DEPARTMENT OF LABOR

Occupational Safety and Health Administration

29 CFR Part 1910

Occupational Exposure to Inorganic Arsenic

AGENCY: Occupational Safety and Health Administration (OSHA), Labor.

ACTION: Supplemental Statement of Reasons for the Final Rule.

SUMMARY: This notice presents the final assessment of the degree of risk from occupational exposure to inorganic arsenic and the signficance of that risk. OSHA issued a standard in 1978 reducing the permissible exposure limit for inorganic arsenic from 500 $\mu g/m^3$ to 10$\mu g/m^3$, the lowest feasible level, based on substantial human data associating excess lung cancer with exposure to inorganic arsenic (43 FR 19589, May 5, 1978; 29 CFR 1910.1018). There was quantitative evidence of risk below 500 $\mu g/m^3$. However, at that time OSHA had not quantitatively estimated risk at low levels nor made a formal signficant risk determination. Subsequently, the Ninth Circuit Court of Appeals ordered the Agency to receive additional evidence and make additional findings on these issues as required by *Industrial Union Department* v. *American Petroleum Institute*, 448 U.S. 607 (1980). Pursuant to that order OSHA published a notice (47 FR 15358, April 9, 1982) presenting three risk assessments and OSHA's preliminary analysis, requesting comments and scheduling a hearing. After analyzing all the evidence, OSHA concludes that a significant risk is presented by inorganic arsenic at the 500 $\mu g/m^3$ level and that the 10 $\mu g/m^3$ inorganic arsenic standard is needed to substantially reduce a significant risk of lung cancer. The 10 $\mu g/m^3$ standard, which has remained in effect subject to limited stays during the reopening of the record pursuant to the Court's order, therefore, continues in effect.

EFFECTIVE DATE: The inorganic arsenic standard went into effect on August 1, 1978. This supplemental statement takes effect on January 14, 1983.

ADDRESS: For additional copies of the Supplemental Statement contact: OSHA Office of Publications, U.S. Department of Labor, Room H–3423, 200 Constitution Avenue, N.W., Washington, D.C. 20210, telephone 202–523–8677.

FOR FURTHER INFORMATION CONTACT: Mr. James F. Foster, OSHA, U.S. Department of Labor, Office of Public Affairs, Rm. N–3641, 200 Constitution Avenue, N.W., Washington, D.C. 20210, Telephone (202) 523–8151.

SUPPLEMENTARY INFORMATION:

Background

In 1971, in accordance with section 6(a) rulemaking procedures of the Occupational Safety and Health Act of 1970, OSHA adopted the consensus standards for "arsenic and its compounds" at 0.5 mg As/m^3, lead arsenate at 0.15 mg/m^3, and calcium arsenate at 1.0 mg/m^3 as determined on an eight-hour time weighted average basis. These levels were based on the 1968 ACGIH list of Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment (TLV's).

OSHA began the process of revising the 1971 standard after receipt of the National Institute for Occupational Safety and Health document, "Criteria for a Recommended Standard . . . Occupational Exposure to Inorganic Arsenic." published in 1973. The National Institute for Occupational Safety and Health (NIOSH) recommended that no worker be exposed to a concentration of arsenic greater than 50 micrograms per cubic meter ($\mu g/m^3$) of air determined as a time-weighted average (TWA) exposure for up to a 10-hour workday, over a 40-hour work week. This standard was based on reports that associated occupational exposure to inorganic arsenic with the induction of cancer. On September 20, 1974, following a notice published in the **Federal Register**, OSHA conducted an informal fact-finding hearing on the potential health hazards associated with occupational exposure to inorganic arsenic.

On November 8, 1974, NIOSH sent to OSHA new recommendations for inorganic arsenic including a more stringent permissible exposure limit of 2 $\mu g/m^3$ of air as determined over a 15-minute sampling period. NIOSH based these new recommendations on additional significant information, along with earlier reports on the carcinogenicity of inorganic arsenic. The new recommendations appeared in a revised criteria document published in 1975.

On January 21, 1975, a proposed standard to control occupational exposure to inorganic arsenic to a limit of 4 $\mu g/m^3$ was published by OSHA in the **Federal Register** (40 FR 3392). The proposal included a detailed preamble describing the rationale for the proposed standard, the information relied upon in its development and the provisions of the proposed standard. The notice requested the submission of written comments, data, views and arguments on all the issues raised by the proposal and scheduled an informal public hearing pursuant to section 6(b)(3) of the Act commencing April 8, 1975. A notice of the availability of a Technological Feasibility Analysis and Inflationary Impact Statement was published on June 24, 1976 (41 FR 26029) and the record on feasibility issues and new scientific data was reopened. Another informal hearing on feasibility issues commenced on September 8, 1976.

On May 5, 1978 a final standard regulating occupational exposure to inorganic arsenic as a confirmed carcinogen was published in the **Federal Register** (43 FR 19584). This standard (29 CFR 1910.1018) applied to all employments in all industries except pesticide application, agriculture, and the treatment and use of arsenically preserved woods. The standard reduced the permissible exposure level from 500 $\mu g/m^3$ to 10 $\mu g/m^3$ and established requirements for monitoring, control strategy, medical surveillance, and other provisions. OSHA concluded, based on the evidence contained in the record, which included a number of high quality human studies associating inorganic arsenic exposure with excess risk of lung cancer, that inorganic arsenic is a carcinogen, that no safe level of exposure can be demonstrated, and that 10 $\mu g/m^3$ is the lowest feasible level to which employee exposure could be controlled.

Shortly after its promulgation, the inorganic arsenic standard was challenged by industry in several U.S. Courts of Appeals. The cases were consolidated in the U.S. Court of Appeals for the Ninth Circuit in three cases, *ASARCO Inc., et al.* v. *OSHA*, No. 78–1959, *The Anaconda Co. et al.* v. *OSHA*, Nos. 78–2764, 3038 and *General Motors, et al.* v. *OSHA*, Nos. 78–2477 and 2478.

The ASARCO case was briefed and argued. Prior to decision, the Ninth Circuit Court on its own motion withdrew the case from consideration pending the decision of the Supreme Court in *Industrial Union Dept.* v. *American Petroleum Institute*, 448 U.S. 607 (1980), the benzene decision. The Supreme Court held in that case that the agency must make a determination of significance of risk prior to issuing a standard.

During the rulemaking proceedings on arsenic, OSHA had not made any estimates of the degree of risk at low levels of exposure to inorganic arsenic. In light of the Supreme Court's benzene decision, therefore, industry representatives petitioned the Ninth

Circuit to vacate the inorganic arsenic standard and remand it to OSHA for reconsideration. OSHA agreed that the standard should be remanded for the purpose of analyzing the quantitative degree of risk and for the purpose of arriving at a determination of the significance of that risk as required by *Industrial Union Dept.* v. *American Petroleum Institute.* However, OSHA requested that the standard remain in effect during the period of the remand because, unlike the benzene standard, there were measured data showing excess cancer risk at levels below the prior (500 $\mu g/m^3$) exposure limit. In addition, three risk assessments performed on inorganic arsenic after issuance of the standard indicated excess risk at levels of exposure well below the 500 $\mu g/m^3$ level.

On April 7, 1981 the Ninth Circuit Court of Appeals issued the following order:

> This matter is remanded to permit respondent to reopen the record to receive additional evidence and to make additional findings in the light of *Industrial Union Department* v. *American Petroleum Institute,* 488 U.S. 607, 100 S. Ct. 2844 (1980). If respondent determines the permissible exposure level for inorganic arsenic should be adjusted, the respondent shall amend the standard accordingly. Jurisdiction is retained. The matter shall be resubmitted to this court on the amended record no later than one year from the date of this order. * * *
>
> The occupational health standard regulating employee exposure to inorganic arsenic shall remain in effect pending the resubmission of this matter to this court, and until further order of this court, except insofar as petitioners have obtained stays from this court or variances from the respondent.

Thus, the inorganic arsenic standard has been and remains in effect for all employers except for limited stays granted by the Ninth Circuit to ASARCO, Inc., on June 19, 1979, the Bunker Hill Co., on December 11, 1979, the Anaconda Co., on December 26, 1979 and Kennecott Copper Corp., on November 19, 1981 for their facilities only. The stays basically permit those companies only, to achieve the 10 $\mu g/m^3$ exposure limit with respiratory protection rather than engineering controls. Except for the requirement to build new filtered-air lunchrooms at their facilities, all other provisions of the standard are in effect for those companies.

Some automotive manufacturers requested permanent variances from the arsenic standard's (as well as the lead standard's) provisions for engineering controls and certain other requirements for their solder-grind operations. Lead-arsenic solder, used to fill body joints, is ground smooth in these operations. The companies stated that there were no feasible engineering controls available to reduce exposure to 10 $\mu g/m^3$ and that supplied-air respirators, hoods and suits provided appropriate protection. OSHA granted variances permitting the affected companies (General Motors, 45 FR 46922, July 11, 1980; Chrysler, 45 FR 74096, November 7, 1980; Ford, 46 FR 32520, June 23, 1981) to use supplied-air respirators to comply with the 10 $\mu g/m^3$ permissible exposure limit. Certain additional requirements were specified in the variance grants, including a provision that the companies were to attempt to eliminate the use of lead-arsenic solder by developing appropriate substitutes.

OSHA published in the Federal Register on April 9, 1982 (47 FR 15358), a notice pursuant to the Court order reopening the inorganic arsenic rulemaking record for the purpose of receiving evidence and making findings on the degree of risk from occupational exposure to arsenic and the significance of that risk, and making any adjustments to the standard as may be warranted by the additional evidence and findings on risk. The notice briefly reviewed the science of risk assessment, summarized three risk assessments performed for inorganic arsenic, stated the reasons for OSHA's preliminary assessment of risk and stated OSHA's preliminary judgment of the significance of the predicted risk. Comments were requested on the above issues, the three risk assessments presented, and OSHA's preliminary judgments. Public comments were requested by June 18, 1982 and an informal public hearing was held on July 13–16, 1982. Post-hearing submissions of additional information were due on August 13, 1982 and final briefs were due on September 3, 1982.

A number of interested parties participated, including trade associations, companies, unions and members of the general public. A number of scientists testified and responded to cross-examination. Many studies, statements and comments were submitted into the record. The record was certified by the Administrative Law Judge on November 24, 1982.

OSHA has now reviewed all the evidence in the record. In this document, as ordered by the Ninth Circuit Court of Appeals, OSHA reviews in depth the evidence on the degree of risk presented by inorganic arsenic and its significance. It sets forth OSHA's final judgments on these issues and OSHA's conclusion that the 10 $\mu g/m^3$ standard for inorganic arsenic is needed to substantially reduce a significant risk of lung cancer. This document does not repeat analysis of studies presented in the preamble accompanying the issuance of the final inorganic arsenic standard unless needed for purposes of updating or to clarify discussion. This document reviews new health data which have become available since 1977.

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I. Summary of OSHA's Analysis

OSHA's overall analytic approach for setting worker health standards is a four-step process consistent with recent court interpretations of the Occupational Safety and Health Act and rational, objective, policy formulation. In the first step, risk assessments are performed where possible and considered with other relevant factors to determine whether the substance to be regulated poses a significant risk to workers. Then in the second step, OSHA considers which, if any, of the proposed standards being considered for that substance will substantially reduce the risk. In the third step, OSHA looks at the best available data to set the most protective exposure limit necessary to reduce significant risk that is both

technologically and economically feasible. In the fourth and final step, OSHA considers the most cost-effective way to achieve the objective.

The Ninth Circuit's remand provided that OSHA consider the issues presented by the first two steps and the elements of the third step dealing with risk issues. This final **Federal Register** document directly addresses those matters. A cooperative evaluation by technical experts from OSHA, the smelter companies and the United Steelworkers of America, which is not part of this record, gives additional consideration to the final steps.

It is appropriate to consider a number of different factors in arriving at a determination of significant risk with respect to inorganic arsenic. The Supreme Court gave some general guidance as to the process to be followed. It indicated that the Secretary is to make the initial determination of the existence of a significant risk, but recognized that "while the Agency must support its finding that a certain level of risk exists with substantial evidence, we recognize that its determination that a particular level of risk is 'significant' will be based largely on policy considerations." (*IUD* v. *API.* 448 U.S. 655, 656, n. 62). In order for such a policy judgment to have a rational foundation, it is appropriate to consider such factors as quality of the underlying data, reasonableness of the risk assessment, statistical significance of the findings, the type of risk presented and the significance of the numerical risk relative to other risk factors.

In the April 9, 1982 (47 FR 15358) document which opened the issue of significant risk, OSHA pointed out that there were a number of high quality epidemiology studies such as Lee and Fraumeni, Pinto and Enterline, Ott et al., and Hill and Faning which strongly associated exposure to inorganic arsenic with excess risk of lung cancer among workers in both smelters and chemical plants. Many of these studies demonstrated a good dose response relationship and provided a good basis for risk assessment. Several demonstrated measured excess risk below the prior 500 $\mu g/m^3$ exposure limit. For example, the Lee and Fraumeni study indicated that for long term exposure to inorganic arsenic a 445 to 567% excess risk (334 to 425 excess cases per 1000 exposed employees) of lung cancer exists at 580 $\mu g/m^3$ and a 150 to 210% excess risk (112 to 158 excess cases per 1000 exposed employees) exists at 290 $\mu g/m^3$.

During the notice and comment period OSHA received published versions of additional studies, including Lee-Feldstein, Enterline and Marsh, Higgins et al., Mabuchi et al., and Lubin et al., which continued to strongly associate exposure to inorganic arsenic with excess risk of lung cancer. Recently, the International Agency for Research on Cancer, the World Health Organization-Arsenic Working Group and the Chemical Manufacturers Association have also judged inorganic arsenic to be a human carcinogen. The new data is of high quality and confirms OSHA's earlier conclusion that inorganic arsenic is strongly associated with excess risk of lung cancer. The new data also includes measured excess risk below 500 $\mu g/m^3$. For example, the Lee-Feldstein study covering 8045 employees and including 4448 low exposure workers whose average exposure was 290 $\mu g/m^3$, and whose mortality was observed over a 39 year period, indicates a 131% excess risk for those low exposure employees. Also, Enterline and Marsh observed a 168% excess risk for employees exposed to an average of 49 $\mu g/m^3$ (estimated from urinary level of 163 $\mu g/l$) for 10–19 years.

In the April 9th document, OSHA pointed out that a number of the epidemiology studies provided a good basis for risk assessment because of their high quality and because of the availability of quantitative estimates of exposure. OSHA presented three risk assessments and reached the preliminary conclusion that they presented reasonable estimates of risk, with OSHA selecting as most reasonable estimates ranging from a 500–620% excess risk (375 to 465 excess cases of lung cancer 1000 exposed employees) for a working lifetime of exposure at 500 $\mu g/m^3$ to a 10–14% excess risk (7 to 10 excess cases per 1000) at 10 $\mu g/m^3$. These estimates were based on a linear model, OSHA also presented estimates based on a quadratic model, but new analysis indicate that the data strongly supports a linear model in the case of inorganic arsenic.

Additional data were submitted which strongly support estimates of risk in this range. Dr. Crump submitted risk assessments based on the new epidemiologic studies which were in this range and which demonstrated good fits between the data and the linear model. Dr. Radford submitted an estimate of risk which was somewhat higher and Dr. Enterline an estimate which was somewhat lower. The National Institute of Occupational Safety and Health agreed with OSHA's estimates and approach.

Based on the earlier data and the data submitted in response to the April 9th document, OSHA concludes that the range of reasonable estimates of risk from a working lifetime of exposure to inorganic arsenic are from 148 to 767 excess deaths from lung cancer per 1000 exposed employees at 500 $\mu g/m^3$ to 2.2 to 29 excess lung cancer deaths per 1000 exposed employees at 10 $\mu g/m^3$. The OSHA preferred estimates within that range are approximately 400 excess deaths per 1000 at 500 $\mu g/m^3$, 40 excess deaths per 1000 at 50 $\mu g/m^3$ and 8 excess deaths per 1000 at 10 $\mu g/m^3$.

Consultants in Environmental and Occupational Health (CEOH) presented an alternate analysis principally based on the results of the study by Higgins et al. Employees with average exposures between 100 and 500 $\mu g/m^3$, including those who had peak exposures over 500 $\mu g/m^3$, had statistically significant increased respiratory cancer mortality. However, they found that employees whose ceiling exposures never exceeded 500 $\mu g/m^3$ had SMR's between 116 and 129 (16 to 29% excess risk), which were not statistically significant (Method I analysis). CEOH, therefore, suggested that 500 $\mu g/m^3$ was a practical threshold and there would be little excess risk for employees with no peak exposures over that limit.

This hypothesis is not nearly as strongly supported as the estimates of risk OSHA has presented. First, the OSHA estimates are based on a generally accepted model, with a biologic basis, which fits well a substantial body of high quality data. Second, both the Lee and Fraumeni, and Lee-Feldstein studies of the entire Anaconda cohort (not just 22%) demonstrated a statistically significant excess risk (from 86% to 213%) for low exposure employees who did not have any peak exposures over approximately 500 $\mu g/m^3$. This result directly contradicts the ceiling hypothesis. Third, the Higgins data was based on a 22% sampling of Anaconda employees, resulting in very low statistical power. The study only had a 16–37% chance of detecting a 50% excess risk, if it actually existed. Fourth, the employees actually had an excess risk (under Higgins Method I analysis) which was not very different (116–129 SMR) from OSHA's estimate (150 SMR) for employees with their relatively low average exposure. Fifth, the ceiling hypothesis has only been preliminarily tested at one location and before the possibility would develop of general acceptance in the scientific community, there would need to be supportive results in a number of locations.

Based on measured data in the record of excess risk below 500 $\mu g/m^3$ and estimates from the risk assessments

summarized above and discussed in depth below indicating approximately 400 excess cases per 1000 exposed employees at 500 $\mu g/m^3$. OSHA concludes that a significant risk is presented by inorganic arsenic at the prior 500 $\mu g/m^3$ limit and that a lower exposure limit is needed. The Ninth Circuit has already agreed with this conclusion stating "it is undisputed that exposure to inorganic arsenic at the level of 500 $\mu g/m^3$ * * * poses a significant health risk . . . "(ASARCO et al. v. OSHA, supra, Memorandum, April 7, 1981, p. 3).

OSHA also concludes, based on the estimates from the risk assessments and the dose-response demonstrated in many of the epidemiology studies, that a 10 $\mu g/m^3$ exposure limit, the lowest level feasible, together with the industrial hygiene provisions in the arsenic standard are necessary and appropriate to significantly reduce the health risk. These requirements will very substantially reduce the risk, by approximately 98%, and will protect employees principally in the nonferrous metal smelting, automobile and arsenical chemical industries.

Finally OSHA concludes that the new inorganic arsenic standard setting exposures at 10 $\mu g/m^3$ does not reduce the risk of the exposure to inorganic arsenic below the level of significance. The level of risk from working a lifetime of exposure at 10 $\mu g/m^3$ is estimated at approximately 8 excess lung cancer deaths per 1000 employees. OSHA believes that this level of risk does not appear to be insignificant. It is below risk levels in high risk occupations but it is above risk levels in occupations with average levels of risk. The OSHA Act was enacted in order to reduce significant risk insofar as feasible. It should be noted that the Supreme Court stated as to a 1 in 1000 level of risk of fatality that "a reasonable person might well consider the risk significant and take appropriate steps to decrease or eliminate it" (*IUD.* v. *API*, 448 U.S. 655). OSHA believes the risk assessments and significant risk analysis support the retention of the 10 $\mu g/m^3$ level.

By achieving the 10 $\mu g/m^3$ limit, industry will have taken reasonable steps to protect their employees from the risks of arsenic. Substantial progress has already been made. Separate from this notice, and not part of this record, OSHA proposed to the affected smelter companies and the United Steel workers of America, which represents smelter workers, a cooperative assessment by technical experts representing the three sectors to evaluate control methodology to protect employees while maintaining the efficiency of the smelting industry. This suggestion was accepted by USWA, ASARCO, and Kennecott. Agreements carrrying out this proposal have been signed by OSHA, ASARCO and the United Steelworkers for 5 ASARCO facilities, and OSHA believes those parties have made exceptional progress in protecting exposed employees.

II. Background and General Considerations

A. Background

Based on legal considerations and Agency policy views applicable at the time, the 1978 inorganic arsenic standard did not include a quantitative risk assessment. OSHA pointed out that the results of quantitative risk assessments were somewhat speculative, that the methodology used bordered on the frontiers of scientific knowledge and that there was no adequate scientific basis to verify the mathematical estimates derived by risk assessments that would reflect a realistic expectation of the incidence of tumor induction (43 FR 19617).

Subsequent to the issuance of the inorganic arsenic standard, however, the Supreme Court ruled that the OSH Act requires that, prior to issuance of a new standard, a determination be made that a significant risk exists and that the new standard will significantly reduce or eliminate that risk. The court stated that "before he can promulgate any permanent health or safety standard, the Secretary is required to make a threshold finding that a place of employment is unsafe—in the sense that significant risks are present and can be eliminated or lessened by a change in practices" (488 U.S. 642). The Court also stated "that the Act does limit the Secretary's power to requiring the elimination of significant risks" (448 U.S. 644).

The Court indicated, however, that the significant risk determination is "not a mathematical straitjacket," and that "OSHA is not required to support its finding that a significant risk exists with anything approaching scientific certainty." The Court ruled that "a reviewing court [is] to give OSHA some leeway where its findings must be made on the frontiers of scientific knowledge [and that] * * * the Agency is free to use conservative assumptions in interpreting the data with respect to carcinogens, risking error on the side of over-protection rather than under-protection" (488 U.S. 655, 656). The Supreme Court thereby acknowledged that risk assessments, which may involve mathematical estimates with some inherent uncertainties, are nevertheless valid for demonstrating the existence of a significant risk.

This finding by the Court mitigates some of the previous concern that OSHA had expressed about quantitative risk assessments. Keeping in mind that the predictions of risk presented are estimates and not certain hard numbers, OSHA believes that the predictions derived from the risk analyses performed on arsenic are reasonable.

B. General Issues in Quantitative Risk Assessment

A quantitative risk assessment is an attempt to predict the degree of risk associated with a specific level of exposure. This is done either through direct observation or by extrapolation, a statistical technique used to estimate risk at levels outside the range of observed exposure levels.

In performing a quantitative risk assessment there are several important components which must be considered.

