to estimate individual exposures and another lacked any quantitative exposure data. In the five smelters with adequate exposure data, the power to detect any association was extremely small for two reasons: (a) the size of the studies was much smaller (in none of these plants were there even half as many workers or person-years as there were in the Garfield smelter), and (b) the exposures were very low. The highest of the five smelters had arsenic levels less than 1/5 the level in the Garfield smelter (which was at the low end of the Tacoma exposures). At lower exposure levels, one predicts smaller relative risks or SMRs. Since power is a function of the true (but unknown) relative risk, the power to detect these low risks is itself low.

Comment: Enterline and Marsh (1982) and Enterline et al. (1987) use extrapolation of urinary data to air exposure, but DHS does not approve of this extrapolation (see page 2-2, paragraph 3), so the data from those papers should not be used for risk assessment (U.S. Borax).

Response: The assessment of urinary to air relationships is complex. Earlier studies found poor relationships, but the range of exposures evaluated was small relative to the range evaluated in the later work by Enterline et al. The paragraph in Chapter 2 has been revised to note that Enterline et al. (1987) found the relationship between a wide range of exposure measurements and urinary data to be useful for estimating air levels of arsenic to which smelter workers had been exposed. DHS staff believe that this use of urinary data was appropriate.

Comment: Higgins' data should be considered along with Lee-Feldstein's because Lee-Feldstein applied only three exposure average measurements to all cohorts, regardless of whether the exposure was prior to 1925 or after 1948; Higgins had 826 measurements dating back to 1943. Regarding page 9-6, paragraph 3, and page 11-1, paragraph 1, Morris' data were three average values, so the exposure estimates used in Lee-Feldstein (1986) are better characterized as "semiquantitative." A clear distinction should be made between "quantitative" and "semiquantitative" data (U.S. Borax).

Response: The commentor's remarks are misleading. First, the data of Higgins et al. (1985) were considered and analyzed in great detail as part of the risk assessment in Chapter 11. Second, Higgins also applied data reduction, by averaging the measurements in each department. Conversely, the three measurements used by Lee-Feldstein were derived from a large number of measurements. In fact, these (Morris') data consisted of 702 measurements, made in 56 locations. (Morris, the industrial hygiene engineer at the Anaconda Company, reported these data in Congressional testimony.) These measurements also dated back to 1943. "Semiquantitative" is not an accurate description of the exposure data used by Lee-Feldstein.

With regard to the best choice of analysis to use for risk assessment, the main question relates to potential bias in the risk assessment stemming from the studies' methodologies. The errors introduced by averaging of exposure measurements will generally be random, thus no bias will occur in slope estimates. Both analyses of Anaconda data, however, had other shortcomings. Lee-Feldstein did not apply time-exposure factors for the fraction of a workday spent at a high-arsenic concentration site. By overestimating exposure, her analysis underestimates potency. Higgins et al. conducted a flawed analysis by assigning each worker's final cumulative exposure to all years of follow-up, including those during which he was accumulating exposure. This also biases the potency value. These issues are addressed in Section 11.1.2 of the document.

Comment: Certain data of Pershagen et al. seem to indicate at least an additive effect of sulfur dioxide and arsenic for nonsmokers (U.S. Borax).

Response: There is no need to adjust for exposures producing additive effects, since additivity is the mathematical equivalent of no interaction. In fact, however, the data cited by the commentor are not adequate to evaluate interaction with sulfur dioxide. It should also be noted that the most recent update on the Swedish smelter workers, by Jarup et al. (1989), found no effect of sulfur dioxide on lung cancer SMR, confirming the findings of Lubin et al. (1981) and Welch et al. (1982) (that were noted on pages 9-12 and 9-13). Similarly, the analysis by Enterline et al. (1987b) of the six smelters with low levels of arsenic found no effect of sulfur dioxide when smoking was controlled, except in one model where sulfur dioxide had a protective effect.

Comment: Certain data of Ott et al. had asbestos and vinyl chloride as confounding factors, and certain data of Mabuchi et al. probably had other confounding factors. Regarding page 9-10, paragraph 3, confounding factors should not be overlooked in insecticide manufacturing (U.S. Borax).

Response: The commentor inaccurately refers to confounding factors, and neither study of insecticide manufacturing detected confounding by any other compound. Ott et al. (1974) noted that only two of the 20 respiratory cancer deaths were of workers with any asbestos exposure, and that no other common denominator was found among these employees to explain the observations. Potential confounding in the data of Mabuchi et al. was discussed in the document (page 9-13); the study provides strong evidence that nonarsenical exposures could not explain the extremely high SMRs (1365 for workers with 15-24 years of high exposure, 2750 for workers with >25 years of high exposure). Section 9.2 of the DHS document discusses confounding in great detail.