1. *A description of the hazard which poses the risk.* The principal hazard that the 10 $\mu g/m^3$ standard addresses is lung cancer. In the 1978 preamble to the final inorganic arsenic standard, OSHA made the determination that although there were other significant health hazards attributable to arsenic exposure, the evidence of respiratory cancer in humans was substantial and unequivocal. There is evidence that arsenic is associated with skin cancer and it is considered a systemic poison at levels substantially higher than 10 $\mu g/m^3$. However, the 10 $\mu g/m^3$ level will provide substantial protection against these other hazards. Because of the serious nature of lung cancer and substantial body of evidence associating arsenic with lung cancer, the quantitative risk assessments discussed below center on lung cancer mortality as the major response.

2. *A description of the potential exposure and worker scenarios.* Comparability in route and duration of exposure as well as carcinogenic response (e.g., same site of tumors) increases confidence in the prediction of risk from one observed population to another population. The use of epidemiological data obtained from one worker population to estimate the risk to another worker population, therefore, has the advantage that it eliminates the need to extrapolate from a more general or heterogeneous population. Furthermore, a greater degree of confidence can be placed in extrapolations from human studies than from results derived from laboratory animal studies.

There are many studies discussed in the 1978 document associating inorganic arsenic exposure with respiratory cancer. A number of these, though good studies, do not provide enough information on degree of exposure to be as useful in performing a quantitative risk assessment. There were three studies in which worker exposures have been documented well enough for quantitative risk assessment purposes. Two of these (Lee and Fraumeni 1969 and Pinto and Enterline 1975) formed the basis of the primary studies used in the three risk assessments presented by OSHA in the April 9, 1982 proposal.

The third, the study by Ott et al. has some data on exposure characterization, though the data are not considered as strong as that in Lee and Fraumeni and Pinto and Enterline. The Ott et al. data have been incorporated into several of the quantitative risk assessments.

Several other studies which have become available during the current rulemaking proceeding and which broaden the base for OSHA's current finding of significant risk are discussed in detail below. Each is assessed for its quality in the following areas which strongly influence the prediction of risk:

(i) Classification of workers' exposure;
(ii) Duration of exposure;
(iii) Concomitant exposures;
(iv) Response for a given exposure.

3. *A description of the dose-response relationship and a quantitative determination of risk.* Determining risk at the pre-1978 PEL of 500 $\mu g/m^3$ involves little estimation because the 500 $\mu g/m^3$ PEL falls within the range of the dose levels actually observed in the epidemiologic studies and no extrapolation of data was necessary. Predicting risk at the 1978 PEL of 10 $\mu g/m^3$ involves estimation at dose levels lower than those seen in the study populations, i.e., a low-dose extrapolation. For each dose group of workers associated with exposure to a certain amount of arsenic (dose), there is a measured risk of lung cancer (response). Generally, as exposures increase, the risk increases. In order to make the low-dose extrapolation, a mathematical relationship between dose and response is established using the experimental data; that is, a curve is "fit" to the data. This is done using statistical techniques involving plausible biological models for the general shape of the mathematical curve. In order to predict a response outside the experimental range, it is then assumed that this same mathematical relationship will hold in the range of doses that were not observed. By "reading off" the curve, one is able to estimate the risk at any dose level. Confidence in the risk estimates is increased if (1) the assumptions "reflect the expected experience of workers in a fashion that most people find reasonable," and (2) the "extrapolation is not required to extend far beyond the range of actual measurement." (Ex. 201–4, p. 2.)

The quantitative estimation of risk depends on the choice of the mathematical model (if one is used) and the biological assumptions which influence the model (such as threshold, promotion, etc.). Factors that impact on the choice of a model and the interpretations that can be placed on the estimates of risk will be discussed later in the document.

Last, considerations of the significance of risk must be made to comply with the mandate of the benzene decision.

4. *Terminology and Definitions.* There are several components which are common to most quantitative risk assessments: there will be a *dose*, a level of exposure which can be quantified for a specific period of time; a *measure of risk* or response, often expressed as excess risk and related to some reference population; and a *model*, the mathematical function used to describe the data.

The expressions of dose found in the quantitative risk assessments for inorganic arsenic encompass two dimensions: 1) intensity, which refers to actual level or degree of exposure which can be attributed to a specific group, and 2) duration, which refers to the length of time the subject is exposed. Intensity is commonly expressed as an "average" exposure or as a ceiling or peak exposure. Measures of cumulative dose include the dimension of duration, such as a *lifetime* dose, or a multiplication of intensity times the number of years exposed to compute a "total" dose ($\mu g/m^3$-years).

Risk statistics are presented in two basic formats. The first is the percentage of excess risk of respiratory cancer above the background level. For example, based on the Lee and Fraumeni data the OSHA estimated excess risk of 68% for workers exposed to 50 $\mu g/m^3$ of arsenic for a working lifetime means that those workers would have a 68% greater chance of dying of lung cancer than an equivalent group of workers not exposed to inorganic arsenic.

In the preamble to the final inorganic arsenic standard, the April 9, 1982 document, and many epidemiology studies, results are presented in the form of a standardized mortality ratio or SMR. The standardized mortality ratio is defined as the observed number of deaths divided by the expected number of deaths and is usually expressed as a percentage. In that system of notation, the normal death rate for a group from a specific cause is stated as 100 and a 68% increase above the normal rate would be indicated as an SMR of 168.

The excess risk of lung cancer from inorganic arsenic exposure is also presented as the number of lung cancer deaths per 1000 exposed workers over a lifetime. For example, a 68% excess risk of lung cancer death for workers, as mentioned above, would be 51 excess lung cancer deaths per 1000 exposed workers over those workers' lifetimes. This number represents the increased number of lung cancer deaths due to inorganic arsenic exposure above the normal level of deaths from lung cancer for each 1000 exposed employees.

The two non-threshold mathematical models for cancer initation which have been employed in the quantitative risk assessments presented are the linear model and the quadratic model. Both of the models have been selected for their biological plausibility in describing the processes of carcinogenesis.

The models predict that risk is proportional to dose (linear model) or the square of the dose (quadratic model) and assume that there will be a common biologic response to the insult over the entire range of doses. Predictions based on the linear model are also consistent with estimates which would result from the multistage model at low doses. The multistage model is based on the theory that several stages are required prior to cancer development, a theory which is also consistent with known biologic mechanisms (Ex. 201–6, 201–7).

A threshold model has been hypothesized by several of the participants in the hearings. A threshold model assumes that there exists some dose of arsenic below which a response (in this case, lung cancer) will not occur.

These factors are the important determinants of the degree of risk predicted from exposure to inorganic arsenic at the 500 $\mu g/m^3$ and 10 $\mu g/m^3$ levels and are discussed in detail in the following sections.

C. Miscellaneous Issues

Several participants suggested that OSHA had not followed its internal management procedures. Though not a matter subject to judicial review, OSHA has followed its internal management procedures which included some modifications for those substances like inorganic arsenic which were quite far along when the internal system was instituted.

Several participants submitted some esconomic feasibility data and argued

that OSHA must reopen the rulemaking on that issue. OSHA does not believe that its is required to do so. This rulemaking was directly pursuant to a Ninth Circuit order which ordered OSHA to consider the issues of degree and significance of risk and any changes to the standard resulting from the analysis, and to complete the consideration within a brief period of time. The Court has retained jurisdiction of the case and did not order OSHA to reopen any other issue. The April 9, 1982 Federal Register document gave notice of reopening the issues ordered reopened by the Court.

OSHA has held two full rounds of notice and comment rulemaking on feasibility issues, each of which included week long oral hearings. At least four major feasibility studies by Arthur Young & Co., Arthur D. Little, Inc., D.B. Associates and Industrial Health Engineering Associates were submitted as was an Inflationary Impact Statement and much other data. OSHA has fulfilled the notice, comments and hearing requirements of the OSH Act.

OSHA has briefly reviewed the feasibility data submitted, has stated it will consider it as a petition to amend the standard and will take appropriate actions based on the merits of the data and other agency priorities. However, the record is ample to support OSHA's decisions and such possible future actions should not be a basis for delaying any judicial review. OSHA is always considering the need to amend standards based on public suggestions, and that possibility, if a basis for not completing a review, would mean that there never would be finality of any agency action.

Several participants suggested technical changes to the monitoring and medical provisions of the standard including the elimination of sputum cytology. The Motor Vehicle Manufacturer's Association suggested a series of changes to the industrial hygiene provisions of the standard. Again, the Court did not order the agency to reopen the record on these issues and no notice was given on them. Some of these suggestions may be reasonable and OSHA will consider proposing technical amendments to the arsenic standard in the future to incorporate them. But they are not a basis for denying finality to a process which is fast approaching a decade in temporal extent.

III. Epidemiologic Studies

A. Introduction

OSHA based its final regulation for occupational exposure to inorganic arsenic primarily on epidemiologic studies indicating a high lung cancer risk among workers exposed to inorganic arsenic. OSHA concluded that inorganic arsenic is clearly a human carcinogen.

For the sake of brevity, the term arsenic will sometimes be used to refer to inorganic arsenic in this preamble. When OSHA intends to refer to organic arsenicals, it will always use the term "organic arsenic".

Studies of copper smelter workers cited by OSHA as evidence of excess cancer risk among workers exposed to inorganic arsenic were authored by Lee and Fraumeni (Ex. 5D), Pinto and Enterline (Ex. 29B and Ex. 111, Attachment 4), and Tukadome and Kuratsune (Ex. 191). In 1978, OSHA also cited the following studies of arsenical pesticide manufacturing workers as evidence for the carcinogenicity of inorganic arsenic: Ott, Holder, and Gordon (Ex. 1A, 3–1), Baetjer et al. (Ex. 1A–24), and Hill and Faning (Ex. 5B). Another group of workers observed to have an excess risk of cancer, as discussed in the preamble to the final regulation, was vineyard workers exposed to arsenic-contaminated wine and arsenical pesticides (Denk et al., Ex. 109C–87 and Roth, Ex. 65, 109C, No. 88).

As discussed in the preamble to the final regulation, the studies listed above were of high quality in terms of their scientific methodology. Therefore, the positive findings of these studies presented very strong evidence for the carcinogenicity of inorganic arsenic. Although these studies confirmed the strong association between arsenic and lung cancer risk, they were not all suitable for quantitative risk analysis.

In its pre-hearing submission to the latest proceeding, the Arsenic Panel of the Chemical Manufacturers Association (CMA) commented that OSHA had failed to demonstrate that inorganic arsenic was carcinogenic (Ex. 202–3). In addition to stating that laboratory animal studies had failed to confirm the carcinogenicity of arsenic, CMA contended that exposures to substances other than arsenic within the studied copper smelters and arsenical pesticide manufacturing facilities may have led to the observed excess of respiratory cancer risk.

In response to CMA's statements, OSHA wishes to reiterate its earlier conclusion that inorganic arsenic has been demonstrated to be carcinogenic to exposed workers. In addition to the studies available before 1977, the new or updated studies available since 1977 found a strong association between arsenic exposure and excess lung cancer risk. Also, subsequent to 1977, both the International Agency for Research on Cancer (Ex. 201–13, p. 114) and the World Health Organization-Arsenic Working Group (Ex. 252) have concluded that inorganic arsenic is a human carcinogen. The fact that this association has been demonstrated in different occupational settings strengthens the evidence for arsenic being a respiratory carcinogen.

At the informal public hearing in 1982, Dr. Lederer, on behalf of CMA, modified the CMA position. He stated that he did "not dispute that there is an association between arsenic exposure and respiratory cancer. Likewise, the evidence indicates that reducing arsenic exposure apparently reduces the carcinogenic risk. However, there may be factors other than arsenic involved, which must be considered" (Tr. 356).

As will be discussed in subsequent sections of this preamble, recent studies indicate that it is highly unlikely that smoking, sulfur dioxide, asbestos, and other exposures were primarily responsible for the excess risk observed in arsenic-exposed workers. Also, strong human evidence of carcinogenicity cannot be dismissed because of the absence of strong evidence of carcinogenicity in animal studies. OSHA's statutory mandate is to protect employees and evidence that reducing exposures to arsenic reduces human risk must weigh heavily in OSHA's decision to regulate.

Since the promulgation of the final regulation in 1978, follow-up studies have been performed on the original study cohorts of Lee and Fraumeni, Pinto and Enterline, and Baetjer and colleagues. In addition, new studies of arsenic-exposed workers have been conducted. The following sections analyze in depth the follow-up epidemiologic studies and the most important new epidemiologic studies.

B. Anaconda Copper Smelter

The preamble to the final arsenic regulation had a detailed analysis of the study by Lee and Fraumeni (Ex. 5D) and should be referred to for more extensive information. What follows is a summary of Lee and Fraumeni's findings.

Lee and Fraumeni studied the mortality of 8,047 white males who had been exposed to arsenic trioxide while working for the Anaconda copper smelter. Smelter workers were eligible for inclusion in the study cohort if they were employed for 12 or more months before December 31, 1956. The mortality experience of the study cohort was observed for the period 1938–1963. The comparison population was the white male population of the state of Montana. The expected numbers of deaths were

derived from the age, calendar period, and cause-specific mortality rates of white males in Montana during 1938–1963.

Standardized Mortality Ratios (SMR's), consisting of the observed number of deaths in the study cohort divided by the expected number of deaths times 100, were calculated for the overall cohort as well as for various groups of workers categorized by length of employment and intensity of exposure to inorganic arsenic.

Workers were classified as having received heavy, medium, or light exposure to arsenic based on industrial hygiene measurements of arsenic trioxide made in their particular work areas and on judgments of industrial hygiene experts. Jobs in the arsenic kitchen, Cottrell, and arsenic roaster areas were considered to involve heavy arsenic exposure. Areas assigned a classification of medium arsenic exposure were the acid plant, ore roaster, reverbatory furnace, casting, and converter. All other work areas were considered as having light arsenic exposures. Most workers had been exposed in several different areas and the authors classified workers based on their heaviest exposure. The authors believed that the relative exposure levels of the work areas classified as having heavy, medium, and light exposure probably did not vary substantially overtime. Workers were also classified as having received heavy, medium, or light exposure to sulfur dioxide. Silicon dioxide (silica), lead fumes, and ferromanganese exposures were also rated for individual workers.

For the overall cohort, statistically significant increases in mortality were observed for respiratory system cancer (SMR-329), tuberculosis, diseases of the heart, and cirrhosis of the liver. Lee and Fraumeni observed that lung cancer risk increased consistently with increasing length of employment, and increasing exposure. Lung cancer SMR's ranged from 214 for lightly exposed workers with less than 15 years of employment to 800 for heavily exposed workers with at least 15 years of employment prior to 1938. See 43 FR 19595 for a detailed table of Lee and Fraumeni's results indicating that risk increased with both increasing duration and degree of exposure to inorganic arsenic.

Lee and Fraumeni concluded that the observed excess in lung cancer mortality probably was not attributable to smoking and other confounding factors including country of birth, socio-economic status, availability of medical care, genetic suseptibility urbanization, and accuracy of death certificates. In their opinion, their findings were consistent with arsenic trioxide being an etiologic agent for the observed increase in cancer risk; however, the potential influence of sulfur dioxide or unknown agents could not be separated from the potential effect from arsenic exposure.

Lee and Fraumeni did not give quantitative estimates of arsenic exposure levels in their heavy, medium, and light categories. However, testimony was submitted to OSHA by H.F. Morris, Consulting Engineer for Anaconda on quantitative exposures (Ex. 28B). Based on air measurements and on experience at the smelter during the 1940's and 1950's, he estimated the mean arsenic measurements for the Lee and Fraumeni categories at the Anaconda smelter for 1943–1959 were as follows: heavy (11.27 mg/m^3), medium (0.58 mg/m^3), and light (0.29 mg/m^3).

Lubin, Pottern, Blot, Tokudome, Stone, and Fraumeni (Ex. 201–17) updated the original study by Lee and Fraumeni by following mortality experience during 1964–1977 for all 5,403 smelter workers alive as of December 31, 1963. Deaths occuring before 1964 were thus excluded from Lubin et al.'s analysis. Expected values for lung cancer mortality were derived from the age-specific, cause-specific, and calender period-specific mortality rates of U.S. white males. SMR's were calculated for the overall cohort and for groups of workers categorized by length of employment. Relative risks (RR's) were also calculated for groups of workers categorized by length of employment, intensity of exposure to arsenic and sulfur dioxide, and estimated cumulative doses of arsenic. Relative Risks are similar to SMR's but are calculated in a slightly different manner. Relative Risks in mortality studies consist of the observed mortality rate for a specific cause in a study group divided by the corresponding mortality rate in the comparison population, which in this study was U.S. white males. The authors calculated the RR's using multivariate models that included several variables related to arsenic exposure, sulfur dioxide exposure, and employment status as of 1964.

Based on the testimony submitted to OSHA on arsenic exposure levels in the Anaconda copper smelter (Ex. 28B), Lubin et al. assigned exposure levels of 11.3, 0.58, and 0.29 mg/m^3 in the heavy, medium, and light exposure categories respectively. Because respirators generally were worn in the heavy exposure areas, Lubin et al. reduced the assigned exposure level to 1.13 mg/m^3 in the heavy exposure category for some of their multivariate analyses. Cumulative arsenic exposure indices for individual workers were estimated by multiplying the number of years spent in each exposure category prior to 1964 by the assigned exposure level and summing over all the exposure categories. For the multivariate statistical analyses, the author combined workers in the heavy and medium categories because of the uncertainty of exposures and the small number of individuals in the heavy category.

In the overall cohort, significant increases were observed for mortality from lung cancer (SMR=166), circulatory diseases, non-malignant respiratory diseases, external causes, and ill-defined conditions and senility. Workers with 25 or more years of employment had the highest lung cancer SMR's. There was an increased risk of respiratory cancer associated with heavy/medium arsenic exposure. Workers who had never been exposed to heavy/medium work areas, some of whom may have had essentially nil exposure, did not have an increased risk of respiratory cancer mortality except for those with 25 or more years of employment. A significant linear trend was observed with respect to years worked at heavy/medium exposure and respiratory cancer.

When relative risks of the quintiles of cumulative arsenic exposure were compared, relative risks increased as cumulative exposure increased. Reducing the heavy exposure levels by 10-fold to reflect the use of respirators did not greatly alter the observed gradient in risk.

Lubin et al. concluded that their study cohort continued to have an excess risk of respiratory cancer during 1964–1977. Lee and Fraumeni observed a respiratory cancer SMR of 329 in their earlier study whereas Lubin et al. observed a respiratory cancer SMR of 165. Lubin et al. attributed the lower SMR in their study to several factors:

1. Respiratory cancer mortality rates have risen in the United States during 1964–1977 compared to 1938–1963;

2. U.S. respiratory cancer mortality rates are higher than those of the state of Montana;

3. Workers of unknown vital status were assumed to be alive as of the study cut-off date, which would tend to produce underestimates of risk;

4. Possibly the individuals most susceptible to lung cancer succumbed to it during the period before 1964.

Lubin et al. stated:

> As in the previous study, the excess deaths from respiratory cancer were linked to employment in areas of the plant where airborne arsenic levels were elevated. Indeed, excess risks were found among employees who had worked in areas with

heavy or medium arsenic exposure regardless of total length of employment at the smelter. Overall there was a strong gradient in risk associated with the index of cumulative arsenic exposure with individuals in the highest quintile of exposure having four times the risk of those in the lowest quintile (Ex. 201–17, p. 783).

Regarding smoking, Lubin et al. stated:

> Arguing against a major confounding role of smoking in this study is that no significant increases was observed for other smoking-related diseases (cancers of the mouth and throat, esophagus, and bladder, and heart disease) (Ex. 201–17, p. 784).

Lee-Feldstein (Ex. 201–16) conducted a follow-up study of the original occupational cohort of the study by Lee and Fraumeni (Note: Lee-Feldstein and Lee are the same author). This follow-up study observed mortality during 1938–1977, combining the follow-up periods of Lubin et al. (1964–1977) and Lee and Fraumeni (1938–1963). Furthermore, Lee-Feldstein's study included the exposure history for those smelter workers who were employed at Anaconda during 1964 to September 30, 1977, whereas Lubin et al. only used exposure data prior to 1964. Therefore, Lee-Feldstein's study reports the complete mortality and exposure experience during 1938–1977 of Anaconda copper smelter workers employed at least 12 months before December 31, 1956. Two females in the original study group of 8,047 workers were deleted, leaving a study cohort of 8,045 white males. The comparison population was composed of white males in the states of Idaho, Wyoming, and Montana, whose age, calendar period, and cause-specific mortality rates during 1938–1977 were the basis for generating expected numbers of deaths.

Lee-Feldstein used the same system for classifying workers into heavy, medium, and light exposure categories as Lee and Fraumeni, with exposure histories updated to reflect smelter employment after 1963. Standardized Mortality Ratios (SMR's) were calculated for the overall cohort as well as for the various exposure and length of employment categories.

Statistically significant increases in mortality in the overall cohort were observed for respiratory system cancer (SMR-285), digestive system cancer, diseases of the heart, emphysema, tuberculosis, vascular lesions of the central nervous system, and cirrhosis of the liver. SMR's for respiratory cancer ranged from 225 in the group with 1–4 years of employment to 408 in the group with 25 or more years of employment. In the light, medium and heavy exposure categories, the respiratory system cancer SMR's were 231, 446, and 512 respectively. In all three categories of exposure intensity and in all five length of emloyment categories, the observed excesses were statistically significant.

When the effect of intensity of exposure was examined within 3 length of employment categories (less than 15 years, 15-24 years, and 25 or more years), a consistent gradient of increasing risk with increasing intensity was observed except for the group with 25 or more years of employment (Table 5 of Lee-Feldstein's paper). In this group, the workers with medium exposure had the highest risk. Observed lung cancer deaths were in excess in all intensity-length of employment categories, including workers in the light exposure category with less than 15 years of employment.

Lee-Feldstein concluded that the findings of the follow-up study supported the hypothesis of Lee and Fraumeni that exposure to arsenic trioxide, possibly interacting with sulfur dioxide or other agents, was responsible for the increased respiratory cancer risk among smelter workers.

Higgins, Welch, Oh, and Burchfiel (Ex. 202–3B) also studied the mortality of workers at the Anaconda copper smelter. Rather than studying the entire cohort of 8047 employees exposed for at least 12 months before December 31, 1956, Higgins et al. studied a random sample of 20% of employees classified as having received medium and light exposures to arsenic. In addition, all employees classified as having been heavily exposed were included in the study cohort. This resulted in a total sampling of 22% of the Anaconda cohort.

> Note.—These exposure classifications of heavy and medium/light were listed on the computer tape sent by the National Cancer Institute (NCI) to Higgins and colleagues. Unlike Lee and Fraumeni's heavy exposure category, individuals assigned to the heavy category by the NCI received at least 24 months of exposure in their category of maximum exposure.

Altogether, the study cohort included 1800 men, 277 of whom were in the heavy exposure category. Follow-up was from 1938-1977.

The comparison population was Montana white males, although a few comparisons were made with U.S. white males. Expected numbers of deaths were derived from age, calendar period, and cause-specific mortality rates of Montana white males.

Higgins et al. also reviewed industrial hygiene data collected by staff of the Anaconda smelter and the state of Montana during 1943-1965 and calculated the average air concentrations of arsenic for 18 departments. For 17 departments with no available measurements, the air concentrations of arsenic were estimated. (Note: As used by Higgins et al., the terms "TWA", "Ceiling", and "peak" do not have the standard regulatory definitions used by OSHA.) Based on his duration of employment in each of the departments, each worker was assigned a *Time Weighted Average* (TWA) arsenic category and a *Ceiling* arsenic category. In addition, workers were categorized by Cumulative arsenic exposure (Ex. 203–5). The TWA consisted of the man's average daily dose rate, and the Ceiling was defined as the highest arsenic category in which a man had spent at least 30 days. *Cumulative* exposure incorporated both duration and intensity of exposure, and was calculated by multiplying the average arsenic concentration for each department during 1943–1965 by the years spent in that department and summing the individual's department exposures over his entire work history.

Cumulative exposure is an approximation of total dose received over a working lifetime. A man exposed 5 years to an average exposure of 100 $\mu g/m^3$ and an additional 2 years to an average exposure of 200 $\mu g/m^3$ would have an estimated *Cumulative* exposure of 900 $\mu g/m^3$-years. *TWA* exposure is an approximation of usual exposure levels, while *Ceiling* exposure refers to maximum exposure levels for 30 days or more. As explained earlier, all of these methods of classifying exposure are useful for exploring dose-response relationships for toxic substances.

The four categories of arsenic exposure for both the TWA and Ceiling classification systems were Low (less than 100 $\mu g/m^3$), Medium (100–499 $\mu g/m^3$), High (500–4999 $\mu g/m^3$), and Very High (greater than 4999 $\mu g/m^3$). For the Cumulative exposure classification system, designated categories were less than 500, 500–2000, 2000–12000, and greater than 12000 $\mu g/m^3$-years. No adjustments were made for respirator use because the authors considered respirator use to be inconsistent prior to 1964.

'Low' and 'Medium' categories of Higgins et al. generally corresponded to the 'Light' category of Lee-Feldstein. The 'High' category of Higgins et al. was generally similar to Lee-Feldstein's 'Medium' exposure category while the 'Very High' category of Higgins et al. corresponded to 'Heavy' in Lee-Feldstein's exposure scheme. To avoid confusion, these differences in nomenclature should be kept in mind when reading this preamble. Higgins et al. rated two areas (Acid Plant, Casting)

as having lower exposure levels and five areas (Maintenance, Surface, Shops, Unknown, Masons) as having higher exposure levels than those assigned by Lee and Fraumeni. Air concentration measurements of arsenic were not available for Maintenance, Surface, Shops, and Unknown departments.

Higgins et al. analyzed the mortality experience of the study cohort by using 5 different methods of defining exposure/follow-up periods. Method I featured complete separation of exposure and follow-up periods in the data analysis. Therefore, each man's exposure was counted only until the date he entered the study cohort. For workers employed at least 12 months prior to 1938, year of entry into the study cohort was 1938. Workers hired in 1938 or later were entered into the study cohort after they had been employed 12 months. Hence, Method I exposure analysis for a large portion of the study cohort was based on 12 months of exposure experience. For Method I, mortality was followed through 1977. Methods II and III included exposure experienced through 1963, and mortality was followed from 1938 through 1963 and 1977 respectively. Method IV included exposure experienced through 1963, and followed mortality from 1964 through 1977. Method V included the complete exposure experience and mortality experience of workers from 1938 through 1977. Because the major body of the report by Higgins et al. discussed Method I findings and because most risk analyses and pre-hearing and post-hearing submissions were based on Method I findings, the remainder of this discussion will focus on study findings of Method I. Data from the Method V analysis, separately submitted, was utilized in some cumulative dose analyses (Ex. 203–5).

Using the classification system of the National Cancer Institute computer tape (*Heavy* defined as at least 24 months in the arsenic kitchen, Cottrell, and arsenic roaster and *Other* defined as all other exposures), Standardized Mortality Ratios (SMRs) were calculated for both categories of exposure. Observed numbers of deaths were significantly elevated for the following causes of death in the Heavy category: respiratory system cancer (SMR=527), all cancers, respiratory diseases, diseases of the heart, and all other causes. In the Other category, the same causes of death were significantly elevated, including respiratory system cancer (SMR=257). In addition, workers in the other category had significant increases in mortality from digestive system cancer, vascular lesions of the central nervous system, and cirrhosis of the liver. For this comparison, Standardized Mortality Ratios (SMRs) were adjusted such that age differences between the 2 categories would not confound the observations (Table 16, Ex. 202–3B).

Using the TWA exposure classification system for arsenic, a gradient of response was apparent, with SMR's ranging from 138 in the Low category to 704 in the Very High category. The observed increases in respiratory cancer mortality were statistically significant except in the Low category (under 100 $\mu g/m^3$) (Table 16, Ex. 202–3B).

Using the *Ceiling* exposure classification system for arsenic, the observed increases in respiratory cancer mortality were statistically significant only in the High and Very High categories (Table 20, Ex. 202–3B). A dose-response gradient was observed. SMR's were 129 and 116 in the Low and Medium categories respectively.

When both *TWA* and *Ceiling* arsenic categories were examined simultaneously, the following respiratory system SMR's were calculated:

TABLE 1

	Ceiling							
	Low		Medium		High		Very high	
	Obs.[2]	SMR	Obs.	SMR	Obs.	SMR	Obs.	SMR
Low	7	115	1	113	3	310	0	
Medium	1	765	3	120	[1]18	398	0	
TWA:								
High					[1]20	318	[1]9	641
Very high							[1]18	704

[1] Statistically significant
[2] Obs = Observed number of lung cancer deaths.

As indicated in Table 1, observed respiratory cancer deaths were increased significantly for the Medium, High, and Very High TWA groups with a High or Very High Ceiling (Table 5, Ex. 203–5).

Using the *Cumulative* exposure classification system for arsenic, significantly increased respiratory cancer deaths were observed in the categories of 2000–12000 and 12000 or more $\mu g/m^3$-years. A non-significant respiratory cancer SMR of 157 was observed in the 500–2000 $\mu g/m^3$-years category. A dose-response gradient was apparent for this analysis.

Consultants in Epidemiology and Occupational Health (Ex. 219, Ex. 232–B) combined the *Cumulative* exposure data and *Ceiling* exposure data from the study of Higgins et al. and calculated the following SMR's for respiratory system cancer:

TABLE 2.—LIFETIME CEILING

	Low/medium		High		Very high	
	Obs.	SMR	Obs.	SMR	Obs.	SMR
CUM less than 500	3	67	1	77	0	
EXP 500–2000 ($\mu g/m^3$ 200.–12000 years)	1	79	8	160	0	
12000 or more	0		[1]22	394	[1]5	637
	1	940	[1]10	409	[1]29	616

[1] Statistically significant.

As indicated in Table 2, significant increases in respiratory cancer mortality were observed for the Cumulative exposure groups above 2000 $\mu g/m^3$-years with Lifetime Ceilings above 500 $\mu g/m^3$.

Higgins et al. also analyzed respiratory cancer mortality by years worked and Cumulative exposure (Ex. 244, Appendix A). Statistically signficant increases in respiratory cancer mortality were generally observed for workers employed for less than 10 years who had Cumulative exposures above 500 $\mu g/m^3$-years, as well as for workers employed for more than 10 years who had Cumulative exposures above 2000 $\mu g/m^3$-years.

Tables 47 and 49 of the report by Higgins et al. (Ex. 202–3B) compare the results obtained from using Methods I–V of exposure classification. For Method III, the results of the TWA analysis differed from Method I only in that the Low category no longer had an excess (non-significant) of respiratory cancer mortality. The results of the Ceiling analysis for Method III in the Low and Medium categories also did not exhibit the excesses (non-significant) of respiratory cancer observed for Method I.

Higgins et al. concluded, "Exposure to arsenic is strongly related to respiratory cancer mortality in this cohort of Smelter workers * * * There is a clear dose/response relationship, from no apparent increased risk among men exposed to low concentrations of arsenic to a roughly seven fold excess

risk in those exposed to the highest concentrations" (Ex. 202–3B, pp. 65). Discussing the nature of the dose-response relationship for arsenic, Higgins et al. suggested that "were men to have worked only in departments with average arsenic concentrations estimated to have been below 500 $\mu g/m^3$, there would have been little excess mortality due to respiratory cancer." They went on to state: "The estimates of arsenic exposure, however, are less precise than we would like." This conclusion regarding the dose-response relationship is based on their assessment that Ceiling had a stronger relationship to respiratory cancer mortality than did TWA. The primary evidence for such an assessment was Table 1, which exhibited signficant excesses only in those TWA groups with Ceiling exposures above 500 $\mu g/m^3$.

Higgins cited his findings with regard to Cumulative exposure as additional evidence for the hypothesis that respiratory cancer risk may be more dependent on *intensity* of exposure, including short-term peak exposures, than on *duration* of exposure or *average* exposure (Ex. 203–5, Ex. 244—Appendix A). Higgins stated that workers with short-term employment had higher respiratory cancer SMRs than workers accumulating the same exposure over a longer period of time. Table 6, which examined Cumulative exposure by Lifetime Ceiling, had statistically significant increases in respiratory cancer mortality only in workers whose Lifetime Ceiling exceeded 500 $\mu g/m^3$.

While Higgins et al. did not propose a mechanism to explain their observations on the effects of short-term peak exposures. Higgins stated: "It does seem, however, that repair and characteristics of deposition and clearance are all factors likely to be involved."

Noting that 12 lung cancer deaths had been observed compared to 9.6 expected in workers whose TWA and ceilings were below 500 $\mu g/m^3$ (see Table 4), Higgins suggested that there may have been perhaps 10 excess lung cancer deaths in this group within the entire Anaconda study cohort.

C. Analysis of Studies of Anaconda Copper Smelter

Regarding the exposure classification system used by Lee and Fraumeni, as well as by Lee Feldstein, Crump (Ex. 206, p. 6), Marsh (Ex. 203–5, p. 2), Enterline (Ex. 203–5, p. 3) and Radford (Ex. 207, p. 10) commented that Lee and Fraumeni's and Lee-Feldstein's approach tended toward overestimation of exposures. Overestimating exposures results in understating true cancer risk for a given level of exposure. This overestimation resulted from classifying workers in the category in which they received their highest exposure for 12 or more months, even though they may have worked in lower exposure areas for the balance of their employment. Workers who received less than 12 months of exposure in their category of maximum exposure were deleted from the comparative analysis of Heavy, Medium, and Light exposures. Therefore, Lee-Feldstein's and Lee and Fraumeni's classification system was similar but not identical to the Ceiling analysis of Higgins and colleagues, differing in the minimum length of exposure required for classification in a category and other features.

Crump (Ex. 206, p. 6), Marsh Ex. 203–5, p. 5), and Radford (Ex. 239, p. 3) noted the uncertainties from a cumulative or total dose viewpoint (i.e. classification by maximum rather than usual exposure or total exposure) of the method of exposure assessment used by Lee-Feldstein and Lee and Fraumeni, and suggested that a more detailed analysis of the exposure data would be helpful. Hence, they considered the exposure reevaluation conducted by Higgins and colleagues to be a worthwhile endeavor.

Radford made the following comments about the exposure classification system of Higgins and colleagues and their statistical analysis:

1. In order to assess the effect of changes in categorization from the Lee-Feldstein system, the numbers of workers in the various departments should have been specified, especially for those departments lacking air measurements which were assigned values of 559 $\mu g/m^3$. "For example, it would be interesting to know whether assignment of a value of, say, 400 $\mu g/m^3$ to these groups would have affected the subsequent results greatly, since now they would be below the 500 $\mu g/m^3$ ceiling. If so, then any conclusion that 500 $\mu g/m^3$ was a critical exposure level rests on a shaky foundation indeed." (Ex. 239, p. 6).

2. Analyzing risk by Ceiling exposure level in addition to TWA exposure level removed a large proportion of the workers from the Medium group and placed them in the High group lowering the statistical power to detect excess risk in the Low and Medium groups (Ex. 239, p. 7).

3. Analyses of the role of peak exposures also should have been performed for definitions of high short-term exposure other than the 30-day Ceiling (Ex. 239, p. 8).

4. "Because of the difference in sample size, the Lee-Feldstein results are much more robust statistically than those of Higgins et al. all other things being equal. Lee-Feldstein has analysed 3522 deaths from all causes and 302 deaths from respiratory cancer; the corresponding numbers in the Higgins study are 816 and 80. * * * It should be emphasized that 136 lung cancer cases were observed in this dose category (Light exposure—Lee-Feldstein), far more than all the lung cancers studied by Higgins et al." (Ex. 239, pp. 2 and 8).

5. There were some findings pointing toward a role for arsenic in the etiology of ischemic heart disease and respiratory diseases, especially for smokers. For non-smokers, the role of arsenic in these diseases could not be explored in the absence of smoking-specific mortality rates (Ex. 239, pp. 4–5).

6. For lung cancer, there was a consistent linear dose-response relationship with regard to cumulative exposure except in the lowest dose category (less than 500 $\mu g/m^3$-years). "But this finding of no excess at the lowest cumulative dose can be given no significance because of the error limits on many of the relative or absolute risks. It is regrettable that no error limits on any of the key derived quantities is provided in the Higgins reports, a major deficiency precisely when one is analyzing dose-response relationships." (Ex. 239, p. 9).

Crump commented as follows on the Higgins exposure classification system and statistical analysis:

1. The SMR's in the Low and Medium exposure categories of the Ceiling analysis were not remarkably different from the SMR's in the categories of the TWA analysis. For example, the 90% confidence interval for the statistically significant SMR of 303 in the Medium TWA category overlapped with the non-significant SMR in the Medium Ceiling category (Ex. 212, p. 4).

2. "More importantly, even if these observed decreases in SMR's are real, this is exactly what would be expected even if mortality does not depend at all upon ceiling exposures * * * because within a given TWA category persons with higher ceiling exposures are also expected to have higher TWA's * * * "(Ex. 212, p. 4).

Note.—Higgins et al. mentioned this phenomenon when discussing effects of sulfur dioxide exposures on carcinogenic risk. See section on *Effects of Other Exposures.*

3. The TWA-Ceiling analysis (See Table 1) did not adequately test the hypothesis of the over-riding importance of short-term peak exposures. Small sample sizes and the fact that persons with higher ceiling exposures also would be expected to have higher TWA

exposures limited the interpretation of the TWA-Ceiling analysis (Ex. 212, p. 4).

4. "I therefore consider the argument that risk depends primarily upon exposure level irrespective of duration to be highly speculative at this point. However, I would not rule out the possibility that measures of exposure other than cumulative exposure might correlate better with respiratory cancer risk. Further analyses of the data from both the Anaconda and Tacoma Smelters utilizing other measures of exposure could be helpful in this regard. Although I consider cumulative exposure to be a very reasonable measure, others are also reasonable. However, the way in which the data have been presented in the published reports has made it difficult to consider other approaches" (Ex. 212, p. 4).

Higgins' comments in both pre-hearing and post-hearing submissions to OSHA (Exhibits 244, Appendix A and 203–5) were mostly included in the section of this preamble summarizing his study results and conclusions. In response to the comments of Radford and Crump concerning his study, he made the following additional points:

1. Criticisms of Method I for defining exposure that were voiced by Crump (Ex. 212, p. 3) and Radford (Ex. 239, p. 7) were not valid because findings from Methods II–V of defining exposure did not differ substantially from findings of Method I. Also, because men could only move into higher Ceiling categories after being classified by Method I, Method I would tend toward overestimation of risk in lower Ceiling categories (Ex. 244, Appendix A, p. 2).

2. In contrast to Radford, Higgins considered dose-response relationships for respiratory diseases and ischemic heart disease to be inconsistent, unimpressive, and possibly due to the effect of other unmeasured factors. Smoking-specific mortality rates would have been desirable for smokers as well as non-smokers. In any case, the number of non-smokers was small such that it precluded meaningful analysis for these diseases (Ex. 244, Appendix A, pp. 7–8).

3. Regarding departments without air measurements that were assigned the mean value for the Low, Medium, and High arsenic categories, Higgins stated that "men in these departments likely worked for significant periods in various areas of the smelter, including those areas with High and Very High measured arsenic concentration." (Ex. 244, Appendix A, p. 9).

4. Contrary to the Lee-Feldstein definition of Light exposure, in which those in this category were reported to have had maximum exposure in the Light work areas, Higgins et al. did not find that these workers had always been exposed to less than 500 $\mu g/m^3$ (Ex. 244, Appendix A, p. 11).

The epidemiologic studies discussed in the preceding section were well-conducted and thorough analyses of the mortality experience of Anaconda Copper Smelter workers. Despite methodological differences, these studies were in substantial agreement in that the authors all concluded that their findings supported the hypothesis of arsenic being a respiratory carcinogen. Furthermore, all of these studies found a dose-response relationship in which increasing exposure to arsenic was correlated with increasing lung cancer risk.

The primary strength of the studies by Lee and Fraumeni and Lee-Feldstein was that the complete population at risk (workers with at least 12 months of employment before December 31, 1956) was included in their study cohorts. In addition, all surviving members of the study cohort would have been able to accumulate over 20 years of latency since first exposure by the end of 1977, which was Lee-Feldstein's study cut-off date.

The generalizability of the findings of the study by Lubin et al. is somewhat more limited by virtue of the fact that their study population was composed of persons alive in 1964, excluding persons who died from lung cancer and other causes prior to 1964. Hence, the mortality experience of the cohort of Lubin et al. was only a partial representation of the mortality of the overall cohort.

One strength of the study by Higgins et al. was their extensive survey of the exposure experience of the Anaconda cohort. This survey featured compilation of exposure data within departments, matching of the exposure data to occupational histories, and classification of individuals' exposures using different types of measures (i.e. TWA, Ceiling, Cumulative exposures). There are several potential problems with the exposure classification system developed by Higgins and colleagues:

1. Seventeen departments had no available measurements of arsenic air concentration. These departments were assigned exposures by analogy or by averaging exposures from departments rated, Low, Medium, and High. Clearly, these assigned exposure measurements may have considerable potential for error.

2. Most available measurements were made in those departments that industrial hygienists deemed to pose the greatest hazard (Ex. 202–3B). Hence, available air measurements may tend to represent higher exposure areas rather than representing overall exposure within the smelter. Also, departments with unknown concentrations may tend to have had the lowest exposure levels. Higgins and colleagues assigned several departments with unknown concentrations to the High exposure category.

3. Although arsenic air concentrations generally declined over the 20 year period for which measurements were available, Higgins and colleagues did not incorporate temporal trends in their exposure measures. For example, a worker exposed between 1955 and 1960 in a particular department would have the same exposure rating as a worker exposed between 1933 and 1938 in that department. Because Higgins and colleagues found that measurements frequently were made in order to test the efficacy of new industrial hygiene control measures, so that measurements would not necessarily reflect overall conditions in the smelter, they decided that temporal trends could not be accurately estimated.

Consultants in Epidemiology and Occupational Health (CEOH), representing CMA, stated that the exposure classification scheme of Higgins and colleagues was "probably a more direct and better estimate than that deriving from the Lee and Fraumeni classification" because it tied exposure estimates more directly to the work history of the individual worker.

Wright, representing the United Steelworkers of America (USW), commented that exposure of maintenance workers, masons, and miscellaneous crushing workers would vary widely from day to day depending on their job assignment (Ex. 231). He suggested that sampling for arsenic may not have taken place during job assignments for which little or no arsenic exposure would be expected. Wright also cited a measurement taken within the stack of the Cottrells as an example of a sample that may have been taken during a cleaning operation that would have been done no more than several times a year. In summary, he suggested that Higgins and colleagues may have overestimated average exposure for some job classifications.

One major shortcoming of the study by Higgins et al. is the incomplete study cohort. Higgins et al. studied only a 20% sample of the group receiving exposures other than Heavy. OSHA is particularly concerned about the incomplete information for the group receiving lower arsenic exposures. Higgins and colleagues acknowledged that the number of men in categories less than

5000 $\mu g/m^3$ was very small and that some of their conclusions were based on a small number of deaths (Ex. 202–3B, Ex. 244—Appendix A). Thus, they recommended that their analysis be applied to the entire Anaconda copper smelter cohort.

One consequence of studying only 20% of workers in categories other than Heavy was that the study by Higgins and colleagues had low statistical sensitivity for detection of an excess lung cancer risk among workers in these categories. As discussed during the public hearing (see Tr. 464), statistical power quantifies the ability of a study to detect an excess risk that truly exists and refers to the probability of not missing a true excess risk.

OSHA staff submissions (Ex. 221, Ex. 237–A, Ex. 237–B) calculated the statistical power of the study by Higgins et al. to detect a 1.5-fold increase in lung cancer risk among workers in Low and Medium exposure categories.

Note.—A 1.5-fold increase in risk refers to a 50% increase in risk, which is generally equivalent to an SMR or 150 or a relative risk of 1.5.

Because risk analyses predicted an approximately 1.5-fold increase in risk in workers exposed to about 150 $\mu g/m^3$ for 15 years, OSHA considered that quantifying the study's ability to detect a 1.5-fold increase in lung cancer risk would be appropriate. Also, a 1.5-fold increase in lung cancer risk would constitute a highly significant risk because lung cancer is a relatively common cause of death. Estimates of statistical power to detect a 1.5-fold lung cancer risk for Ceiling categories of less than 100 $\mu g/m^3$ and 100–500 $\mu g/m^3$ were 23% and 14% respectively (Method I analysis). Combining these 2 categories of exposure below 500 $\mu g/m^3$ yielded a power estimate of 37% (Method I analysis). Therefore, the Higgins et al. study had less than a 37% chance of detecting a true 50% excess risk. For the TWA category of less than 100 $\mu g/m^3$, statistical power was estimated to be 31% (Method I analysis).

For Methods III and V of analysis, the statistical power to detect an excess risk for ceiling exposures below 500 $\mu g/m^3$ was 28% and 25% respectively (Ex. 237 B). It should be noted that Methods III and V, which did not find excesses of respiratory cancer mortality below a ceiling of 500 $\mu g/m^3$, had lower statistical power than Method I, which did find excesses below a 500 $\mu g/m^3$ ceiling. Thus, decreased statistical power was associated with non-positive findings using Methods III and V of analysis.