Comment: Regarding page 9-8, paragraph 3, the data of Rencher et al. should be viewed with caution, because the follow-up period was very short (U.S. Borax).

Response: DHS staff agree that the data of Rencher et al. (1977) are not strong; for this reason, the document gives little attention to this study.

Comment: Regarding page 9-13, paragraph 2, and Table A-4, why were certain data of Pershagen et al. relating to the interaction of arsenic and sulfur dioxide discounted, while data of Pershagen et al. relating to arsenic and smoking were accorded great significance (U.S. Borax)?

Response: For nonsmokers the data cited by the commentor are not adequate to evaluate interaction with sulfur dioxide; the number of cases who were nonsmokers was small and therefore the estimated rate ratios were unstable. Furthermore, for small rate ratios, additivity cannot be distinguished from multiplicativity. For smokers, the data are not adequate to exclude an additive effect on lung cancer of sulfur dioxide and arsenic. With no data to support an interaction, there was no need to adjust for interaction. In contrast, the combined effect of smoking and arsenic was greater than additive in Pershagen et al.'s study and numerous others. A phenomenon that is well supported by the data deserves greater weight than one for which the data are scant. A further reason for giving much greater weight to the smoking/arsenic relationship is that smoking is a known human carcinogen, while sulfur dioxide is not.

Comment: Regarding Section 9.4, the similarity of smoking habits of workers with different levels of arsenic exposure simply means that the general community had homogeneous smoking habits. The statement regarding dose-related effects among smokers and nonsmokers separately does not indicate whether the whole Anaconda smelter cohort showed a dose-related effect (it well may not), and the wide geographic distribution of the arsenic-related effect just means that smelter workers get cancer (U.S. Borax).

Response: The commentor misses the point by arguing that this similarity in smoking habits simply means that the general community had homogeneous smoking habits. Most likely, they did not. Most likely, the men smoked more than the women, the adults more than the children, etc. The similarity in smoking habits at different dose levels is epidemiologic evidence that the observed association between arsenic exposure and lung cancer cannot be attributed to confounding from smoking. This is a critical point since the attributable risk from smoking, among the general population, is quite high.

The point about dose-related effects among nonsmokers and smokers also is evidence that confounding from smoking can be ruled out. The commentor did not recognize the basic epidemiologic principle that stratified analyses can reveal the presence or absence of confounding.

The answer to the question about the whole cohort is obvious: all six studies of the whole cohort have shown a dose-related effect of arsenic.

Finally, the wide geographic distribution also provides evidence that the arsenic-lung cancer association is not due to confounding by some local behavior or exposure.

Comment: The two mechanisms discussed in Section 10.1 have commonly been used to explain some of the toxic effects of arsenic once detoxification mechanisms "slow." What evidence is there that these are carcinogenic mechanisms? If they were, there would have to be some type of threshold, because they obey the "normal 'laws' of toxicology." [The commentor recognized that it is stated in paragraph 3, page 10-1, that "the clinical significance of most of these inhibitions is uncertain".] (U.S. Borax).

Response: Threshold effects in toxicology do not necessarily rely on saturation of detoxification mechanisms. Rather, they commonly operate on the principle of functional reserve. If an arsenic compound inactivates a single molecule of an enzyme required for energy metabolism, there will probably be other functional enzyme molecules remaining in the cell or nearby cells; frank toxicity would not be observed until enough molecules in a sufficient number of cells have been affected. On the other hand, a single insult can be carcinogenic if it affects DNA (directly or by disrupting a critical enzyme at a critical time) in such a way as to inactivate (or activate) a gene that regulates cell growth and division.

Comment: Why should arsenolysis be important in teratogenesis (U.S. Borax)?

Response: Different genes are active during organogenesis than during later life, necessitating unusual conformations of DNA and histones. Unusual stress might be exerted on the sugar-phosphate backbone of DNA, rendering it especially susceptible to breakage if As(V) replaces a phosphate group. In addition, if arsenolysis disrupts RNA during organogenesis, it may affect the synthesis of critical proteins that turn on or off genes at critical times or that effect cell-cell adhesion or attraction at critical times.