Most epidemiologic investigators, when initiating a study, attempt to choose a study cohort of sufficient size to have at least 80% power to detect a true difference in the variable of interest. Therefore, the statistical power estimates for the study of Higgins et al., all of which are less than 40%, are much lower than desirable. The problem of low statistical power was worsened by the TWA-Ceiling and Cumulative exposure-Ceiling analyses (Tables 1 and 2) because the already small number of person-years were spread among more categories by these analyses.

Given the low statistical power of the study by Higgins and colleagues to detect increased respiratory cancer risk among workers in the Low and Medium exposure categories, and given the dose-response gradients observed in their study, it is appropriate to consider excesses of respiratory cancers in these categories as evidence of potential risk, even if such excesses are not statistically significant when considered individually. Hence, the respiratory cancer SMR's of 138, 129, and 116 in the Low TWA exposure category, Low Ceiling category, and Medium Ceiling category respectively should not be disregarded (Method I analysis).

Further evidence of the low statistical sensitivity of the study by Higgins et al. was their failure to observe significant excess mortality from digestive cancer and tuberculosis. The study by Lee-Feldstein, which included the mortality experience of the entire study cohort, did find significant increases for these causes of mortality. Radford (Ex. 239, p. 3) was not concerned about this discrepancy between the findings of Lee-Feldstein and Higgins; however, OSHA considers the discrepancy to be one indicator of potential problems with low statistical power in the study by Higgins et al.

Higgins cited Table 7 as evidence for his conclusion that duration of exposure had a relatively unimportant relationship to risk (Ex. 244, Appendix A, p. 3). Higgins is correct in stating that workers with less than 10 years of employment who received a particular Cumulative exposure had higher respiratory cancer SMR's than their counterparts who received the same exposure over a longer period of time. The differences in the magnitude of the SMR's, however, were not necessarily of biological or statistical significance. For example, respiratory cancer SMR's of 476 and 439 were calculated for the group of workers with less than 10 years and 30 or more years respectively. As mentioned earlier, another potential problem may be confounding effects from age in the comparison of SMR's.

Also, Brown and Chu (Ex. 241–B), in their multivariate analyses of factors contributing to lung cancer risk, observed duration of exposure to arsenic be the most important single etiologic factor. Brown and Chu studied 8014 of the 8045 Anaconda cohort members, increasing the statistical confidence which can be placed on their findings compared to those of Higgins et al.. See *Estimating Risks* section for a fuller discussion of Brown and Chu's study (Ex. 241–B).

OSHA considers it appropriate to examine the findings from all methods of exposure classification. First, clear dose-response gradients have been obtained for duration of exposure, cumulative exposure, average exposure, and maximum exposure classification systems. Second, there is no scientific consensus as to the exact mechanism of carcinogenesis. Another reason for examining the results of different exposure analyses is the low statistical power in the study by Higgins and colleagues for detection of a risk in Low and Medium exposure categories. Results from analyses by TWA exposure, Cumulative exposure, Ceiling exposure, and other methods of classifying exposures were all reviewed by OSHA in reaching a decision on significance of risk posed by inhaled arsenic.

A major consideration is that the studies of Lee and Fraumeni and Lee-Feldstein, that included the entire cohort, found a significantly increased respiratory cancer risk among workers categorized as having received Light exposures who had never been employed in Medium or Heavy exposure work areas. Lee and Fraumeni's and Lee-Feldstein's findings, which diverge from those of Higgins et al., may be due to differences in ascription of exposure for work departments or may be due to their studies' greater statistical power. With the exposure data available to OSHA, OSHA is not able to choose whether Lee-Feldstein or Higgins and colleagues developed the most appropriate exposure ascription scheme. Both exposure ascription systems had strengths and limitations, and both appear reasonable. However, because Higgins et al. studied only a limited sample of the cohort, resulting in low statistical power, OSHA places less weight on their findings for the Anaconda cohort than those of Lee-Feldstein and Lee and Fraumeni.

The hypothesis of Higgins and colleagues that respiratory cancer may be more a function of intensity of exposure than a function of duration of exposure of average exposure stemmed

from their analyses of risk by 30-day ceiling exposures. In effect, Higgins et al. and CEOH are proposing a threshold by suggesting that little risk would occur from arsenic exposures below 500 μg/m.³ This hypothesis would represent a mechanism of carcinogenesis different from that upon which standard dose extrapolation models for humans are based. OSHA is not aware of any studies that have definitively demonstrated the existence of a threshold for human carcinogens. Even if a threshold was clearly demonstrated in laboratory animals for a particular carcinogen, that carcinogen would not necessarily have a threshold for humans. This is because humans are exposed to carcinogens in ambient air, diet, cigarette smoke (either by direct inhalation or by sidestream smoke), alcohol and other sources at levels ranging from infinitesimal to considerable. Additional carcinogenic exposures in the workplace may have a synergistic or additive effect on cancer risk when combined with these background carcinogenic exposures.

Other biological evidence against thresholds for human carcinogens includes the self-replicating nature of cancer and the wide range of individual susceptibilities to carcinogens. Because of the possibility of synergism between workplace exposures and other carcinogenic exposures and because of biological evidence against there being a threshold for human carcinogens, evidence concerning the existence of a threshold would have to be considerable in order for the concept of a threshold for carcinogenesis to be generally accepted by the scientific community.

As discussed in this section, the limitations of the study by Higgins et al. preclude the study from providing strong evidence for the existence of a threshold. Nor do any of the studies of other arsenic-exposed populations demonstrate a threshold. In support of a threshold, Dr. Lamm of CEOH suggested that the human lung could clear the arsenic under ordinary circumstances of exposure through ciliary action, but be overwhelmed by high arsenic exposures such that the process of clearance through the bronchial mucus ladder would be inhibited and particles would be retained (Tr. 510–512). This suggested mechanism must be considered speculative. The limitations of the study by Higgins et al. and the biological data against thresholds for human carcinogens seriously weaken the findings of Higgins et al. concerning the effects of Ceiling exposures below 500 μg/m.³

Furthermore, as discussed earlier, OSHA considers that findings from all exposure classification systems should be incorporated into the agency's assessment of risk. While Higgins et al's findings with respect to Ceiling arsenic exposure suggest that cancer risk may be low below 500 μg/m³, their TWA analyses found that workers with average arsenic exposure between 100–499 μg/m³ had increased respiratory cancer risk. Furthermore, significantly increased respiratory cancer mortality was observed in workers with 500–2000 μg/m³-years of cumulative exposure. (The average of 500–2000 μg/m³-years is 1250 μg/m³-years. This total dose could be accumulated for 45 years of exposure to 28 μg/m³).

D. ASARCO Copper Smelter

A series of epidemiologic studies have been conducted of the ASARCO Copper Smelter in Tacoma, Washingon, (Ex. 3Z; Ex. 29 B; Ex. 111, Attachment 4; Ex. 133; Ex. 201–8; Ex. 201–9; Ex. 201–19; Ex. 205–2). The preamble to the final arsenic standard extensively analyzed the studies which were available to OSHA during rulemaking (Ex. 3Z; Ex. 29 B; Ex. 111, Attachment 4; Ex. 133) and should be referred to for more detailed information concerning these earlier studies. What follows is a short summary of the earlier studies and a more detailed summary of the subsequent studies.

Pinto and Enterline studied the mortality of 526 men who had retired from the ASARCO copper smelter and were receiving pensions (Ex. 298; Ex. 111, Attachment 4). To be eligible for the cohort, retirees had to be alive as of January 1, 1949 and had to have reached age 65 by December 31, 1960. The mortality experience was observed for the period 1949–1973. Expected numbers of deaths were generated from age-specific, calendar period-specific, and cause-specific mortality rates of white males in the state of Washington during 1949–1973. Based on urinary arsenic concentrations collected in 1973 from active employees, Pinto and Enterline estimated the total (cumulative) arsenic exposure (μg/As/1-years) and average arsenic exposure (μg/As/1) for their cohort of retirees. From employment records of the retirees, a cumulative arsenic exposure index was computed by multiplying average urinary values in 1973 for each department by the number of years during which the employee worked in that department and then summing values across all departments. The average arsenic exposure was calculated by dividing each man's total exposure by the total number of years worked at the smelter.

Standardized Mortality Ratios (SMRs) were calculated for the overall cohort as well as for groups of workers categorized by duration of employment, total exposure, and average exposure. For the overall cohort, respiratory system cancer mortality was significantly increased (SMR=300.3). Significantly increased respiratory cancer mortality was observed in all arsenic average exposure categories for workers with 25 years or more of employment, with SMRs increasing from 273.7 to 859.5 in the low to high category. A similar dose-response gradient was noted for men with less than 25 years of employment, although only one SMR was statistically significant. Workers with more than 25 years of employment consistently had higher SMRs than workers in the same average exposure category who were employed less than 25 years.

For both the total (cumulative) arsenic exposure index and the average arsenic exposure index, Enterline described their relationships to respiratory cancer as "linear" (Ex. 111, Attachment 4, p. 1). Pinto and Enterline stated, "In conclusion, results thus far indicate that there is a relationship between exposure to arsenic trioxide, or associated agents in the smelter atmosphere, and increased risk of respiratory cancer" (Ex. 29B, p. 7).

In published articles on the mortality of their cohort of retirees, Pinto et al. (Ex. 201; Ex. 203–2) suggested that a threshold of safety for arsenic trioxide may exist, based on their not having observed an increased risk of respiratory cancer among men with an average exposure below 200 μg/1 who had been employed less than 25 years. They did note the possibility that this group of men may not have been observed for an adequate length of time, but went on to state that the carcinogenic effects of arsenic had declined with increasing time since cessation of exposure. Commenting on the possibility of a threshold based on the Pinto-Enterline data, OSHA in the preamble to the final regulation noted the small number of workers in the exposure category at which no excess was observed.

Pinto et al. compared the measured urinary arsenic concentrations in 1973 with 800 urinary samples collected during 1948–1952 mostly from men in high exposure jobs (Ex. 29B; Ex. 205–2). The 1948–1952 urinary arsenic values were roughly twice as high as the 1973 values upon which their exposure analysis was based, although a few departments had higher values in 1973. In addition, Pinto et al. indicated that

"scattered" air measurements made on an irregular basis during that late 1930's and early 1940's exhibited airborne arsenic concentrations about 5 to 10 times as high as in 1973. Therefore, Pinto et al. recommended that their findings of elevated risk be interpreted as resulting from levels of airborne arsenic higher than the 1973 values.

Pinto et al. (Ex. 201–19; Ex. 203–5) stated that both duration of arsenic exposure and average arsenic exposure contributed to the excess of respiratory cancer among workers at ASARCO copper smelter, and that average exposure predicted lung cancer risk better than duration of exposure.

Subsequent to publication of studies on the mortality of ASARCO retirees, Enterline and Marsh expanded their study cohort to include all 2802 men employed one year or more during 1940–1964 (Ex. 201–8, Ex. 201–9). In addition, arsenic exposure indices were revised to better reflect historical arsenic exposures, involving linear extrapolation to 1948–1952 from 1973, 1974, and 1975 urinary arsenic values. Exposure levels during 1940–1948 were assumed to be the same as those measured during 1948–1952 (Ex. 201–9). Average urinary arsenic levels, Cumulative (total) arsenic levels, and Cumulative arsenic levels minus the 10 years of exposure preceding death or the study cut-off date were estimated for each worker. Subtracting 10 years of exposure was done on the theory that the exposure immediately preceding death from lung cancer probably would not have been responsible for the death because of the latency period between the onset of exposure and illness.

The period of observation of mortality was 1941–1976. Age-specific, cause-specific, and calendar period-specific mortality rates of white males in the state of Washington during 1950–1976 generated the expected numbers of deaths. Because background lung cancer mortality rates were lower during 1941–1949 than during subsequent years, the expected number of lung cancer deaths were overstated for the period 1941–1949, leading to underestimates of the excess risk. Enterline and Marsh also generated expected numbers of deaths from the specific age, cause, and calendar period mortality rates of U.S. white males during 1941–1976.

For the overall cohort, respiratory system cancer mortality was significantly increased. Compared to U.S. males and Washington males, the respiratory cancer SMRs for the study cohort were 198.1 and 189.4 respectively (Ex. 201–9, Table 6, p.8).

Cumulative exposure categories, expressed in micrograms or arsenic per liter of urine years (μg As/1-years), were less than 500, 500–1500, 500–3000, 3000–5000, and 7000 or more. Respiratory cancer SMRs ranged from 158.4 to 243.4 in these categories, with no clear trend of increasing SMRs with increasing dose. When the 10 years of exposure accrued before death or the study cut-off date were subtracted from the Cumulative exposure (hereafter referred to as the 10 Year Lag exposure), an inconsistent dose-response gradient emerged (Ex. 201–9, Table 8, p. 10).

For the 2 lowest Cumulative exposure categories (less than 500 and 500–1500), respiratory cancer SMRs of 202 and 158.4 respectively were observed, although these increases were not statistically significant. For the same categories of 10 Year Lag exposure, respiratory cancer SMRs of 155.4 and 176.6 respectively were observed, with the increase in the 500–1500 group attaining statistical significance. Hence, increased respiratory cancer risk was observed in relatively low dose categories (Ex. 201–9, table 8, p. 10). Using a urinary to air conversion factor of 0.3, 500 μg As/1-years is equivalent to 150 $\mu g/m^3$-years of airborne arsenic. Furthermore, the average exposure in the less than 500 μg As/1-years group was 302 μg As/1-years, which is roughly equivalent to 90 $\mu g/m^3$-years of arsenic. A dose 90 $\mu g/m^3$-years can be accumulated by one year of exposure to 90 $\mu g/m^3$ or by more years of exposure to lower levels (i.e. 45 years to 2 $\mu g/m^3$).

A somewhat clearer dose-response gradient was observed for 582 retired workers at ages 65 or over. Respiratory system cancer SMRs ranged from 136.8 to 393.2 (Ex. 201–9, Table 10, p. 11). When Enterline and Marsh analyzed respiratory cancer mortality by latency from initial exposure and duration of employment, they observed that respiratory cancer SMRs were significantly in excess during the first decade or two after cessation of exposure. For the second or third decades following cessation of exposure, the observed number of respiratory cancer deaths (SMR=137.9) no longer was significantly in excess.

When Enterline and Marsh examined respiratory cancer mortality by duration of employment and by average exposure, respiratory cancer SMRs increased both with increasing duration and increasing average exposure. This particular analysis was confined to workers who had either left the active smelter work force or retired by December 31, 1976. Enterline and Marsh stated that this analysis showed "that both duration of exposure and intensity of exposure contribute to respiratory cancer mortality" (Ex. 201–9, p. 14). Respiratory cancer SMRs in the "low" average exposure group (defined as having an average less than 290 μg As/1, with a group mean of 163 μg As/1) ranged from 169.9 to 302.0. The respiratory cancer excesses observed in the low average exposure group were statistically significant, except for workers with less than 10 years of exposure. Using a urinary to air conversion factor of 0.3, 163 μg As/1 is equivalent to 49 $\mu g/m^3$.

Enterline and Marsh reached the following conclusions:

(1) Concerning the relationship between arsenic and cancer, "the carcinogenic response apparently can occur rather quickly—in this study apparently in about 10 years" (Ex. 201–9, p. 16).

(2) The carcinogenic effects of arsenic appeared to decline with time following the cessation of exposure.

(3) Arsenic appears to act as a cancer promoter rather than an initiator, based on evidence of lack of an effect of latency and based on the apparent decline in risk after cessation of exposure.

E. Analysis of Studies of ASARCO Copper Smelter

For purposes of risk analysis, the most recent epidemiologic study by Enterline and Marsh of ASARCO copper smelter (Ex. 201–9) has an advantage compared to the earlier studies available to OSHA because it included the entire cohort at risk from a year or more of exposure (2802 men) rather than only the pensioned retirees (527), who might have been unrepresentative of the overall employee population of the smelter. Including the entire cohort at risk yield 104 respiratory cancer deaths with which to analyze dose-response relationships, whereas the earlier studies observed only 32 respiratory cancer deaths. Another advantage of the most recent study by Enterline and Marsh was their reconstruction of the individual worker's probable exposure based not only on 1973 urinary arsenic levels but on 1948–1952 urinary arsenic levels. A urinary arsenic level is a biological indicator of arsenic exposure that would reflect protection provided by respirator use.

Much of these studies' analyses entailed comparison of SMR's and relative risks among different exposure groups. This is a common analytical procedure of epidemiologic studies. As noted in the staff submission on SMR's (Exhibits 241–A, 237–N, 237–PP), the SMR is a risk measure that is dependent on the age structure of the study population. Cancer incidence, including

lung cancer incidence, rises with age. Hence, an older study cohort will be expected to have a greater number of deaths from cancer compared to a younger study cohort. Sometimes, comparison of SMR's among different study populations may be confounded by age if their underlying age distributions are different, which may in turn obscure the true nature of the excess risks. A hypothetical example given in the staff submission (Ex. 241–A) shows the rate of excess deaths attributable to an unspecified agent doubling for each successive 10-year age group while SMR's remain constant across the age groups.

Groups of workers in different exposure categories may have different age distributions, thereby causing age to confound the comparison of SMR's among exposure categories. Absolute risk analysis is one method of addressing age confounding in SMR comparison. Crump performed an absolute risk analysis of the Enterline and Marsh study, the results of which will be discussed extensively in the *Estimating Risks* section. Absolute risk will also be explained in that section.

Crump commented on Enterline and Marsh's observation of declining respiratory cancer risk following cessation of exposure:

> The concept of absolute risk may also help to explain certain other features of the Enterline and Marsh analyses. When they considered (their Table 11) SMR's by duration of exposure and by latency (time since first exposure) they detected a drop-off in SMR's past about 10 years after the termination of exposure * * *
>
> The effects in their Table 11 that partially evoked these interpretations are based upon small numbers of cancers and it appears to me that they may simply be an artifact. However, assuming that the observed drop-off in SMR's is real, it could be that absolute risk is holding steady or even increasing. The evidence provided by Enterline and Marsh's Table 11 for designating arsenic as a promoter seems tenuous at best (Ex. 206, pp. 18–19).

Radford also noted the problem of small numbers of deaths as an impediment to determining whether arsenic-induced cancer risk declined after cessation of exposure in the study by Enterline and Marsh (Ex. 207, p. 8). Radford also stated that the continuing respiratory cancer excess in retired workers contradicted evidence of a decreased risk after cessation of exposure, and thus constituted evidence against arsenic acting as a promoter.

Enterline, in a pre-hearing submission to OSHA (Ex. 203–5), pointed out that revising his exposure estimates for the ASARCO workers to include historical exposures lowered the observed regression coefficients (approximations of carcinogenic potency) in the various exposure categories. Enterline suggested that even his current regression coefficients were overstated by a factor of 2 because of the lack of historical exposure data for years preceding 1948.

For reasons explained below, OSHA concludes that cumulative exposure is one of several appropriate methods of analyzing the dose-response of workers in the ASARCO copper smelter. The use of cumulative dose is supported by the good dose-response observed in Table 10 of Enterline and Marsh's paper, which examines SMRs by cumulative dose in retirees age 65 and over (Ex. 201–9, p. 11). In addition, Table 12 of the paper exhibits a risk gradient with increasing duration of exposure for both "low" and "high" intensity exposure categories (Ex. 201–9, p. 14). Enterline and Marsh interpreted Table 12 as demonstrating that both duration and intensity of exposure contributed to excess respiratory cancer risk. In addition, Crump's absolute risk analysis for Cumulative exposure data and 10 Year Lag data found a strong linear trend of increasing risk with increasing cumulative dose.

OSHA judges that Enterline and Marsh's observations of declining respiratory cancer risk after cessation of exposure are inconclusive for the following reasons. Age may confound the comparisons of SMRs of cohorts' successive decades following cessation of exposure. Interpretation of finding is further hampered by low power to detect a statistically significant risk in some of the categories analyzed. In addition, the decreased SMRs two to three decades following cessation of exposure were not markedly different from the statistically significant SMRs of the preceding decades.

With regard to low dose risk, OSHA considers the respiratory cancer SMRs in low dose categories, which indicate excess risk, in Table 8 and 10 to constitute some additional evidence of a potential risk from low levels of arsenic exposure. Some of these SMRs were not statistically significant; however, these exposure categories had low statistical power to detect a 1.5-fold lung cancer risk. Although an isolated statistically non-significant excess risk would have relatively little meaning, statistically non-significant excess risks in some circumstances can be meaningful when they fit reasonably closely curves derived from statistically significant excess risks or are consistent with observed trends. At the relatively low predicted excess risks for low level exposures, there would have to be large numbers of workers before statistical significance is obtained.

F. Urine-Air Correlation

A published article by Pinto et al. (Ex. 210) reported the results of a study of the relationship between airborne arsenic trioxide and urinary arsenic. A total of 24 workers participated in this study, for which they wore personal air samplers and did not wear respirators for 5 successive days. Also, workers were asked to not eat fish for 2 days preceding and during the study period. Pinto et al. stated, "A fairly good correlation was found between airborne arsenic concentrations and urinary arsenic levels over the range studied" (Ex. 201–19, p. 128). The conversion factor was 0.304 so that a urinary level of 100 $\mu g/l$ of arsenic was roughly equivalent to 30.4 $\mu g/m^3$ of arsenic in air.

Note— Some authors rounded off 0.304 to either 0.3 or 0.31.)

Consultants in Epidemiology and Occupational Health (CEOH) (Ex. 202–3D, p. 28) refit the regression line of Pinto et al. so that it did not pass through zero and obtained a steeper slope indicating higher air levels per unit of urinary arsenic. They estimated the slope as approximately twice as high as Pinto et al.'s slope.

ASARCO presented Pinto et al.'s study on the relationship of urinary arsenic concentration to airborne arsenic during earlier proceedings as the best available data on this subject. In the most recent proceedings, ASARCO characterized OSHA's use of Pinto et al.'s conversion factor as "extremely questionable", due to limitations of Pinto et al.'s data base (Ex. 202–7, p. 22). ASARCO criticized the small number of workers in Pinto et al.'s study, the short study period, the lack of data on the urine-air relationship at high arsenic air concentrations, and the lack of adjustment for background urinary arsenic concentrations. ASARCO suggested that:

> OSHA should have conducted risk assessment based on the Tacoma studies in terms of urinary concentrations. The attempt to convert from urine to air concentrations should have been the last step in the assessment rather than one of the first, and the uncertainties on any such conversion should have been noted (Ex. 202–7, p. 22).

The study of Pinto et al. had some limitations. Because the men studied by Pinto et al. were asked to not eat seafood, which would be the major source of urinary arsenic in the absence of air exposure, Pinto et al.'s assumption of zero urinary arsenic from zero air

arsenic exposure appears reasonable. Therefore, OSHA considers Pinto et al.'s correlation coefficient to be the best available measure of the relationship between urinary arsenic and airborne arsenic and it has been used by a number of scientists. The steeper slope suggested by CEOH would result in approximately halving the estimates of risk based on the data of Pinto and Enterline and Enterline and Marsh. These lower estimates would still result in significant risk.

G. Additional Studies

Mabuchi, Lilienfeld, and Snell studied the mortality of 1393 persons employed at an inorganic arsenical pesticide manufacturing plant between 1946 and 1974 (Ex. 237 BB; Ex. 237 CC). Included in the study cohort were 1050 males and 343 females. Baetjer et al. (Ex. 1A–24) had performed a preliminary study of the retirees of this plant, the results of which were extensively discussed in the preamble to the final arsenic regulation in 1978.

The study cohort of Mabuchi and colleagues was composed of all 952 workers employed 4 months or longer and a 20% sample (441) of the 2189 workers employed for less than 4 months. The comparison population was Baltimore City whites, whose sex, age, calendar period, and cause-specific mortality rates generated the expected numbers of deaths. Vital status as of August 1977 was ascertained for 87% of males and 67% of females. The period of observation was 1946–1977.

Workers were exposed to both inorganic arsenicals and non-arsenical compounds, including DDT and other chlorinated hydrocarbons. In 1972, the arsenic concentration in the insecticide building was estimated as 0.5 mg/m^3 as a time-weighted average. Exposures in the 1940's and 1950's were reported to be higher.

No statistically significant increases in mortality were observed for females. For males, a statistically significant lung cancer SMR of 168 was observed. When U.S. white males instead of Baltimore City white males generated the expected values, a lung cancer SMR of 265 was observed. When workers employed less than a year were excluded from the analysis, the overall male cohort had a lung cancer SMR of 271 (Baltimore City comparison). Unlike the previous study by Baetjer et al., lymphatic cancer mortality was not significantly in excess.

A strong gradient of lung cancer risk with increasing duration of exposure was observed, with SMRs renging from 94 in workers with 4 to 11 months of high exposure to arsenicals to 2750 in workers with 25 or more years of high exposure to arsenicals. Mabuchi et al. stated: "A dose-response relationship was demonstrated from an SMR increasing with length of high exposure to arsenicals" (Ex. 237 BB, p. 318).

Consultants in Epidemiology and Occupational Health (CEOH) interpreted Mabuchi et al.'s findings as demonstrating that "the risk of lung cancer does not increase with duration of exposure for a given exposure category" (Ex. 202–3D, p. 35). CEOH's statement is not supported by the observed gradient of response with increasing length of employment, as remarked upon by Mabuchi and colleagues.

Production workers were categorized as having had high exposures; maintenance/shipping workers were categorized in the medium exposure group; and office workers were categorized in the low exposure group. Lung cancer SMRs were 156 and 0 for the medium and low exposure groups respectively. Low statistical power may have been responsible for the lack of statistically significant increases in risk in the medium and low categories. Also, office workers may have had essentially nil arsenic exposure.

Mabuchi et al. did not have smoking histories for the cohort members. They thought it unlikely that smoking could explain the cohort's excess of lung cancer because other smoking-related diseases were not in excess and because of the dose-response observed for arsenic exposure.

Mabuchi and colleagues concluded that their "findings provide strong evidence for a causal relationship between occupational exposure to inorganic arsenicals and lung cancer" (Ex. 237 CC, p. 51).

Axelson, Dahlgren, Jansson, and Rehnlund performed a case-control study in Sweden to determine whether copper smelter employment was associated with increased mortality (Ex. 237D). Cases were selected from a registry of deaths occurring during 1960–1976 within a parish in Sweden and had to have died from lung cancer, cardiovascular disease, other cancers, cerebrovascular disease, and cirrhosis of the liver. Controls were selected from the same registry of deaths and died from causes other than those listed above. Industrial hygiene data were available such that the degree of past arsenic exposure could be assigned to each case and control. A 5-fold increase in lung cancer risk was observed among arsenic-exposed workers. In addition, a 2-fold increase in cardiovascular disease risk was observed among arsenic-exposed workers. A dose-response for lung cancer risk and arsenic exposure was apparent, although not statistically significant.

Axelson et al. considered that their data were insufficient to permit conclusions about the relationship of lung cancer to arsenic exposures below 500 $\mu g/m^3$. Axelson et al. stated: "exposure to arsenic is likely to be the major cause of the increased mortality, but other factors, particularly agents associated with arsenic, may also play a part" (Ex. 237 D, p. 14).

A cohort mortality study of another Swedish copper smelter was conducted by Wall (Ex. 237 MM). A total of 3919 male workers first employed at least 3 months during 1928–1966 at the smelter were included in the study. Mortality was observed during 1960–1977. Compared to the expected values derived from age and calendar year-specific mortality rates of Swedish males, the observed lung cancer SMR was 288. Compared to the expected values derived from the mortality rates of the county in which the plant was located, the lung cancer SMR was about 500. Wall concluded: "A dose-response analysis clearly indicates that the roasters and arsenic departments are risk places for the development of cancer, especially lung cancer" (Ex. 237 MM, p. 73).

ASARCO submitted an epidemiologic study by Cooper of employees of a lead smelter located in East Helena, Montana (Ex. 202–7A). A study of lead refinery workers in Omaha, Nebraska, where exposures to arsenic were reported as being extremely low, was also submitted (Ex. 214). OSHA believes that the Omaha study is not relevant because of the low levels of arsenic exposure and it will not be discussed further in this preamble.

At the lead smelter in East Helena, Montana, Cooper studied all 437 males employed for at least one year during 1946–1970 (Ex. 202–7A). Expected numbers of deaths were generated from the calendar period and age-specific mortality rates of U.S. white males. Some employees at East Helena were exposed to arsenjc; however, the number of employees exposed to arsenic was not specified. Also, mortality experience was not analyzed for the specific group of arsenic-exposed workers. Two lung cancer deaths were observed compared to 3.4 deaths expected. Although Cooper recognized the low statistical power of his study to detect an excess risk of respiratory cancer, he stated that the lack of trends with regard to latency and duration of exposure indicated little excess cancer risk at the plant.

Landrigan of NIOSH calculated that Cooper's East Helena study had 21% statistical power to detect a 1.5-fold relative risk for lung cancer mortality (Ex. 215). Because of the small number of employees in the East Helena cohort, resulting in low statistical power, and lack of analysis of the mortality of employees known to be exposed to arsenic, no conclusions can be drawn about the relationship between arsenic exposure and lung cancer risk from this study.

Koppers Company submitted studies performed by Tabershaw Occupational Medicine Associates of workers at two wood preserving plants using chromated copper arsenate (Ex. 202–6B). Both studies were cross-sectional health and industrial hygiene surveys of the active work force. At the first plant, exposures to pentavalent arsenic averaged 2.1 $\mu g/m^3$, with a peak exposure of 5.2 $\mu g/m^3$. Sixty-three employees were included in the health survey. Urinary arsenic levels were below the limits detectable by laboratory assay.

At the second plant, exposures to pentavalent arsenic averaged 0.7 $\mu g/m^3$, with a peak exposure of 3 $\mu g/m^3$. Forty-six employees participated in the health survey. Specific urinary arsenic levels were not reported, but were described as showing no excess arsenic.

Neither of the two surveys detected any cases of lung cancer. While cross-sectional health surveys are useful for purposes of medical surveillance and studying some occupational diseases, such studies usually have limitations that restrict their usefulness for epidemiologic analysis of cancer risk. These two studies were confined to the active work force, who may not have been representative of the total population at risk, and surveyed a small number of employees, resulting in near zero statistical power to detect excess cancer risk. In addition persons who had lung cancer and already died or who left or retired and then developed lung cancer would not be covered. The study would have only detected persons who just developed lung cancer and had not yet quit or died. In addition, these two studies did not follow employees over a sufficient period of time to allow for the long latency period of lung cancer. For these reasons, no conclusions can be drawn from these studies concerning excess cancer risk and exposure to the chromated copper arsenate wood preserving process. It should also be noted that the reported levels of exposure to arsenic were very low, well under the 10 $\mu g/m^3$ level.

A number of epidemiologic studies have been submitted to the record which attempt to analyze the relation of arsenic ingestion from the public water supply to cancer risk. Also, studies of cancer risk among members of the general population exposed to air levels of arsenic well below 10 $\mu g/m^3$ have been submitted to the record. Although in some circumstances environmental studies may be relevant to assessing occupational risks, in the case of arsenic OSHA believes there is no need to discuss these studies because their ability to define exposure and consider other variables, such as latency, related to excess cancer risk was lower compared to other studies discussed by OSHA in the final regulation and in this preamble and because in the case of arsenic OSHA has available high quality occupational studies.

In some of the environmental studies, the authors concluded that results were negative and in some the authors concluded that the results were positive. OSHA has reached no conclusions concerning the results of these studies and has no authority to regulate either the public water supply or the general environment.

Several commenters have stated, incorrectly, that environmental (ambient air) levels of arsenic might be as high as 40 to 70 $\mu g/m^3$. In one case, this mistake was probably the result of a typographical error in the study by Ott et al. (Ex. 1A, 3–1). Data of the U.S. Public Health Service (Ex. 1A–23) and the World Health Organization (Ex. 252) indicate that maximum environmental exposures are substantially lower than 2 $\mu g/m^3$. Another consideration is that much of the arsenic that is ingested in drinking water or seafood is organic arsenic, which OSHA does not regulate as carcinogenic.

OSHA concludes that the epidemiologic studies of Mabuchi et al., Axelson et al., and Wall provide additional evidence in support of the strong causal association between inorganic arsenic exposure and excess lung cancer risk (Ex. 237 BB; Ex. 237 CC; Ex. 237 D; Ex. 237 MM). OSHA considers the study results of Cooper and Tabershaw Occupational Medicine Associates to be inconclusive because of the nature of their study design and analysis.

H. Effects of Smoking

Smoking is a major cause of respiratory cancer mortality in the United States. Therefore, smoking is a potential confounding factor for any epidemiologic study of humans exposed to a respiratory carcinogen. The preamble to the final arsenic regulation (43 FR 19584) discussed the potential role of smoking in the elevated respiratory cancer risk of arsenic-exposed workers. Based on testimony by Weir (Ex. 29N) and the study of Enterline (Ex. 111, Attachment 4), OSHA stated that it was "unwilling to assume that smoking alone accounted for more than a 17 percent excess in lung cancer mortality" among arsenic-exposed workers (43 FR 19590).

The **Federal Register** notice of April 9, 1982 announcing the limited reopening of the inorganic arsenic rulemaking record (47 FR 15358) also discussed the effects of smoking on arsenic-induced respiratory cancer. The aforementioned study by Enterline was included in the discussion. Enterline found a 2.6-fold increase in respiratory cancer risk among smoking copper smelter workers compared to smokers in the general population. Enterline also observed a 4.6-fold increase in respiratory cancer risk among non-smoking copper smelter workers compared to non-smokers in the general population (Ex. 111, Attachment 4). Based on this analysis Enterline stated that the observed excess in SMRs for respiratory cancer did not appear to be due to smoking. A subsequent publication by Pinto et al. (Ex. 205–2) observed substantially similar increases in risk among smoking and non-smoking copper smelter workers and reached the same conclusion as the original analysis of smoking by Enterline (Ex. 111, Attachment 4).

The **Federal Register** notice of April 9, 1982 also discussed data from studies by Ott et al. (Ex. 1A 3–1) and Lee and Fraumeni (Ex. 5D). It presented a hypothetical example of the effect of higher smoking prevalence in a cohort of arsenic workers to demonstrate the minimal potential confounding effects of smoking. The hypothetical study cohort of arsenic workers had a 60% prevalence of smoking while a comparison population had a 40% prevalence of smoking.

Note.—This large a difference in smoking habits seems very unlikely.

Such a 20% difference in the proportion of smokers between the study and comparison populations would contribute only about a 40% increase in lung cancer risk in the study cohort over the risk of the comparison population. This estimate was calculated by assuming a 10-fold excess of lung cancer among smokers as compared to non-smokers. Compared to non-smokers, a population consisting of 60% smokers would have about a 6.4-fold lung cancer excess and a population consisting of 40% smokers would have a 4.6-fold lung cancer

excess. Therefore, the relative risk of a 60% smoker population compared to a 40% smoker population is 1.4 (6.4/4.6) or 40% increased risk attributable to the smoking differential. Much larger increased risks than 40% were observed in arsenic-exposed workers, including 7-fold increases in respiratory cancer risk. Hence, the likelihood of a difference in smoking prevalence between exposed and comparison populations accounting for these large increases in risk is extremely low.

Ott et al. collected smoking histories from active employees exposed to arsenic (not study cohort members) and did not observe differences in smoking prevalence compared to the population at the location or differences in smoking prevalence by exposure category. Assuming that this survey reflected the smoking experience of the study cohort, smoking could not account for the observed excess of respiratory cancer deaths.

While Lee and Fraumeni did not have smoking histories for workers in the Anaconda smelter, they suggested that the dose-response observed among workers in heavy, medium, and light categories made it unlikely that smoking alone could explain the increased lung cancer risk.

Since publication of the April 9, 1982 Federal Register notice, additional data on the effects of smoking have been submitted to the OSHA record on inorganic arsenic. A discussion of the additional data follows.

Higgins and colleagues conducted an interview survey in addition to the mortality study in order to collect information on smoking habits of the study cohort. Live cohort members were interviewed by telephone or received mail questionnaires. Proxy respondents furnished smoking data for dead cohort members. About 83% of the total cohort of 1800 men participated in the interview surveys.

Using proxy respondents to furnish smoking histories for deceased cohort members created several potential problems. One problem is the possibility of Berksonian bias: proxy respondents may know the relationship between smoking and lung cancer and may be more likely to report smoking when the cohort member died from lung cancer. Higgins et al. compared respondent and proxy smoking histories for 83 men and found 88% agreement (Ex. 205–1). These proxy histories were obtained one year after the respondent was questioned; perhaps poorer agreement would have been obtained if more time had elapsed since questioning of the respondent. Also, 30% of the non-smokers in the sample of 83 men were classified by proxies as smokers compared to about 5% of smokers who were classified by proxies as non-smokers. Therefore, one cannot assume that there is an equal amount of over-reporting and under-reporting across all smoking status categories.

For their analysis of the mortality of smokers and non-smokers, Higgins et al. derived expected values from the specific age, race, and calendar year mortality rates of the state of Montana. This created another problem for the analysis, as noted by Higgins and colleagues. Presumably, Montana males resemble U.S. males and thus have roughly a 50% prevalence of smoking. Thus, Higgins et al. compared non-smoking workers to a standard population with 50% smokers. This caused the non-smoking workers' expected values for lung cancer to be too high, consequently underestimating the excess risk for non-smoking arsenic workers, and the smoking workers' expected values for lung cancer to be too low, consequently overestimating the excess risk for smoking arsenic workers.

Respiratory cancer SMRs for cigarette smokers and non-smokers were 327 and 205 respectively. When divided by exposure category, workers in the Heavy category had higher SMRs regardless of their smoking status.

Regarding their study results, Higgins and colleagues stated:

> This analysis showed that arsenic exposure was more important than smoking in relation to mortality from all causes, respiratory cancer, and ischemic heart disease. Smoking appeared to be the more important factor for all respiratory diseases. Taken as a whole, there was no evidence to indicate that cigarette smoking confounded the relationship of arsenic exposure to respiratory cancer (Ex. 202–3B, p. 45).

Crump examined the effects of smoking and concluded that "failure to control for smoking can not have been the sole cause of the increased cancer incidences observed in these studies" (Ex. 206, p. 21). He estimated that correcting for increased prevalence of smoking among ASARCO and Anaconda smelter workers would lower the observed respiratory cancer SMRs by about 13%. Crump considered the available data to be consistent with both an additive and multiplicative effect from smoking combined with exposure to arsenic, and noted that both smokers and non-smokers were at increased risk of developing respiratory cancer from arsenic exposure.

Pershagen, Well, Taube, and Linnman performed additional statistical analyses on the study results reported by Wall (Ex. 237MM) in order to explore the interaction between exposure to arsenic and tobacco smoke. For each of 76 copper smelter workers who had died from lung cancer, 2 referents were chosen who had been employed at the same copper smelter and had died from other causes. Arsenic-exposed non-smokers were observed to have a 3-fold increased risk of lung cancer death compared to non-smokers with no history of arsenic exposure. Smoking arsenic workers had a 14.6-fold increased risk of lung cancer death compared to non-smokers with no history of arsenic exposure. The authors did not compare smoking arsenic workers to smokers who had no arsenic exposure; however, an increased lung cancer risk of roughly 2-fold for smoking arsenic workers compared to smokers with no arsenic exposure can be estimated from Table 1 of their paper (Ex. 202–71, p. 304). Pershagen and colleagues concluded that combining tobacco smoking with arsenic exposure had a multiplicative effect on lung cancer mortality rather than additive effect. Pershagen et al. did not explain how their findings differed from those which would be expected from an additive relationship between arsenic and tobacco smoke.

OSHA concludes that the additional data on the effects of smoking support OSHA's previous conclusion that the excess lung cancer risk observed among arsenic-exposed workers could not be attributed primarily to smoking. Furthermore, the authors of the studies providing additional data on smoking generally are in agreement with this conclusion. Whether tobacco smoke and arsenic exposure have an additive or multiplicative relationship does not affect OSHA's conclusion concerning the effect of smoking. The following observations, among others, indicate that smoking cannot be the primary etiologic factor for the increased respiratory cancer risk:

1. Non-smoking arsenic workers had significantly increased risk.

2. Smoking arsenic workers had significantly increased risk relative to smokers not exposed to arsenic.

3. The magnitude of increased respiratory cancer risk among arsenic workers was higher than what would have been observed if smoking was the major etiologic factor for the excess risk.

4. Differentials in smoking prevalence would be an extremely unlikely explanation for the dose-response gradient observed for arsenic exposure.

I. Effects of Other Exposures

Lee and Fraumeni (Ex. 5D) stated that the potential carcinogenic effects of

exposure to sulfur dioxide or other unknown agents could not be distinguished from the effects of arsenic exposure. This was because workers who received heavy exposure to arsenic also received medium or heavy exposure to sulfur dioxide. Pinto and Enterline also could not rule out potential carcinogenic effects from agents associated with arsenic exposure in the smelter atmosphere (Ex. 29B).

Lubin et al.'s multivariate analyses of the Anaconda cohort enabled examination of the question of the potential carcinogenic effects of exposure to sulfur dioxide independently or with contemporaneous exposure to arsenic (Ex. 201–17). When multivariate models controlled for heavy/medium arsenic exposures, no significantly increased lung cancer risk was observed from heavy/medium exposure to sulfur dioxide (RR=0.9 for workers with heavy/medium exposure to sulfur dioxide who had no heavy/medium exposure to arsenic). However, there was a non-significant 5-fold increased risk among workers with heavy/medium exposure to sulfur dioxide who had also been employed 15–24 years. When multivariate models controlled for heavy/medium sulfur dioxide exposures, heavy/medium arsenic exposure continued to be associated with increased respiratory cancer risk (RR=2.3 for workers with heavy/medium exposure to arsenic who had no heavy/medium exposure to sulfur dioxide).

With regard to the role of sulfur dioxide in producing the observed excess of respiratory cancer, Lubin et al. noted that statistical power of their study to detect an increased risk from exposure to sulfur dioxide by itself or in combination with arsenic was not high. Nevertheless, in their opinion, multivariate analyses demonstrated that the excess risk of death from respiratory cancer was primarily associated with exposure to arsenic.

Brown and Chu (Ex. 241–C) also examined the effects from exposure to sulfur dioxide for 8014 members of the Anaconda study cohort. Both arsenic and sulfur dioxide were assigned exposure categories of light, medium and heavy.

After adjusting for the effects of age at initial exposure, duration of exposure, and time since employment stopped, excess lung cancer mortality rates within each of the three arsenic exposure categories were examined with adjustment for the effects of sulfur dioxide exposure, and vice versa. A clear dose-response gradient was observed for lung cancer risk and arsenic exposure.

Sulfur dioxide did not exhibit a dose-response gradient when excess lung cancer mortality rates were adjusted for the effects of arsenic exposure. Brown and Chu concluded:

> This Table [3] shows that SO_2 level by itself, i.e., unadjusted for arsenic level, shows an increasing trend of excess mortality risk with increasing level of the contaminant. However, when the effect of one atmospheric contaminant is adjusted for the possible confounding effect of the other, the relationship of excess risk with arsenic level remains unchanged, while the effect of SO_2 level disappears. Therefore, these results . . . indicate that arsenic level is the more important measure of carcinogenic contamination than is SO_2 level (Ex. 241–C, p. 15–16).

Mabuchi et al. (Ex. 237AA; Ex. 237BB; Ex. 237CC) attempted to distinguish the potential carcinogenic effects of exposure to non-arsenicals, including chlorinated hydrocarbons, from the effect of exposure to arsenicals in their cohort of pesticide manufacturing workers. When the cross-classified workers by duration of high exposure to arsenicals and non-arsenicals, they continued to observe increasing SMRs for lung cancer with increasing duration of exposure to arsenic. With regard to the effect of exposure to non-arsenicals, Mabuchi et al. stated: "no substantial differences in SMR by duration of non-arsenical exposure were apparent for a given duration of arsenical exposure * * * Thus, no dose-response pattern is apparent for non-arsenical exposure" (Ex. 237BB, p. 318). In addition, a case-control study of workers within the plant found no association between DDT exposure and lung cancer risk. Mabuchi et al. noted that "the interval of observation after exposure to the maximum doses of these non-arsenical chemicals may not have been sufficient to allow for a prolonged latent period for cancer" (Ex. 237BB, p. 318).

The Chemical Manufacturers Association-Arsenic Panel stated, in their pre-hearing brief, that the presence of copper oxide, dry lime sulfur, and powdered sulfur in the pesticide plant studied by Mabuchi et al. was evidence that pesticide plant exposures were similar to the copper and sulfur dioxide exposures of the copper smelter workers (Ex. 202–3, p. 42). Therefore, CMA considers that these other chemicals may have been responsible for the observed excess cancer risk. OSHA judges that the non-arsenical chemical exposures within copper smelters and arsenic pesticide plants cannot be considered similar; for example powdered sulfur differs greatly from gaseous sulfur dioxide.