Comment: Regarding page 10-2, paragraph 2, pentavalent arsenic is not more potent than As(III) in certain aspects of teratogenesis. This was a misreading of Hood (1983). Each route of administration should be compared separately. By the oral route As(III) is five times as toxic as As(V) (U.S. Borax).

Response: As discussed above, Hood (1983) found As(V) to produce more serious malformations than As(III), and to produce higher rates of malformations at optimal teratogenic doses in animal experiments. Because the optimal teratogenic doses for As(V) and As(III) are different, the word "potent" has been changed in the paragraph at issue.

Comment: A reference should be stated for the first sentence of Section 10.3 (U.S. Borax).

Response: This has been done in the revised document.

Comment: On page 10-3, paragraph 1 (Section 10.3), several articles by Lee et al. should be reviewed. Some of this section should be placed in the chapter on genotoxicity (U.S. Borax).

Response: DHS staff have considered this information and have made mention of findings of Lee et al. in Chapter 10. Staff do not believe that these findings need also be discussed in the genotoxicity chapter.

Comment: Regarding page 10-3, paragraph 3, it should be noted that the healthy worker effect normally applies to a greater extent at high and very high exposure levels (U.S. Borax).

Response: That the healthy worker effect applies differently at different exposure levels is not established, and this comment is not documented. There is substantial literature showing that the healthy worker effect declines with length of follow-up and with age (e.g., McMichael et al. 1975, Fox and Collier 1976, McMichael 1976, Tola and Hernberg 1983, Enterline 1983b, Pearce et al. 1986). Since both of these are directly related to length of employment, and since cumulative exposure also increases with length of employment, there is a strong possibility that among the most exposed workers, the healthy worker effect would be least pronounced.

Comment: It is highly probable that the "low" level exposures at the Anaconda smelter were grossly underestimated, particularly for those workers who were hired before 1950 (U.S. Borax).

Response: DHS staff agree that low-level exposures may have been underestimated; this possibility was discussed on page 11-16. The effect of such misclassification, as pointed out, would be to cause a nonlinear dose-response similar to what was observed. DHS staff also agree that applying measurements from later periods to earlier times would underestimate exposures; this possibility was discussed on pages 11-6 to 11-8. However, as stated in the document, the application of earlier measurements to more recent times, as was done for the Anaconda smelter, would be likely to overestimate exposures. Among the numerous exposure assumptions, some would lead to overestimates and some to underestimates. As stated in the document, the net effect of all these errors cannot be determined.

Comment: Regarding page 10-4, paragraph 3, the size of low-dose-level cohorts is not always too small to have the statistical power to detect the small increase in risk which might be predicted from low-level exposure. DHS staff should recheck this point after updating the data (U.S. Borax).

Response: DHS staff recognized the fact that the low-dose subgroups were not always too small to detect increases. The paragraph of the document preceding the one cited by the commentor discusses low-dose subgroups that did have statistically significant increases in lung cancer risk.

Comment: A threshold dose for arsenic carcinogenicity can probably be deduced by examining the data (U.S. Borax).

Response: The document states that threshold models for carcinogenesis have not been convincingly demonstrated. The burden would be on the commentor to establish a threshold model or threshold dose, and the commentor has not attempted to do so.

Comment: Regarding Section 10.4.2, it would be appreciated if DHS would reconsider its position in light of an EPA SAB [Science Advisory Board] recommendation. It should be noted that most of the EEC [European Economic Community] nations use rating systems dissimilar to that of IARC [the United Nations' World Health Organization's International Agency for Research on Cancer] (U.S. Borax).

Response: This comment is insufficiently referenced for complete evaluation. DHS staff are aware, however, of suggestions within EPA that arsenic be considered less potent by the oral route of exposure because an associated cancer endpoint, skin cancer, is less severed than other cancers. Staff believe that it is unnecessary to discuss the rating systems of EEC nations in the document.

Comment: Regarding page 10-5, paragraph 3, does the third sentence imply that DHS discounts all bioassays not conforming to the NTP [National Testing Program] protocol? A number of other protocols have wide acceptance in the scientific community (U.S. Borax).

Response: No, the document refers to protocols "such as" that of the NTP.

Comment: Regarding page 10-6, paragraph 2, and page 10-7, paragraph 1, will this argument be applied by DHS to substances other than arsenic (U.S. Borax)?

Response: This paragraph observes that the lungs of humans and lab animals differ, and mentions the possibility that lab animal lungs can detoxify arsenic (or other compounds) where human lungs cannot. As indicated, DHS staff may consider this line of reasoning with regard to other compounds, as appropriate.