Seeking to explore the potential role of sulfur dioxide in the respiratory cancer excess among ASARCO copper smelter workers, Enterline and Marsh compared the mortality experience of the Arsenic department workers to that of the Cottrell department workers (Ex. 201–9). In the Cottrell department, arsenic exposures were considered very high, exceeding 500 $\mu g/m^3$ and sulfur dioxide exposures were considered moderate, ranging from 5 to 20 ppm. Arsenic exposures were also considered very high in the Arsenic department, also exceeding 500 $\mu g/m^3$, while sulfur dioxide exposures were considered nil. For this comparison, none of the workers categorized in the Arsenic department had ever worked in the Cottrell department. Respiratory cancer SMRs were 370.4 and 334.6 in the Cottrell and Arsenic departments respectively. Both increases in respiratory cancer mortality were statistically significant. Enterline and Marsh stated: "Respiratory cancer SMR's were quite similar suggesting that SO2 exposure did not play an important role in the respiratory cancer excess at this copper smelter" (Ex. 201–9, p. 15).

Higgins and colleagues also sought to determine the potential confounding effects of exposure to sulfur dioxide and asbestos among workers in their study cohort (Ex. 202–3B). For sulfur dioxide, departments were categorized as having low, medium or high exposure. Workers were classified as having received either low *Ceiling* or medium/high *Ceiling* exposures to sulfur dioxide. *Ceiling,* for this analysis, was defined as maximum category in which each worker spent one year or more.

Air concentrations of asbestos were not measured during 1943–1965. Potential exposure to asbestos was defined as working with asbestos or insulation or working in the mason, pipefitter, or boiler shops.

Regarding the effects from exposure to sulfur dioxide and asbestos, Higgins et al. stated that these substances did "not appear to account for respiratory cancer excess in this population." (Ex. 202–3B, p. 65). Higgins and colleagues were not able to completely separate the sulfur dioxide, asbestos, and arsenic exposures in their analysis, yet they concluded that arsenic appeared to be the major factor in the increased respiratory cancer risk of Anaconda workers. Their conclusion regarding asbestos was based on the lack of a decrease in respiratory cancer SMRs when men with asbestos exposure were excluded from the analysis.

Workers with medium/high exposure to sulfur dioxide did appear to have

increased respiratory cancer SMRs relative to workers with low sulfur dioxide exposure within the same *Ceiling* arsenic category. However, Higgins and colleagues found that workers with medium/high sulfur dioxide exposure had higher *average* arsenic concentrations than their counterparts with low sulfur dioxide exposure. Hence, while a potential carcinogenic effect from sulfur dioxide exposure could not be ruled out, Higgins and colleagues judged that "arsenic exposure could have been responsible for the apparent association between sulfur dioxide and excess respiratory cancer" (Ex. 202–3B, p. 39).

OSHA realizes that many occupational environments involve exposure to multiple substances. When an excess of cancer is observed in an occupational population, it is not always possible to attribute the excess solely to the suspect etiologic agent. Additional studies of the same type of workplace and of other types of workplaces which find carcinogenic risk associated with the suspect agent strengthen the causal evidence. Excess respiratory cancer risk has been observed in copper smelter workers, pesticide manufacturing workers, and vineyard workers exposed to arsenic. These three types of workplaces had dissimilar exposures except for their common exposure to arsenic. In addition, analyses by Lubin et al., Brown and Chu, Mabuchi et al., Enterline and Marsh, and Higgins et al. suggest that arsenic exposure was the primary cause of the respiratory cancer excess in their study cohorts. While these investigators' analyses cannot completely rule out carcinogenic effects from substances other than arsenic, their fiindings further strengthen the evidence for arsenic causing respiratory cancer.

OSHA concludes that the increased respiratory cancer risk observed among arsenic workers is primarily due to arsenic exposure, based on the excess risk observed in dissimilar work environments and based on the analyses performed by Lubin et al., Brown and Chu, Mabuchi et al., Higgins et al., and Enterline and Marsh.

J. Conclusions

In keeping with OSHA's statutory mandate to review the latest available scientific evidence, OSHA's conclusions regarding the epidemiologic evidence on the carcinogenicity of inorganic arsenic are based on the most recent studies as well as on the studies available earlier. OSHA concludes that the findings of the most recent studies (Lee-Feldstein, Lubin et al., Higgins et al., Enterline and Marsh, Mabuchi et al., Axelson et al., Wall) and the older studies (Lee and Fraumeni, Pinto and Enterline, Tukadome and Kuratsune, Ott et al., Hill and Faning, Baetjer et al., Denk et al., Roth) are strong evidence that inorganic arsenic is a human carcinogen (Exhibits 5D, 29B, 111—Attachment 4, 191, 1A 3–1, 1A–24, 5B, 109 C–87, 65, 109C–88, 201–17, 201–16, 202–3B, 203–5, 201–8, 201–9, 205–2, 237BB, 237CC, 237D, 237 MM). The International Agency for Research on Cancer, the World Health Organization—Arsenic Working Group and NIOSH concur with this judgment (Exhibits 201–13, 252, 227).

Data concerning the quantitative relationship of inorganic arsenic to increased lung cancer risk are available for the study cohorts of Lee and Fraumeni, Lee-Feldstein, Higgins et al., Pinto and Enterline, Ott et al., and Enterline and Marsh. In addition to confirming that a dose-response exists for arsenic exposure and lung cancer risk, these studies provide direct evidence of excess risk at and below the previous OSHA permissible exposure limit of 500 $\mu g/m^3$. *Measured* estimates of excess risk at specific levels of exposure for these study cohorts, as distinguished from estimates of risk *predicted* by dose-extrapolation models, indicated excess lung cancer risk from levels of exposure to inorganic arsenic less than 500 $\mu g/m^3$.

Table 3 summarizes measured estimates of respiratory cancer risk from exposure to relatively low air concentrations of inorganic arsenic. Statistically significant increases in respiratory cancer mortality were observed at average arsenic exposures of 49 $\mu g/m^3$ and at cumulative arsenic exposure of 150–450 $\mu g/m^3$-years.

Note.—A cumulative exposure of 150 $\mu g/m^3$-years represent 150 $\mu g/m^3$ for one year or 3.3 $\mu g/m^3$ for 45 years, or other exposure levels adding up to 150 $\mu g/m^3$-years.

Also, other increases in risk were observed at low levels of exposure but these were not statistically significant increases. As explained in previous sections, these increases are meaningful because small numbers of employees in each category may prevent true excess risks from attaining statistical significance. Another reason why these increases are meaningful is that trends in mortality data, as well as stistical significance, are important.

In addition to low statistical power, another factor might be responsible for the fact that some of the observed excess risks were not statistically significant in some of the low exposure categories. This factor is simply that some workers classified as receiving low exposure may have had close to zero exposure to arsenic (for example, company farm workers).

TABLE 3.—RESPIRATORY CANCER RISK OBSERVED IN LOW EXPOSURE CATEGORIES

Studies and exposure categories	Resporatory cancer SMR's
Maximum Exposure (Table 5, 6)	
Lee-Feldstein (Ex. 201–16):	
Light (12 or more months) [1]	[4] 231
Light (1–15 Years)	[4] 223
Light (15–24 years)	[4] 186
Light (25 or more years)	[4] 313
Cumulative Exposure (Table 8) [2]	
Enterline and Marsh (Ex. 201–9):	
Less than 150 $\mu g/m^3$-years	155.4
150–450 150 $\mu g/m^3$-years	[4] 176.6
450–900 150$\mu g/m^3$-years	[4] 226.4
Average Exposure by Duration of Exposure (Table 12) [3]	
Less than 10 years (49 $\mu g/m^3$)	169.9
10–19 years (49 $\mu g/m^3$)	[4] 268.2
Average Exposure (Table 16)	
Higgins et al. (Ex. 202–3B, 203–5):	
Less than 100 $\mu g/m^3$	138
100–499 100 $\mu g/m^3$	[4] 303
Ceiling Exposure (Table 20)	
Less than 100 $\mu g/m^3$	129
100–499 100 $\mu g/m^3$	116
Cumulative Exposure (Table 6)	
Less than 500 $\mu g/m^3$-years	69
500–2000 $\mu g/m^3$-years	157

[1] Light estimated to average 290 $\mu g/m^3$ by H.F. Morris.
[2] Based on 10 year Lag Data and 0.3 conversion factor for urinary levels to air levels.
[3] Based on 0.3 conversion factor for urinary levels to air levels.
[4] Statistically significant (P less than 0.05).

A few investigators did not observe increases in lung cancer risk for some low exposure categories. For example, as listed in Table 3, Higgins et al. observed an SMR of 69 for those workers with cumulative exposures less than 500 $\mu g/m^3$-years. As with the low exposure groups which did have lung cancer excesses that were not statistically significant, low statistical power might have been responsible for the lack of excess risk observed in these instances. Also, the exposure levels for some workers in these categories such as office workers and farm workers may have been 10 $\mu g/m^3$ or well below that level. OSHA does not consider these no-risk findings to constitute evidence for a threshold of arsenic carcinogenesis. Nor do these findings counterbalance the preponderance of the epidemiologic evidence indicating significant risk from exposure to relatively low levels of arsenic.

In summary, increased respiratory cancer risk was observed at and far below the former PEL of 500 $\mu g/m^3$. OSHA believes that these data are sufficient by themselves to support a finding that the risk is significant. It is not necessary for OSHA to establish the significance of risk by using mathematical dose-extrapolation models. Both measured estimates of risk and estimates of risk predicted by dose

extrapolation models are valid methods of establishing significance of risk.

Using different measures of exposure, including average exposure levels, cumulative exposure, ceiling or maximum exposure, and duration of exposure, a dose-response gradient of increasing lung cancer risk with increasing exposure was observed in the various studies. Significant reduction in risk from lowering workplace exposure levels is likely, based on the dose-response data indicating lesser risk from lower exposures.

Higgins et al. suggested that peak exposures exceeding 500 $\mu g/m^3$ rather than average exposure or cumulative exposure may be the primary determinant of arsenic-induced lung cancer risk. This hypothesis should be considered preliminary, given that Higgins et al. studied only 20 percent of workers who received relatively low exposures, resulting in very low statistical power to detect excess lung cancer risk in the low exposure categories. In contrast, Lee and Fraumeni and Lee-Feldstein, who studied the entire cohort at risk, found that workers in the light exposure category (estimated as having average exposures of 290 $\mu g/m^3$) who had never been exposed to medium or heavy levels of arsenic had significantly increased lung cancer risk. In addition, a potential confounding effect from average exposures hinders interpretation of the effects from peak exposures, because workers with higher peak exposures would be expected to have higher average exposures. For these reasons and other reasons discussed in Section VI, OSHA placed more weight on Lee and Fraumeni's and Lee—Feldstein's findings than on the findings of Higgins et al. regarding peak exposures. An additional factor contributing to OSHA's decision concerning the question of peak exposures was the good dose-response observed for measures of exposure other than peak exposure and measured excess risks for employees who had average exposure well under 500 $\mu g/m^3$. Both these factors tend to indicate excess risk for employees who had no peak exposures over 500 $\mu g/m^3$.

Since publication of the final regulation, additional data have strengthened OSHA's earlier conclusion that smoking and occupational exposure to agents other than arsenic could not be primarily responsible for the excess respiratory risk of arsenic-exposed workers. Increased respiratory cancer risk has been observed in both non-smokers and smokers in occupational cohorts exposed to arsenic. Whereas good dose-response has been observed for arsenic exposure, consistent dose-response has not been observed for sulfur dioxide and other non-arsenical exposures. Also, observing excess risk in different occupational environments with arsenic exposure, including copper smelters, arsenical pesticide plants, and arsenic-exposed vineyard workers, is strong evidence for arsenic rather than other substances being the etiologic agent for lung cancer.

IV. Quantitative Risk Assessment

Section II in the April 9, 1982 document and Section II. C above offer general discussions on risk assessment and background information. Those aspects of risk assessment will not be repeated here.

A. Summary of Risk Assessments

Table 4 summarizes all of the estimates of risk presented during the rulemaking proceedings. There were nine separate risk assessments discussed. The following section will briefly describe the methodology used and conclusions drawn by each author. Datailed discussions of the issues can be found in the subsequent analytic sections. The first three risk assessments are those presented in the April 9, 1982 document which formed the basis of OSHA's preliminary determination of significant risk.

Dr. Kenneth Chu, while on detail to OSHA from the National Toxicology Program, performed a risk assessment based on the Lee and Fraumeni and Ott et al. studies and the Pinto and Enterline data. He based his assessment of risk on a linear, non-threshold relative risk versus cumulative dose model. (Dr. Chu also calculated risk according to a quadratic model, although he indicated in his report that the linear model was more representative of the risk associated with arsenic on the basis of statistical fit, as measured by R^2. The R^2 values were, in general, higher for the linear model than for the quadratic model. R^2 is discussed in more detail in Section IV–B). Dr. Chu's risk assessments predict a risk of 375 to 713 excess cancer deaths per 1000 workers with a lifetime exposure at 500 $\mu g/m^3$ and 7.7 to 25 deaths per 1000 at 10 $\mu g/m^3$.[1]

[1] Dr. Chu also made predictions from the Ott et al. study, but he did not include them in his preferred estimates.

TABLE 4.—SUMMARY OF RISK ASSESSMENTS EXCESS RISK OF LUNG CANCER PER 1,000 WORKERS RISK AT 10/50/500 μg/Cubic Meter

Model used	Lee and Fraumeni	Pinto et al.	Ott et al.	Lee-Feldstein	Enterline and Marsh	Higgins et al.
Chu:						
Linear RR[1]	10/51/393	25/125/713	29/146/767			
Quadratic RR	0.3/7/–	2/49/–	2.1/52–			
Clement Associates: Linear RR	7.7/39/394	9.1/46/465				
EPA-CAG: Linear RR	[2]8/38/375					
Crump:						
Linear RR	8.7/43/321	19/92/518	25/117/578	8.3/40.6/310		[3]9.4/45.8/342
Linear AR [4]				3.2/16.0/148	7.8/38.6/315 Lag 0 7.6/37.3/303 Lag 10.	5.2/25.9/228
Radford: Linear RR			[5]18.8–37.5/–/–			
Enterline: Linear RR					2.7/13.4/– Lag 10 2.2/11.2/– Table 12.	
Bleier and Wagner	Recommends 2 $\mu g/m^3$.					
World Health Organization: Linear RR	[6]61/305/–					
CEOH						No excess risk if exposure <500 $\mu g/m^3$.[7]

[1] Relative risk (Observed/Expected).
[2] Combined estimates from Lee and Fraumeni, Pinto et al. and Ott et al. studies.
[3] Cumulative exposure data, Ex. 202-8, Appendix D.
[4] Absolute risk (Observed-Expected)/Person-Years.
[5] Range of estimates from Ott et al., Lee-Feldstein, and Enterline and Marsh studies.
[6] Calculated by OSHA using WHO's methodology for risk analysis.
[7] Ex. 202-3A.

Clement Associates performed a risk assessment based on the Lee and Fraumeni study and the Pinto et al. study published in 1977. (Dr. Chu based his assessments solely on data in the arsenic record, which closed in 1976). Clement concluded that the Ott et al. study was not as well suited for risk assessment and did not include it in its analysis.

The Clement risk assessment is based on a linear non-threshold model with dose measured as an average lifetime exposure. Clement estimated that a 45-year working lifetime of exposure to 500 $\mu g/m^3$ of arsenic will result in a 525% to 620% excess risk of lung cancer or 394 to 465 excess deaths per 1000 workers over a lifetime, and that exposure at 10 $\mu g/m^3$ of arsenic will result in a 10% to 12% excess of lung cancer or 7.7 to 9.1 excess deaths per 1000 exposed workers over a lifetime.

The EPA-Carcinogen Assessment Group (EPA–CAG) also performed a risk assessment on arsenic. The judgment of the group was that the data in the Lee and Fraumeni, Pinto et al. and Ott et al. studies were of sufficient quality to perform a risk assessment and that a linear model was appropriate. It estimated, as a best estimate, an 8.1% increase in lung cancer per 1 $\mu g/m^3$ of arsenic for an environmental exposure of 24 hours a day, 365 days a year over a natural lifetime. The EPA–CAG averaged results from all three studies in making its overall risk estimate.

Since a working year exposure (40 hours per week for 46 weeks) is only about 20% of an environmental exposure, the estimate of risk had to be adjusted to a working year estimate before comparisons could be made with the other risk assessments. The formula the EPA–CAG used, based on a 46-week work year, was:

$$\frac{46 \text{ weeks} \times 40 \text{ hours}}{365 \text{ days} \times 24 \text{ hours}} = 0.21$$

In addition, a natural lifetime averages 74 years while a maximum working lifetime is considered to be 45 years. Therefore, the EPA–CAG's risk factor has to be further reduced to take into account the shorter number of years exposed during work.

The conversion is $45/74 \times 0.21 = 0.128$. This conversion was presented in the April 9, 1982 document and was not challenged. Therefore, the 8.1% excess risk per 1 $\mu g/m^3$ of arsenic exposure estimated by EPA–CAG must be multiplied by 0.128 to convert to a working lifetime equivalent of an excess risk of 1.0368% or approximately 1% excess risk per 1 $\mu g/m^3$ of arsenic exposure. This results in a 500% excess risk of lung cancer at 500 $\mu g/m^3$ of arsenic exposure, or 375 excess deaths per 1000 workers over a working lifetime, a 50% excess risk at 50 $\mu g/m^3$ or 38 excess deaths per 1000 workers over a working lifetime, and a 10% excess risk at 10 $\mu g/m^3$ or 8 excess deaths per 1000 workers over a working lifetime.

In addition to the three risk assessments discussed in the proposal six additional risk assessments were presented, or became available, during the rulemaking proceedings: Drs. Crump, Radford and Enterline, and Consultants in Epidemiology and Occupational Health each presented analyses on data presented in the arsenic record. An analysis by Blejer and Wagner (1976) gives a "projection" of risk from exposure to inorganic arsenic and the World Health Organization-Arsenic Working Group (WHO-AWG) also presents an evaluation of the risk from inorganic arsenic exposure.

The results from the independent assessments performed by Dr. Crump support the preliminary estimates of risk proposed by OSHA, falling within the same range: 8.7 to 29 excess deaths per 1000 at 10 $\mu g/m^3$ and 321 to 578 per 1000 at 500 $\mu g/m^3$. Employing a linear model, he used an age-adjusted method for estimating risk from lifetime exposure to arsenic with both relative risk and absolute risk. Dr. Crump concluded that any of the 3 studies, Lee and Fraumeni (1969), Ott et al. (1974) and Pinto et al. (1977), "would be an adequate basis for a quantitative risk assessment of respiratory cancer risk from occupational exposure to arsenic. Moreover, in evaluating the Ott et al. study, Dr. Crump did not consider its shortcomings "severe enough to prevent its use in quantitative risk assessment." (Ex. 206, p. 2).

Dr. Crump also performed risk assessments on the more recent studies by Lee-Feldstein, Enterline and Marsh, and Higgins et al. The predictions from these analyses are consistent with estimates from the previous studies. Using a relative risk model, at 10 $\mu g/m^3$, they predict a lifetime excess risk of 8.3 and 9.4 deaths per 1000 for the Lee-Feldstein and Higgins et al. data respectively. The comparable predictions of risk when absolute risk is incorporated are approximately half those predicted by a relative risk model (3.2 per 100 and 5.2 per 1000, respectively). When Dr. Crump fit a linear absolute risk model to the Enterline and Marsh (1982) data (which, as discussed in the next section, may be a more appropriate method) the predicted risks were very similar to estimates presented earlier (7.6 per 1000 at 10 $\mu g/m^3$ and 303 per 1000 at 500 $\mu g/m^3$ in the 10 Year Lag group).

Dr. Radford presented his estimates of risk in terms of a "doubling dose", that is, the cumulative dose at which one would expect a doubling of the risk (SMR=200). He calculated the doubling dose for the Lee-Feldstein data (approximately 2900 $\mu g/m^3$-years) and the Enterline and Marsh data (doubling dose approximately 500–3000 $\mu g/m^3$-years from Table 12). He also computed the doubling dose for the Ott et al. data to be approximately 1500 $\mu g/m^3$-years.

Taking a value of 1000–2000 $\mu g/m^3$-years as a "best range", he estimated that a lifetime occupational exposure (45 years) to the 10 $\mu g/m^3$ level would yield approximately a 25 to 50% increased risk of lung cancer (18.8 deaths per 1000 to 37.5 per 1000), which was similar to the upper risk estimates of Dr. Chu. Dr. Radford concluded that "the risk estimates presented by OSHA in the April 9 summary must be raised in light of the new information" (Ex. 207, p. 13).

Dr. Enterline made predictions of risk in a prehearing submission (Ex. 202–8 Appendix C). He employed a linear regression model with relative risk and a cumulative measure of dose to arrive at a risk of 5.4 excess deaths per 1000 workers at 10 $\mu g/m^3$. Eliminating the duration of exposure dimension (i.e., plotting risk versus average intensity rather than a cumulative measure) he predicted 4.5 per 1000 from a lifetime exposure at 10 $\mu g/m^3$. Dr. Enterline concluded that since earlier exposure may have been considerably higher and considering factors of urinary arsenic concentrations, he may have overestimated the risk. He commented: "My guess is that regression coefficients are overstated by at least a factor of 2. This would thererefore reduce excess deaths related to arsenic exposure by 50%," thus leading to the estimates in

Table 4 of 2.7 and 2.3 deaths per 1000 at the 10 $\mu g/m^3$ level (Ex. 202–8, Appendix C, p. 8).

Blejer and Wagner (1976) reviewed much of the literature associating respiratory (and other) cancer with exposure to inorganic arsenic. They determined that both the Lee and Fraumeni (1969) and the Ott et al. (1964) studies "correlated work exposure levels of inorganic arsenicals with observed mortality experience" (Ex. 237–I, p. 180). Using only the data in the published literature Blejer and Wagner determined that the dose-response relationship found in Lee and Fraumeni was semiquantitative, but that the quantitative dose measures found in Ott et al. were adequate to perform a "projection" of risk from exposure to inorganic arsenic. (Blejer and Wagner did not have available the Morris submission presented at OSHA's 1975 hearing which provided numercial estimates for the Lee and Fraumeni categories. Their determination that the dose-response was semi-quantitative was based on measures "light, medium, and heavy"). Blejer and Wagner concluded:

> Occupationally, there are no data to document a noncancerigenic exposure level for inorganic arsenic. Moreover, our evaluation of the occupational dose-response relationship appears to indicate that nonresponse level of exposure may not exist. Therefore, because of the ubiquity of arsenic in the environment and because of the necessity of preventing occupational exposure from increasing the arsenic body burden, the most prudent and logical approach would be to limit these occupational exposures to those of approximately the *natural ambient level.*

Consequently, Blejer and Wagner recommended an occupational 8-hour time-weighted average of 2 $\mu g/m^3$.