Comment: Regarding page 10-8, paragraph 2, could DHS please cite an instance where a chemical is an initiator carcinogen and is not a carcinogen in animals? What experiments suggest that there is an arsenical metabolite which appears in humans but not animals (U.S. Borax)?

Response: The purpose of Chapter 10 is to present relevant data and to consider possible mechanisms of arsenic toxicity and carcinogenesis. Arsenic is an atypical carcinogen (because of the discrepancy between positive findings in humans and equivocal data in animals). This part of the discussion merely states a possibility that DHS staff believe is worth mentioning.

Comment: Regarding page 10-8, paragraphs 3 and 4, the mechanisms suggested in these paragraphs would all produce tumors in animals (U.S. Borax).

Response: This part of the discussion is not intended to address the discrepancy between human and animal data. As is suggested elsewhere in the document, the data do not rule out the possibility that an animal model will be found. The paragraphs at issue discuss whether arsenic is an initiator and/or a promoter of cancer.

Comment: Regarding page 10-9, paragraph 2, and Appendix B, the link between latency and arsenic as an ititiator or promoter is not mainstream science and hence should be backed up with references or peer review by "top-flight" pathologists such as Francis J.C. Roe, scientists such as Richard Doll, or others of their standing. Appendices B and E need peer review by top-flight specialists in those areas in order to be accepted by the scientific community (U.S. Borax).

Response: At this point in time, mainstream science has not been able to resolve the question of whether arsenic is an initiator, promoter, or an agent inducing proliferation. The data on latency are one part of a complex puzzle; the role of latency periods can only be understood by more detailed analyses involving other age/time factors, while the whole puzzle will certainly require work on many fronts, including pathology, cell biology, genetic toxicology, biostatistics, and epidemiology. The document has been revised to emphasize the complexity of the "stage" issue. With respect to peer review, DHS staff have discussed these issues with other scientists at conferences, in journal articles, and in numerous personal communications. In addition, the DHS document has already been the subject of a round of public comments and responses, and has been reviewed by in-house staff and other consultants. As to the analysis of latency and time-related factors with epidemiologic data, DHS staff would be delighted if Richard Doll and others of his caliber were to take up these issues as they pertain to the stage of arsenic's carcinogenic activity.

Comment: Regarding page 11-1, paragraph 1, a clear dose-response relationship was often not observed and the reasons for this should be considered. Often negative data can be instructive (U.S. Borax).

Response: The commentor provided no references that showed a lack of dose-response. A dose-response relationship between arsenic and lung cancer was observed by many investigators as noted in the document. Other studies which did not have quantitative exposure measurements but did have some ordinal measure of either intensity or duration of exposure also frequently showed an increasing risk with increasing exposure. On the other hand, a lack of correlation between duration of employment and cancer risk generally reveals the inadequacy of duration as a measure of exposure.

Comment: Regarding page 11-1, paragraph 1, it should be remembered that smelter workers at high exposure levels swallowed large quantities of arsenic. If total risk assessments are to be commonly used by the ARB and DHS, they should be discussed in Part B, and the problem of a threshold or detoxification level will assume greater importance (U.S. Borax).

Response: DHS staff have not been asked to prepare a risk assessment for combined routes of exposure to arsenic for the identification phase of the Toxic Air Contaminants Program. Detoxification is discussed in the health assessment document. Although detoxification mechanisms in internal organs

(e.g., the liver) play a role in protecting humans against the toxic effects of inhaled arsenic, it should be remembered that the effect of most concern here, lung (or respiratory system) cancer, occurs where the toxicant first contacts the body. Detoxification at the contact site in humans has not been shown.

Comment: Regarding page 11-2, paragraph 1, the datasets of Lee-Feldstein and Higgins et al. should both be considered. Lee-Feldstein's data tapes might be useable with Higgins et al.'s more complete exposure measurements (U.S. Borax).

Response: The datasets of Lee-Feldstein (1986) and Higgins et al. 1985 were both considered in the risk assessment. While Lee-Feldstein's data tapes might be useable with the exposure measurements used by Higgins et al., DHS staff believe it would not be worthwhile to undertake the substantial effort that would be required for such an analysis. Furthermore, since the dose-response relationship characterized by Enterline et al. is consistent with the data from several other cohorts, there is no need to conduct such an analysis.

Comment: Regarding page 11-2, paragraph 2, why not fit models to Osborne's data as well as those of Enterline et al. (U.S. Borax)?