In its review of arsenic, the World Health Organization-Arsenic Working Group presents an assessment of cancer risk from exposure to inorganic arsenic based on the study of Pinto et al. (1977). WHO-AWG assumed that the lifetime cancer risk is a function of the total dose of arsenic." They continued:

> This is a necessary assumption because occupational exposures begin at maturity, whereas exposure to airborne arsenic in the general environment begin at conception. Furthermore, in the case of lung cancer risk estimates, it is assumed that there are no age or sex differences in susceptibility to cancer induced by arsenic. There is not much basis in scientific fact for assuring the validity of these assumptions. It is not unreasonable to assume that the cancer response is proportional to the total dose, since the occupational smelter exposures extended over a substantial portion of the life span (Ex. 252, p. 145).

The WHO-AWG predicted risk for an average daily lifetime dose of 0.8% per 1 $\mu g/m^3$. Using the same assumption (of excess risk associated with total dose) OSHA calculated that for a *working* lifetime average dose of 10 $\mu g/m^3$, the WHO-AWG method predicts a risk of approximately 61 per 1000 excess lung cancer deaths.[2]

The Consultants in Epidemiology and Occupational Health (CEOH) reviewed the health data on exposure to inorganic arsenic and analyzed it as to degree of risk. CEOH concurred with other commenters that a clear dose-response relationship exists when peak exposures are above 500 $\mu g/m^3$ and that such exposure constitutes a significant risk. CEOH concluded, however, that there may be a threshold for exposure to arsenic. In support of this conclusion, they relied on the Higgins et al. "ceiling" analysis which indicated that there was no statistically significant excess risk for employees who had less than 30 days exposure at levels above 500 $\mu g/m^3$.

For further support CEOH stated its opinion that the dose-response relationship for arsenic was not a strong one. Dr. Lamm of CEOH cited several tables (Lee Feldstein, Ex. 201–16, Table 4, Enterline and Marsh, Ex. 201–9 Table 10) as evidence of a "plateau effect" in the dose-response curve. That is, in CEOH's view, unless exposures are at very high concentrations, or for very long durations, one does not see increasing risk with increasing dose. CEOH did not employ a regression analysis and its conclusions concerning dose were based solely on evaluation of the exposure measurement parameter intensity and not an evaluation of other parameters, such as duration.

B. Estimating Risks

In its April 9, 1982 document, OSHA presented the results of three independent risk assessments, based on 3 studies of high quality found in the arsenic record. OSHA concluded that the Lee and Fraumeni and Pinto and Enterline studies are excellent epidemiologic studies and provide a strong basis for quantitative risk assessment and that it was reasonable to utilize data from the Ott et al. study for risk assessment.

As pointed out in the proposal, and discussed in Section III, several recent reports have become available which continue to show excess lung cancer risk among smelter workers exposed to inorganic arsenic. The data received in these rulemaking proceedings and the analyses of these new studies have some effect on the quantitative estimates of risk proposed in the April 9, 1982 document.

Several questions were raised in the proposal regarding the dose-response curve, and questions of ascription of historical dose. Many of these were addressed in comments and at the July, 1982 hearings and their impact on risk assessment will also be detailed here.

The three risk assessments presented in the April 9, 1982 proposal predicted excess risk at the 10 $\mu g/m^3$ level based on a linear model to describe the dose-response relationship. OSHA preliminarily concluded that "the linear hypothesis appears to be the most reasonable approach for estimating the risk presented by occupational exposure to inorganic arsenic." (47 FR 15364). OSHA relied on Dr. Chu's R^2 calculations in reaching this conclusion as well as the fact that both Clement Associates and EPA-CAG had chosen a linear model for their analyses.

As pointed out in the April 9, 1982 document, R^2 or correlation coefficient squared, indicates how close the measured points are to the dose-response curve predicted by the model. The closer the R^2 is to one, the better is the fit. That is, if the model predicts the observations perfectly, then R^2 equals one. It was pointed out in Dr. Chu's report that it can be seen that R^2 values are, in general, higher for the linear model than for the quadratic model.

In his pre-hearing submission, Dr. Crump analyzed five[3] of the major studies presented in the rulemaking proceedings. He used different models and methods for fitting the models to the data and estimating the lifetime risk and employed a Chi-squared goodness-fit test to assess the fit of the models.

Like the R^2 statistic, the Chi-squared goodness of fit statistic is also a measure of how close the measured points are to the predicted curve. The quality of the fit is judged by a P value associated with each Chi-squared statistic. The closer the P value is to one, the better the fit. However, many statisticians consider P values far less

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[2] The computation was as follows:

Total dose (Pinto et al.) = 8 m^3/day × 240 days × 50 $\mu g/m^3$ × 25 years = 2,400,000 $\mu g/m^3$ = 2400 mg.

Total dose (environmental) = 12 m^3/day × 365 days × 8 $\mu g/m^3$ × 70 years = 2,452,000 μg = 2452 mg.

which was assumed to produce an excess relative risk of 200%.

Total dose (workplace, OSHA) = 9.6 m^3/day × 230 days × 10 $\mu g/m^3$ × 45 years = 993,600 μg = 993.6 mg.

$2452.8/993.6 = 2/x$

where x is the excess relative risk for working lifetime exposure to arsenic of 10 $\mu g/m^3$. x = 0.81, or 81%. Therefore, the excess risk is 0.81 × 0.075 (background) = 0.06075 or 61 deaths per 1000.

[3] Lee and Fraumeni, Ott et al., Pinto et al., Enterline and Marsh, Lee-Feldstein.

than one as indicative of an acceptable fit.

In a pre-hearing submission the CEOH (Ex. 202–30 p. 23) criticized the use of the R^2 statistic as a measure of goodness-of-fit, suggesting this was an "inaccurate" interpretation of the statistic. Dr. Crump's use of the Chi-squared goodness-of-fit test addresses many of the shortcomings of the R^2, including assumptions of normality for the underlying data.

In his independent assessments, Dr. Crump fit both linear and quadratic dose-response models to the data, concluding that, based on Chi-squared goodness-of-fit tests, the linear model was a more appropriate model. In most cases, the P values were substantially higher for the linear model than for the quadratic model. Overall Dr. Crump has characterized the fit of the linear model as "good" (P values ranging from 0.14 to 0.97) but noted that the Lee-Feldstein data fit was "marginally acceptable". In his testimony Dr. Lamm characterized the fit of the Lee-Feldstein data as "unacceptable" (Tr. 522). Dr. Crump commented further however, that he believes the lack of fit in the Lee-Feldstein data is due to imprecision of the exposure estimates rather than any inherent deviation from linearity. In reaching this conclusion, Dr. Crump also fit a linear model to the Higgins et al. cumulative exposure data. (Higgins and colleagues may have done a better job of describing an individual's cumulative exposure than did Lee-Feldstein). Crump characterized the fit of the linear model in this instance as "excellent" (P values equaled 0.46 and 0.75) and the data are supportive of a strong linear dose-response relationship for the Anaconda data.

During a question and answer period at the hearing, Dr. Lamm also pointed to the fit of the quadratic curve for several studies, noting that where there is an adequate fit for the linear model, there is usually a more than adequate fit for the quadratic model. He concluded that while there may be quite a good fit for the linear, ". . . your quadratic fits sufficiently well that it would be inappropriate to exclude that as a reasonable or feasible explanation of the behavior [of the data]" (Tr. p. 519). OSHA disagrees with this conclusion. In all but one study, the P value from the Chi-square goodness of fit test for the linear model is substantially higher than that for quadratic. OSHA concludes there is strong evidence to support the use of the linear model in this risk assessment. As Dr. Crump concluded: "These [chi-squared] analyses indicate that it is reasonable to use a linear model to assess risk from occupational exposure to arsenic, but it would not be reasonable to use a quadratic model" (Ex. 206, p. 5).

Dr. Radford also supported the use of a linear model, pointing out: "The fact that a linear no-threshold convention has been widely applied for chemical initiators represents a conservative position reflecting our uncertainty about biochemical mechanisms of low doses of initiators" (Ex. 207, p. 6).

In addition, the WHO–AWG summarized the support for a linear non-threshold model in carcinogenic risk assessment. It concluded:

> The use of the linear non-threshold model is recommended for extrapolation of risks from relatively high dose levels, where cancer responses can be measured, to relatively low dose levels, which are of concern in environmental protection where such risks are too small to be measured directly either through animal or human epidemiological studies.
>
> The linear non-threshold model has been generally accepted amongst regulatory bodies in the USA for chemical carcinogens (IRLG) and for ionizing radiation on an international basis (ICRP). The linear non-threshold philosophy was accepted by a Task Group on Air Pollution and Cancer in Stockholm in 1977 (Task Group on Air Pollution and Cancer, 1978). The scientific justification for the use of a linear non-threshold extrapolation model stems from several sources: the similarity between carcinogenesis and mutagenesis as processes which both have DNA as target molecules, the strong evidence of the linearity of dose-response relationships for mutagenesis, the evidence for the linearity of the DNA binding of chemical carcinogens in the liver and skin, the evidence for the linearity in the dose-response relationship in the initiation stage of the mouse 2-stage tumorigenesis model, and the rough consistency with the linearity of the dose-response relationships for several epidemiological studies; for example, aflatoxin and liver cancer, leukaemia and radiation. This rationale for the linear non-threshold dose-response model is strongest for the genotoxic carcinogens (Ex. 252, p. 144).

Another issue raised in the proceeding is the question of the dose ascription methods in several studies. When ascribing dose levels, one must consider such issues as historical exposures and temporal trends, the choice of mean, median, or peak values as representative of exposure, and urinary-airborne exposure conversion levels. The influence of dose ascription on the shape of the dose-response curve (and consequently the estimates of risk) can sometimes be substantial, particularly when it affects shifting between exposure classes.

In analyzing the Lee and Fraumeni data, Clement Associates' and Dr. Chu's risk assessments utilized the extensive exposure data in the arsenic record, based on data submitted by Morris of measurements taken at the Anaconda Smelter (Ex. 28 B). Both excluded data for the workers in the highest exposure category for some of their analyses. (Those workers frequently wore respirators and, therefore, the levels of arsenic inhaled would have been lower than the level of arsenic measured in the workplace air.)

The EPA-CAG risk assessment utilized a 1975 National Institute of Occupational Safety and Health (NIOSH) survey of the Anaconda smelter as the basis for estimating exposures of workers in the Lee and Fraumeni study. These exposure data were "derived from a single survey of copper smelters conducted after the period of employment of the workers studied" in the Lee and Fraumeni study (Ex. 201–4, p. 4). The "heavy" and "medium" exposure classifications as determined by NIOSH were virtually identical in this analysis and, therefore, the EPA averaged the two exposure levels for its analysis.

There were several updates to the original Lee and Fraumeni study. The study by Higgins et al. attempted a more accurate calculation of an individual's exposure particularly his cumulative exposure. Several commenters expressed reservations about the classification scheme of Higgins et al. The method of estimating cumulative exposure by multiplying exposure times average duration used by several experts is also a reasonable approximation. This is borne out by the similarity in the estimates of risk from analyses using both methods of dose ascription.

There were also questions on the ascription of dose in the Pinto et al. studies. The exposure levels used in the risk assessment based on the Pinto and Enterline results are derived from urinary arsenic levels. All three risk assessments utilized the same factor, 0.3, which was estimated by Pinto et al. (Ex. 201–19), to convert urinary levels to airborne levels.

The risk assessment performed by Dr. Chu on the Pinto and Enterline data utilized data contained in the arsenic record, that the urinary arsenic levels in 1948 were twice the 1973 level, to estimate exposures prior to 1948. Dr. Chu believes that these estimates are good estimates of exposure. They take into account the protection afforded by the respirators that were sometimes used. Higher exposures would have resulted in acute symptoms, which were infrequent.

Both the Clement and EPA–CAG assessments are based on estimates presented in the Pinto and Enterline 1977 update that stated that exposures before 1948 were 5 to 10 times higher than the 1973 levels. These higher estimates of past exposures are based on estimates made by ASARCO, though these estimates were not based on detailed studies. Since an assumption of higher exposures in the past would result in lower estimates of risk per unit of exposure, this particular assumption was the principal explanation for the higher estimates of risk in the assessment performed by Dr. Chu.

OSHA concluded in its April 9, 1982 proposal that it accepted "the [5 to 10-fold] higher estimates of past exposure because they are documented in the published literature and because ASARCO has had extensive programs for monitoring arsenic going back to the late 1930's." However, OSHA pointed out that Dr. Chu's estimates were also "reasonable" (47 FR 15364). As pointed out in section III, recent reports (Ex. 201–8, 201–9) tend to support Dr. Chu's determination that pre-1948 levels were approximately twice as high as those of 1973, and lend support to his higher estimates of risk.

The new study by Enterline and Marsh (1982) confirmed OSHA's conclusion in the preamble to the final standard that there is significant excess risk of lung cancer from exposed to inorganic arsenic, even at low exposures. There was some question, however as to the strength of the dose-response relationship in this data.

Some of the participants pointed to the Enterline and Marsh (1982) analysis as evidence of a "plateau effect" in the dose-response curve. They used this term to define a phenomenon that, at lower doses, there is little or no gradient of risk with increasing dose, and that one only sees an increase or "jump" at very high doses. Some commenters pointed to Table 10 of Enterline and Marsh noting that the data failed to show a gradient of risk for doses less than or equal to 5000 μg/l-years (Exhibit 202–3, Table 10). Drs. Crump and Radford have suggested, however, that this lack of a dose-response relationship may be a result of the way dose was accumulated and that, perhaps, an "absolute risk" model may be more appropriate than a relative risk model to examine these data. Absolute risk is a measure of excess risk defined by Dr. Crump as (Observed Deaths-Expected Deaths)/Person-Years.

Dr. Crump noted that cohorts in higher exposure categories in the study might tend to be older than those in lower exposure categories. For illnesses which increase with age, this creates the possibility of age confounding. To address this potential problem of age confounding the comparison of SMR's, Dr. Crump calculated absolute risk by exposure category.

Absolute risk differs from SMR's and relative risk by *subtracting* the expected values from the observed number of deaths rather than *dividing* the expected deaths into the observed deaths. Hence, the expected value for cancer deaths, which is age-dependent, still figures in the calculation of absolute risk. Relative risks and SMR's are directly proportional to the expected values because they are multiples of the expecteds. Absolute risk is not directly proportional to the expected values and thus is less subject to age-confounding than SMR's and relative risks. Also, absolute risk corrects for differences in person-years at risk between study cohorts by dividing person-years into (Observed Deaths—Expected Deaths). As discussed by Dr. Crump (Ex. 206, p. 17) and the OSHA staff submission (Ex. 241–A), even if respiratory cancer mortality rates increase with increasing dose, older cohorts who received higher exposure, may not exhibit higher SMR's that reflect their greater risk. Absolute risk measures would reflect their greater risk of dying from respiratory cancer.

Dr. Crump stated:

> In an absolute risk model, the increase in cancer risk due to arsenic exposure at a given age does not depend upon the background risk (i.e., the risk in the absence of exposure to arsenic). In a relative risk model this increase is proportional to the background risk. If an absolute risk model is correct and if cohorts with higher dose also tend to be older (which was probably the case in the Enterline and Marsh analysis, due to the way exposure was accumulated) then even if respiratory cancer age-specific mortality rates increase linearly with dose, relative risks might not increase with dose, and they could actually decrease (Ex. 206 p. 17).

Dr. Crump (Ex. 206) analyzed the mortality data of Enterline and Marsh using an absolute risk model for the Cumulative exposure data and 10 Year Lag data (Ex. 206, Table 3). A clearer dose-response gradient for respiratory cancer risk was apparent using absolute risk measures. Dr. Crump suggested that "an absolute risk model may more nearly approximate the carcinogenic effect of arsenic than a relative risk model." In support of this hypothesis, Dr. Crump cited the better dose-response observed using SMR's when Enterline and Marsh confined their analysis to workers age 65 and over (Ex. 201–9, Table 10, p. 11). Since dose and age would not be related for this group, a dose response with SMR's would be expected, as well as for absolute risks (Ex. 212, p. 17–18).

Dr. Enterline responded that since absolute risk measures ignore the magnitude of the background risk and since most known industrial carcinogens interact with background cancers he prefers the use of relative rather than absolute risk models. He added that consideration of background is particularly important for agents suspected as cancer promoters. (Ex. 244, Appendix B, p. 1). However, to predict the excess risk attributable solely to arsenic exposure, independent of the background level, an absolute risk would also be an acceptable measure of risk.

Though use of absolute risk in place of relative risk does change the shape of the dose-response curve, estimates of risk based on the two measures do not differ substantially (See Table 4).

Based on observations at the Tacoma smelter, Enterline and Marsh suggest that for arsenic, "effective dose is not simply a multiplication of time times dose rate of intensity. Short exposures seem to have a disproportionately greater effect than long exposure * * * It is also possible that * * * it is not historic but recent exposure that is most important in any particular case, and the cumulative exposure to arsenic as a measure of dose have no overall meaning." In a post hearing submission (Ex. 244, Appendix B) Dr. Enterline reiterated that duration may be a "poor surrogate" for amount of exposure, a concept which may be supported by findings in the Higgins' report.

In addition, Enterline and Marsh further suggested that arsenic may be a cancer promoter, rather than a cancer initiator. This issue was raised in light of its impact on the shape of the dose-response curve and the threshold hypothesis. In general, initiation refers to the processes involved in starting or "initiating" a carcinogenic tumor. It may involve a single event, or several independent events. Promoting generally refers to an increase in the tumor growth rate; promotion can only take place once a cell is initiated. The terms initiator and promoter refer to the mode of action of the carcinogenic event; that is, whether it is an initiator, promoter, or both, it is considered a carcinogen.

Drs. Enterline and Marsh noted arsenic appeared to be a promoter because of the short latency period for arsenic-induced cancer observed in the ASARCO studies and the strong (Ex. 201–9) relationship bewteen lung cancer risk and age at initial exposure observed by Brown and Chu (Ex. 241–B, 241–C). In his post-hearing submission Dr.

Enterline concluded that if arsenic is a late stage promoter and if the multistage theory of carcinogenesis[4] is valid, then "use of a linear time-weighted dose-response relationship for arsenic would overstate response at low dose" (Ex. 244, App B, p. 1).

Brown and Chu (Ex. 241–C, 241–B) analyzed the mortality of 8014 members of the Anaconda cohort in order to determine whether excess respiratory cancer risk was related to duration of exposure, age at initial exposure, and follow-up time since exposure stopped. Their interest in these factors stemmed from the multistage theory of carcinogenesis, which predicts that risk will be differentially affected by these factors depending on whether the carcinogen acts on an early stage or late stage of the process of carcinogenesis.

Brown and Chu found that excess respiratory cancer mortality risk was a function of increasing age at initial exposure, duration of exposure, and exposure concentration. Duration of exposure was observed to be the most important single factor in the excess lung cancer risk. They considered their finding of increased risk with increased age of initial exposure to be consistent with arsenic having a late stage effect, since older individuals presumably would have more initiated cells susceptible to carcinogenesis.

Evidence against arsenic having an effect on promotion and growth cited by Brown and Chu included the relatively long latency period and continuing excess risk 20 years after cessation of exposure that they observed in the Anaconda cohort. This is inconsistent with animal models of promotion of carcinogenesis, where short latency periods and tumor regression after cessation of exposure to the promoter are characteristic.

Brown and Chu concluded that while their results suggested that arsenic primarily may have an irreversible effect on the late stage of the cellular transformation process, they could not rule out an additional effect at the initial carcinogenic stage from arsenic exposure (Ex. 241–C, 241–B).

In support of the use of a linear model, Dr. Radford noted that certain toxic agents may act as initiator *and* promoter; he posited (as did Dr. Enterline) that a promoter's dose-response curve may be curvilinear upward (less effect per unit dose at lower doses), whereas the studies of Enterline and Marsh and Lee Feldstein seemed to find more effect per unit dose at lower doses (Ex. 207, p. 7).

Even if a substance were clearly found to be a promoter rather than an initiator, humans are exposed to a variety of carcinogens such that a linear model might still be appropriate.

Several commenters suggested that there may be a "plateau effect" for inorganic arsenic in the Anaconda data as well.

Dr. Lamm cited the Lee-Feldstein study as one example about which he suggested "there is a plateau of risk unaffected by increasing duration for an extended period" (Ex. 202–3D).[5]

Dr. Crump commented: "I [therefore] consider the argument that risk depends primarily upon exposure level irrespective of duration to be highly speculative at this point." (Ex. 212, p. 9). Moreover, as discussed earlier, Brown and Chu concluded that duratrion of exposure is the most important single factor in determining lifetime risk (Ex. 241–C, p. 19).

Dr. Lamm has applied a very narrow definition to the dose-response relationship, insisting that there must be a statistically significant increase in the SMR's for each successive employment group (i.e., significant change from group to group). Applying such a definition lends support to the "plateau" effect theory. Dr. Lamm's definition is not the usual criteria for a dose-response curve and the authors of the studies OSHA discusses consider that their data demonstrate dose-response relationships. For example, Drs. Lee-Feldstein stated: "The excess respiratory cancer mortality increased with length of employment and was positively related to degree of arsenic exposure" (Ex. 202–3A).

Dr. Crump addressed many of these issues stating that the "plateau" effect; " * * * rather than being an inherent property of the dose-response is more probably due to small sample sizes and the fact that it is more appropriate in this particular situation to look for a dose-response in absolute risk rather than relative risk." (Ex. 212, p. 7). As with the Enterline and Marsh data, Dr. Crump noted that the "plateau effects" disappear almost entirely when absolute risk is plotted against length of employment." He elaborates, however, that if the plateaus of risk are "real" one must also accept the conclusion that there are possibly very sizable risks associated with small cumulative doses (i.e., arsenic is more potent than thought earlier.)

As was pointed out earlier in this discussion, the dose-response ralationship seen in the Lee-Feldstein data was not as strong as that in the Lee and Fraumeni data, and Dr. Crump characterized the linear fit as "marginally acceptable." He believed, however, that this was due to imprecisions in the exposure estimates rather than an inherent deviation in linearity.

Lee-Feldstein assigned workers to exposure categories in the same manner as Lee and Fraumeni. Dr. Marsh (Ex. 202–8 Appendix F. p. 23) commenting on that classification scheme, stated that assigning workers in the manner used by Lee and Fraumeni (1969) will "dilute effects seen in the high and medium groups" thus producing an artificial decrease in slope (lower risk per unit dose). He also noted that classification by highest exposure is confounded by duration. Marsh recommended that a time-weighted average over a work history would be a "more representative scheme."