Response: Much of the material in Appendix A of the commentor's submittal that is presented as a description of Osborne's data is actually verbatim text from page 11-5 of the draft DHS document, in which DHS staff summarize the analysis published by Enterline et al. Dr. Enterline and colleagues' analysis of the exposure data does not appear to be flawed. That the estimates of earlier exposures used by Enterline et al. were not as high as those of Osborne does not necessarily support the validity of the Osborne estimates. In fact, in the 1982 paper by Enterline and Marsh, it was noted that the respiratory cancer SMRs in the years 1941 to 1976 were slightly higher for those hired after 1939 than for those hired before 1940. This observation would suggest that exposure levels may not have been dramatically higher before 1940 and that the assumptions of Enterline et al. in their 1987 paper were justified.

Comment: Regarding point 1 in the paragraph on the strengths of the studies of Anaconda and Tacoma smelter workers that appears on pages 11-3 and 11-4, the quality of the data and the data's relationship to the workers' actual exposure have not been considered. Higgins' exposure data are of higher quality than those of Lee-Feldstein. Regarding this point and page 11-5, paragraph 2, Osborne's data for the Tacoma plant are probably more realistic than Enterline's for early exposures (their later data are the same). Regarding point 2, this means that one has large cohorts and follow-up periods; it does not alleviate the difficulty of estimating exposure levels. Regarding point 3 and page 11-6, paragraph 2, high exposures for a relatively large number of workers prior to "entry into the cohort" have not been assessed. Regarding point 4, this only means that the general community had homogeneous smoking habits. Regarding point 5, it is not stated whether the analysis of the whole Anaconda cohort also showed this. Regarding point 6, why were the workers who had been exposed to asbestos not removed from the analysis as a matter of course? Regarding point 7, the difference between

the data from Tacoma and Anaconda, and certain data from the Ronnskarsverken smelter [in Sweden] should be discussed (U.S. Borax).

Response: The comment raises several issues regarding problems in the exposure data for the epidemiologic studies. These problems were acknowledged and discussed on pages 11-6 to 11-8 of the draft document. The relationship of such exposure data to the workers' actual exposures is never known precisely. Scientists can only make use of the data that exists, not the data one wishes were there. DHS staff have no information to indicate that the data of Osborne are better than those of Enterline; it is worth noting, in this context, that the Osborne data have not appeared in the peer-reviewed literature, while Enterline's analysis has been published. Furthermore, Enterline was undoubtedly aware of Osborne's work, since he served as the chairperson of her thesis committee in 1984, prior to his 1987 analysis that was used by DHS staff for risk assessment. In that analysis, Enterline and colleagues considered Osborne's approach and found that "it now appears ... that the translation of urinary arsenic levels to air arsenic levels presented here is the more appropriate" (Enterline et al. 1987a, page 938). Regarding point 2, the assertion that large cohorts represent a strength of the epidemiologic data is an entirely valid statement. The objection to point 3 was discussed on page 11-7 of the draft document. The comment on point 4 appears to be irrelevant since point 4 is presented as an argument for the internal validity of the data. The answer to the question about point 5 is that all six studies of the whole cohort have shown a dose-related effect of arsenic. The question about point 6 is addressed to the authors of the epidemiologic study, not DHS staff. As to the comment on point 7, there was no difference in this regard between the findings from the American and Swedish smelters: an effect of arsenic independent of sulfur dioxide exposure was found at the Ronnskar smelter as well as in Tacoma and Anaconda. This has been noted in the revised document.

Comment: The data presented in paragraph 2, page 11-4, were used by Higgins et al. but not by Lee-Feldstein (U.S. Borax).

Response: The comment is correct. The document has been revised to describe the exposure data used by Lee-Feldstein.

Comment: Sulfur dioxide should be used, like smoking, as an "interaction" substance (U.S. Borax).

Response: DHS staff know of no evidence supporting a sulfur dioxide-arsenic interaction. As noted above, the data of Pershagen on sulfur dioxide and arsenic among nonsmokers and smokers do not contradict an additive effect. The analysis by Enterline et al. (1987b) of 6 cohorts of smelter workers having adequate exposure data showed, after controlling for smoking, either no effect of sulfur dioxide on lung cancer risk or a protective effect that was modified by arsenic exposure.

Comment: Regarding the exposure assessment for the Anaconda smelter workers, the quality of the data and their relationship to what the workers were exposed to has not been considered. Certain descriptive passages from a 1988 report on "the Great Greenhill Arsenic Works" that operated in England until 1925 are worthy of note. High exposures prior to "entry into the cohort" of many workers have not been assessed. (U.S. Borax).

Response: The quality of exposure data was considered carefully and discussed in great detail (on pages 11-6 to 11-8 of the draft document). Workers exposed prior to 1925 constituted a small fraction (less than 12%) of the Anaconda smelter cohort (Lee and Fraumeni 1969). In the Tacoma smelter cohort, about 18% were hired prior to 1930, and hence even fewer before 1925. A strong influence from underestimating early exposures is unlikely. In fact, at the Tacoma smelter, mortality from lung cancer was lower among those hired before 1940 than among those hired later (Enterline and Marsh 1982).

Comment: There is a need to know about the mechanism(s) by which arsenic causes lung cancer. Is it (are they) related to cumulative exposure or elevated dose or bioavailability? Is there a threshold (U.S. Borax)?

Response: At this point, the answers to many questions regarding mechanisms are not known. The document can only address and utilize current knowledge and understanding. In the absence of sufficient evidence to the contrary, DHS uses nonthreshold models of carcinogenesis.

Comment: The interactions of arsenic with copper, sulfur, and other compounds that have always been present at high levels when respiratory cancer has been linked with arsenic in smelters, are of importance, but are difficult to measure or quantify (U.S. Borax).

Response: Data in the literature that would allow quantification of interaction with copper, sulfur, or other compounds do not appear to be available at this time.

Comment: The factors involved in extrapolating from the white male cohorts of the risk assessment studies to the general population are not fully understood (U.S. Borax).

Response: Uncertainty due to the extrapolation from adult white males to the general population was discussed on pages 11-9 and 11-10 of the draft document. Again, there are insufficient data to draw definitive conclusions. This discussion was designed to make explicit the assumption for this risk assessment and to give a rough estimate of the magnitude of uncertainty associated with this assumption.

Comment: The third sentence of paragraph 2, page 11-19, is difficult to understand because the risk assessment uses urinary measurements. Enterline's data converts urinary data to air measurements at the beginning of the calculations. Urinary measurements should be retained until the final step (U.S. Borax).

Response: At no point does the risk assessment directly use urinary measurements. Since the goal of the risk assessment is to estimate risks associated with ambient airborne exposure, the use of air measurements avoids the need to make any conversion. Fortunately, Enterline and colleagues were able to obtain air measurements for many time periods and departments and were also able to develop a urine-to-air conversion, so that dose-response data were available in their published report relating air measurements to lung cancer SMRs. Other studies also expressed exposures as air measurements.

Comment: Regarding page 11-30, paragraph 3, it is not certain that the result underestimates the risk because arsenic is known to have detoxification mechanisms and exposures were greatly underestimated for large numbers of workers in all the cohorts (U.S. Borax).

Response: The data on detoxification mechanisms do not show complete detoxification in that excreted arsenic includes non-methylated as well as methylated forms at a wide range of doses. It also has not been shown that significant detoxification occurs in the lung. Since the target site for carcinogenicity of inhaled arsenic is the site of contact, detoxification in other organs may be irrelevant. The commentor believes that exposures were greatly underestimated for large numbers of workers in all the cohorts. The issue of exposure misclassification is discussed fully in the document and there is no new information that would substantially alter the findings of the risk assessment.

Comment: Regarding the "Equivalent Ambient Exposure" column of Table 11-2, it should be noted that the earlier workers were exposed 10 or 12 hours per day and more than 250 days per year. In addition, most of the workers were exposed to environmental concentrations which were much higher than 2 ng/m^3 (U.S. Borax).

Response: That workers were exposed for 10 to 12 hours per day is possible, but documentation would be needed to incorporate such information into the risk assessment. Most of the person-years accrued over the period from 1940 on, and the 40-hour work week had already been enacted for most unionized workers in the United States (see Schlesinger AM (1940) The New Deal In Action, 1933-1939, New York:The Macmillian Company). The environmental exposures of workers would still have been far lower than their occupational exposures and would not alter the risk estimates.

Comment: Using three levels of smoking for the risk assessment seems extreme. The sections of Appendix E on smoking should be sent to a specific epidemiolgist, Peter N. Lee, for review (U.S. Borax).

Response: The use of three levels of smoking was not extreme; it provides useful information to the public and to risk managers. Dr. Lee is welcome, like any member of the public, to comment on Appendix E.