The question of the suitability of cumulative dose for risk assessment was also investigated with data from the Higgins et al. study. Dr. Higgins and colleagues classified individuals by time-weighted averages and cumulative total exposure. A significant risk for lung cancer was observed and a clear dose-response relationship is seen between TWA and respiratory cancer mortality (Table 16) and when respiratory cancer is plotted against cumulative exposure as well. When Dr. Crump fit his models to the cumulative lifetime exposure data presented by Dr. Higgins (Ex. 202–8, Appendix D, Table 6) the data demonstrated an excellent fit (P values 0.46, 0.75) for both relative risk and absolute risk. Dr. Crump concluded that there was a strong dose-response relationship and that these data are consistent with a linear dose-response model.

The CEOH and Dr. Higgins have suggested that the data in the Higgins et al. report constitute evidence of a threshold of exposure to inorganic arsenic. They contend that there is no increased risk when exposures are not allowed to exceed 500 $\mu g/m^3$, and they stress that peak exposures are the major determinant of risk, regardless of length of exposure.

This conclusion must be assessed in light of the discussion presented in Section III. The exposure groups under 500$\mu g/m^3$ had a very low power to

[4] The multistage theory of carcinogenesis postulates that cancers are initiated only through a series of independent stages, and that all stages must be completed before a tumor will appear. In general, a polynomial curve (curvilinear upward) is used to describe this relationship; this curve will tend to approach zero much more quickly than a linear model.

[5] Dr. Lamm has included some qualifications to these conclusions, stating that a relationship exists only with very high concentrations or exposure of more than 25 years.

detect a 50 percent excess risk, even if one existed, and that classification by "ceiling" exposure may have had an artificial effect on the dose-response relationship due to "class shifting."

Despite the fact that Dr. Crump obtained an excellent fit using a linear regression, a standard statistical technique, Dr. Lamm did not employ a regression analysis. He stated: "Our lines here connect the data points rather than being a line, which is a linear regression, to *represent* [emphasis added] the data points" (Ex. 247, corrected transcript p. 451). He notes that this method of analysis has the advantage that no assumptions on the behavior of the curve are made as they are in the regression analysis.

Based on his non-regression analysis, Dr. Lamm concluded that there appeared to be a threshold at approximately 500–800 $\mu g/m^3$-years. It should be noted, however, that for 45 years exposure this is a "safe" level of approximately 10 $\mu g/m^3$.

A further issue presented was the quality of the Ott et al. data and its facility for risk assessment. In the preamble to the final standard, OSHA concluded that due to methodological limitations, the Ott et al. data would not be used to "draw firm conclusions as to the exact nature of the dose-response curve." However OSHA also concluded that the Ott et al. study did provide "firm evidence of excess lung cancer mortality of workers exposed to arsenicals." (43 FR 19596). Because of the high percentage of pentavalent arsenic in the environment where the study took place, OSHA also relied on the Ott et al. study as evidence of the carcinogenicity of pentavalent arsenic.

Several experts made use of the Ott et al. data for risk assessment purposes subsequent to the publication of the preamble to the final standard. Based on this, in the April 9, 1982 document, OSHA stated that it was reasonable to use the Ott et al. study for risk assessment purposes but did not include estimates of risk based on the Ott et al. study in its preferred estimates.

The CMA-Arsenic Panel disagreed with the use of the Ott et al. study for risk assessment, citing the limitations that were discussed in the preamble to the final standard. While OSHA recognizes these problems with the Ott et al. study, still, a number of the experts during the proceedings reaffirmed the quality of the Ott et al. study noting that both dose and response were characterized well enough for it to be used for risk assessment. Both Dr. Chu and the EPA–CAG employed the Ott et al. data in their risk assessments.

Dr. Crump stated that because of its shortcomings he did not consider the study as well-suited for risk assessment as either the Pinto et al. or the Lee and Fraumeni studies. Nevertheless, he did not consider the shortcomings severe enough to prevent its use in quantitative risk assessment. Dr. Crump also cited consistency with estimates of risk from other studies as affirmation of the use of the Ott et al. study. Dr. Radford also cited the Ott study in his estimates of risk. In fact, he believed that the estimates of risk from Ott et al. data were, in fact, in the correct range of risk and that estimates from the other studies needed to be raised in light of new information.

Some commenters have stated that the arsenic trioxide present in the chemical plant, not the pentavalent arsenic , may be the active carcinogenic agent. If this were the case, given the small quantity of arsenic trioxide in the plant, this would suggest that trivalent arsenic was much more potent than previously thought. In view of the consistent data on the risk from arsenic, the best conclusion is that the pentavalent arsenic is the major factor.

OSHA concludes, in view of all the new expert opinion that the Ott et al. study is an adequate basis for risk assessment and produces estimates of risk consistent with those from other studies.

C. Conclusions

OSHA concurs with many of the experts that the linear regression analysis appears to be the most reasonable approach for estimating the risk presented by occupational exposure to inorganic arsenic. The linear model provides an excellent fit to the data and is consistent with current biologic interpretations. It has been utilized in prior estimates of risk at low levels based on epidemiologic data (41 FR 4673, October 22, 1976).

OSHA considers that relative risks, SMR's, and absolute risk measures are well-established and valid methods of estimating increased risk from exposure to an etiologic agent of disease. While absolute risk (also referred to as excess risk and attributable risk) is not as common a risk measure as the SMR, its use is recommended in epidemiologic textbooks (Ex. 237–J; Ex. 237–Z; Ex. 237–EE). OSHA considers Dr. Crump's absolute risk analysis of the Enterline and Marsh study valuable and has utilized it in reaching a conclusion about findings of the ASARCO studies.

It is clear that inorganic arsenic is a carcinogen, but, the evidence of whether it acts as a promoter or initiator, or both, is indeterminative. As stated earlier, the final determination on the mode of action does not affect the decision to regulate arsenic as a carcinogen and the use of a linear model in such a case is reasonable for making estimates of risk.

OSHA believes that the suggestion of a threshold for carcinogenicity is not nearly as well supported by the evidence, and consequently, OSHA accepts the more broadly supported no-threshold model; this also promotes the interest of worker protection.

OSHA concludes that reasonable estimates of risk for a 45-year working lifetime exposure at 10 $\mu g/m^3$ range from 2.2 excess deaths per 1000 workers to 29 per 1000, and from 148 to 767 excess deaths per 1000 at 500 $\mu g/m^3$. Within this range, OSHA believes the preferred estimate for a 45-year working lifetime is an excess risk of 8 deaths per 1000 at 10 $\mu g/m^3$, 40 per 1000 at 50 $\mu g/m^3$ and 400 deaths per 1000 at 500 $\mu g/m^3$. Additional rationale for these conclusions are stated below.

V. Other Health Issues

A. Animal Studies

The carcinogenicity of inorganic arsenic has been based on the strong evidence of human epidemiologic studies. Most animal studies have obtained negative results. These have been reviewed by IARC (1980) (Ex. 201–13). There have been some animal studies which have obtained positive results. A summary of several recent negative and positive studies and comments will be presented.

Furst (Ex. 202–3A; 232F) reviewed the animal studies concerning the question of carcinogenicity of inorganic arsenic. Furst concluded that "studies in which attempts were made to induce any cancer in experimental animals have proven uniformly negative." He further stated that "the very few experiments which propone to show positive effects do not stand up to any statistical analysis."

Berteau et al. (1978) reported in an abstract of their work on a long-term inhalation study of an arsenic aerosol on "tumor susceptible" mice. This study represents the only major long-term inhalation study involving inorganic arsenic reported in the published literature. His group exposed Strain A female mice to an aerosol (range 0.8 to 5 μm mass medium diameter) of 1% aqueous solution of sodium meta arsenite every working day for the first 26 days and for 20 minutes per day thereafter. The dose was 2.3 mg/kg/day. At the end of the experiment, 208 days, there were no significant differences in

the pulmonary adenomas found in the treated mice compared to the controls.

CMA-Arsenic Panel indicated during the hearings that more details of this study were available and submitted an unpublished report on this inhalation study by Berteau et. al. (Ex. 260). Berteau et al. concluded that sodium arsenite is probably not a carcinogen in mice. They also suggested some possible reasons for the negative findings, including potential inappropriate choices of strain of mice, species, chemical form of arsenic, and exposure level. The author suggested that arsenic may require a co-factor and pointed out that the study had not been conducted for the full lifetime of the animals.

Rodricks and Brett (Ex. 238) in post-hearing comments on the Berteau et al. study noted several deficiencies in the study. First, only one dosage was tested and the exposure level may be too high or too low. One dose level could not determine whether a dose-response relationship existed nor could a no-effect level be estimated. Second, the dosage was selected on the basis of the results of an acute inhalation study, but dosages are usually selected on the basis of subchronic studies, which more closely resemble long-term exposure situations. Third, the concentration of sodium arsenite was not adjusted during the exposure period, thus, the animal did not maintain a constant dose level. It was unclear whether animals were dosed five or seven days per week. Finally, Rodricks and Brett noted that no mortality data were given in the report. They noted that 27 percent of the treated group were sacrificed during the exposure period, only approximately one-third of the animals received gross or histopathological examinations for organs other than the lungs, and that the duration of the study was less than the generally accepted two-years minimum for cancer bioassays in rodents.

Knoth (1966) (Ex. 237–V) noted a significant frequency of tumors in 30 NMRI mice exposed to Fowler's solution (1 percent potassium arsenite) given orally one drop per week for 20 weeks. Adenocarcinomas of the skin, lung and lymph nodes were found. No tumors were seen in 15 control mice of both sexes or their offspring observed up to 2 years. There was an absence of experimental details provided which would be helpful for critical assessment.

Osswald and Goerttler (1971) (Ex. 237–HH) administered daily subcutaneous doses of 0.5 mg/kg of sodium arsenate as a 0.005 percent aqueous solution of sodium arsenate to 24 female Swiss mice throughout pregnancy. Eleven of the treated mice developed lymphocytic leukemia or lymphomas within 24 months after the start of the experiment and none of 20 untreated females which died during the same period developed such tumors. During the 24 month observation period, 13 to 71 untreated progeny and 41 of 97 treated progeny developed lymphomas or lymphocytic leukemia. The IARC working group was critical of this experiment since 19 of 55 control animals and some of the experimental animals were still alive at the time of reporting.

Ishinishi et al. (1977) (Ex. 237–R) administered to groups of 14–23 Wistar King rats a total of 15 intratracheal instillations of 0.26 mg arsenic troxide, 2.5 mg copper ore (containing 3.95 percent arsenic) or 2 mg flue dust (containing 10.5 percent arsenic) alone or in combination with 0.4 mg benzopyrene (BP). No malignant lung tumors were observed in the rats treated with arsenic trioxide or copper ore alone and no statistically significant increase in the incidence of malignant lung tumors was found when these compounds were given in combination with BP. One adenocarcinoma by the lung occurred among 7 surviving rats given instillations of flue dust alone. Many commenters stated this study was only suggestive because of the small number of animals and would require more studies for proper evaluation.

Ivankovic et al. (1979) (Ex. 237–T) administered to a group of 25 male BD IX rats a single intratracheal instillation of 0.1 mlof an arsenic-containing mixture (calcium arsenate, copper sulfate and calcium hydroxide), which is known as Bordeau mixture (dose of arsenic, 0.07 mg). Ten rats died within the first week after treatment and the remaining 15 were observed for their lifespan. Nine treated rats developed lung lumors (7 bronchiogenic adenocarcinomas and 2 bronchiolar-alveolar-cell carcinomas). No lung tumors occurred in 25 controls given intratracheal instillations of saline. It should be noted that the experiments of Ivankovic et al. are incomplete since they do not include simultaneous studies on individual ingredients in the Bordeau mixture. That is, no copper sulphate or calcium hydroxide or copper sulphate plus calcium hydroxide exposure groups were studied (Exs. 201–13, 232F).

Rudnai and Borzsonyi (1981) (Ex. 237–LL) administered subcutaneously an aqueous solution of arsenic trioxide to lung tumor susceptible mice. A dose of 1.2 ug/g of arsenic trioxide was administered to pregnant LAJI: CFLP mice in a single dose on the 15. 16, 17 or 18th day of pregnancy. The offspring of the treated mice were given subcutaneouly 5 μg arsenic trioxide per day per animal for 3 days. Lung tumor incidence was significantly higher in animals treated on the 16th day and again during neonatal life (12/19, 63.1 percent) than in controls (3/17, 17.6 percent). Rudnai and Borzsonyi described the lung tumors histologically in part as papillary adenomas and as malignant adenocarcinomas.

IARC (Ex. 201–13) analyzed the animal studies and came to the conclusion that inorganic arsenic had not yet been demonstrated to be carcinogenic in animal studies. The CMA also reached that conclusion in its pre-hearing submission. Dr. Rodricks, an expert in toxicology, made the point that none of the studies were of the quality required for the National Cancer Institute Bioassay programs (Ex. 226).

OSHA concluded in the preamble to the final standard that a clear animal study demonstrating the carcinogenicity of inorganic arsenic had not been demonstrated and that continues to be OSHA's conclusion, though there are some studies indicating positive results.

OSHA does not believe that the lack of a good animal study detracts from its conclusion that arsenic is a human carcinogen. OSHA's statutory responsibility is to protect employees. The overwhelming evidence associating inorganic arsenic exposure with excess lung cancer in exposed employees clearly outweighs the lack of a clear definitive animal model. Dr. Furst in a post-hearing submission argued that agencies require positive animal, human and short-term tests before classifying a substance as a carcinogen. OSHA is not aware of any regulatory agency requiring all three types of evidence. OSHA along with NIOSH, IARC and WHO-AWG concludes that the strong human data alone is a strong basis justifying reducing employee exposure to inorganic arsenic.

B. Mutagenicity and Cytogenetic Effects

Mutagenicity is the property of inducing alterations in the information content (DNA) of an organism or cell that are not due to the normal process of recombination. Cytogenetic effects involve changes or damage to the genetic material which does not necessarily involve a mutational change. Many of these effects can be measured with short-term tests or assays. These changes in DNA or genetic material may be an early indicator that a substance may be a potential carcinogen.

Leonard and Lauwerys (1980) (Ex. 237–Y) concluded that most of the studies performed on the mutagenic and cytotoxic activity of arsenic have provided positive results. These studies

involve experiments on microorganisms, plant material and drosophila as well as observations on the ability of this metal to induce, in vitro and in vivo, chromosomal aberrations in mammalian cells. In contrast, a review by Simmon (1982) (Ex. 202–3A) concluded that the evidence for inorganic arsenic being a hazard because of its mutagenic activity is poor. This was the view of the CMA-Arsenic Panel. Simmon indicated that the majority of arsenic compounds are not capable of inducing point mutations in mammalian or microbial cells and suggested weaknesses in studies on DNA repair, as well as advising caution in interpreting the clastogenic effects. A summary of some of the literature will be presented.

Nishioka (1975) (Ex. 237–GG) and Kanematsu et al (1980) (Ex. 237–U) have demonstrated that arsenicals have caused an increase in unscheduled DNA repair (i.e. damaged the DNA so that repair activity was abnormally high). This is called the bacterial rec-assay system. The rec-assay system using recombination -proficient and deficient strains of Bacillus subtilis was used to screen a large number of metal compounds for mutagenicity. Nishioka found that both As+3 and As+5 produced positive rec-assay results. It was also shown that arsenic compounds ($AsCl_3$ $NaAsO_2$) having a valence of +3 seem to be more mutagenic than (Na_2HAsO_4) possessing a valence of +5 because more distinct rec-effect was seen in the former than in the latter. In 1980, Kanematsu et al. again demonstrated that strong positive rec effects were noted with both trivalent and pentavalent compounds of arsenic (As_2O_5, As_2O_3, $AsCl_3$, $2AsO_5$, Na_2HAsO_4).

Simmon (1982) (Ex. 202–3A) was critical of the two Japanese studies because, in an unpublished report to the Koppers Co., Pierce and Simmon (1981) could not reproduce their results. The report by Pierce and Simmon was not submitted to the record.

Simmon (1982) (Ex. 202–3A) had pointed out that a number of assay systems had demonstrated that arsenic was not mutagenic. Lofroth and Ames (1978) reported that neither arsenite nor arsenate was mutagenic in the Salmonella/microsome assay, commonly known as the Ames Test. Ikeshelashville et al. (1980) reported that sodium arsenate had no effect on the fidelity of DNA synthesis using E. Coli DNA polymerase activity. Rossman et al. (1980) reported results that showed arsenate was not mutagenic to either E. Coli or to Chinese hamster cell line V79, although Rossman et al (1977) (Ex. 237 KK) had previously reported on positive mutagenic effects of arsenite in E. coli.

In contrast, a number of recent studies have reported positive effects of both trivalent and pentavalent forms of arsenic. DiPaolo et al. (1979), found that arsenate causes cell transformation in Syrian hamster embryo cells and Castro et al. (1979) found arsenite to enhance the frequency of transformation induced by the Simian adenovirus SA 7. Paton and Allison (1972) found that both arsenite and arsenate significantly increased chromosmals aberrations in leukocyte culture. Petres et al. (1977) (Ex. 237 JJ) found that arsenates cause transformation in human peripheral lymphocytes. Ohno et al (1982) reported statistically significant increases in frequency of induced sister chromatid exchanges in Chinese hamster cells resulting from treatment with sodium arsenite, sodium arsenate and arsenic pentoxide. Larramendy et al. (1981) (Ex. 237 X) reported that non-toxic concentrations of inorganic arsenic salts (sodium arsenate and sodium arsenate) caused transformation of Syrian hamster embryo cells (HEC) and induced sister chromatid exchanges (SCE) and chromosome aberrations of HEC and human peripheral lymphocytes. The authors concluded that the induction of SCE and chromosomal aberrations by metals reemphasized the sensitivity of cytological assays and their importance for detecting genetic damage caused by carcinogens.

Some observations have been made on the somatic cells of people exposed to arsenic for medical or professional reasons and in the workplace. An increased frequency of chromosomal aberrations has been observed among workers exposed to inorganic arsenic compounds, as well as in patients who had taken drugs containing arsenic (Petres et al. 1977 (Ex. 237 JJ); Nordenson et al. 1978).

As the above review of the literature indicates, there is a growing number of studies which have demonstrated positive mutagenic and genetic effects by both trivalent and pentavalent forms of arsenic. The number of positive studies is sufficient to outweigh the contrary views of Simmon and CMA-Arsenic Panel which appeared to be based principally on negative results in some test systems. The Agency now believes that the positive mutagenicity results support the strong human evidence for the carcinogenicity of inorganic arsenic. However, the human carcinogenicity data are so strong that even if the mutagenicity data were consistently negative, OSHA would still conclude that inorganic arsenic is a human carcinogen.

C. Teratologic and Reproductive Studies

The reproductive or teratogenic effects of arsenicals were not addressed in the preamble to the final OSHA standard. A few human epidemiologic studies and animal studies have provided evidence of arsenic-induced reproductive or teratogenic effects. Animal studies have shown that sodium arsenate induces developmental malformations in a variety of test animals: embryo chick, hamster, rat, and mouse. Hood (1982) (Ex. 202–3A) has recently reviewed the toxicology of prenatal exposure to arsenic. A summary will be presented.

Ridgeway and Karnosky (1952) reported chicken embryos injected on the fourth day with sodium arsenate were stunted and had mild micromelia and abdominal edema. The first detailed report of arsenic teratogenicity in a mammal was that of Ferm and Carpenter (1968). They administered intravenously high doses of sodium arsenate to hamsters on gestation day eight which resulted in a high percentage of malformed fetuses, increased prenatal mortality and resorbed litters.

Hood et al. (1977) (Ex. 237 P) compared the prenatal effects of oral and intraperitoneal administration of sodium arsenate in mice. Intraperitoneal administration had a considerably greater effect than oral administration on prenatal mortality, reduction of fetal weights, and occurrence of fetal malformation. Hood et al. (1977) also studied the effects of intraperitoneal injection of sodium arsenite in mice and found increases in prenatal mortality and developmental malformations.

One important problem with most studies involving teratogenic effects of arsenic was the use of high doses which often resulted in more than 10% death rates. Several reproductive studies in animals have been negative involving exposure to low levels of arsenic. In one such study, Kojima (1974) administered arsenic trioxide at 10, 50, and 100 ppm in the food to Wistar rats prior to and during gestation. This treatment caused no significant effect on the number of litters. This study demonstrated no significant reproductive effects but did not assess the effects on the unborn fetuses. No teratogenic studies in animals exposed to inorganic arsenicals by inhalation have been reported.

Some human data have been reported on teratogenic and reproductive effects of workers employed in the smelting industry. Studies of pregnant women

employed at the Ronnskar smelter in Sweden provided information with direct bearing on the issue of human teratogenicity of inorganic arsenicals. Children born to women who worked during pregnancy at a Swedish copper smelter and were exposed to airborne arsenic showed a significantly higher frequency of congenital malformations (Nordstrom et al. 1979). The frequency of all malformations in the children of women employed at the smelter was twice as high as that in the children of other women in the region. A 5-fold higher frequency was noted for multiple malformations. At this stage the carcinogenicity data remain the best for basis for regulatory decision.

D. Interconversion of Pentavalent to Trivalent Arsenic

In the preamble to the final standard, OSHA concluded that though the available evidence went both ways, on balance the stronger data indicated that there was probably little or no conversion of pentavalent to trivalent arsenic in the body. Given the unknown relevance of acute toxicity and biochemical reactions of trivalent and pentavalent arsenic to the assessment of carcinogenic risk and the findings that pentavalent arsenic was probably not converted to trivalent arsenic, OSHA relied principally on the findings of the epidemiological studies, expert opinion and general policy considerations in deciding to regulate pentavalent arsenic as a carcinogen.

Since promulgation of the final regulation, new data concerning interconversion of pentavalent to trivalent arsenic have become available. Yamauchi and Yamamura (Ex. 211) and Vahter have studied the metabolism of pentavalent arsenic. Yamauchi and Yamamura studied three men who ingested seaweed known to be rich in pentavalent arsenic. Measuring the amount of arsenic excreted by the three subjects, Yamauchi and Yamamura concluded that most of the pentavalent arsenic was reduced to trivalent arsenic within the body and that the trivalent arsenic was subsequently methylated to monomethylarsonic acid and dimethylarsine acid. Vahter administered pentavalent arsenic in single oral or intravenous doses to mice and found trivalent arsenic in the urine of the mice. Vahter concluded that "it is evident from the data that trivalent inorganic arsenic is present in the plasma and urine of mice exposed to inorganic pentavalent arsenic."

Dr. Radford, at the July 1982 hearings stated, based on the new evidence: "arsenates are converted in significant amounts in the body to trivalent arsenic, perhaps as part of the pathway for excretion in the urine of methylated forms" (Ex. 207). Dr. Radford also noted that "there is yet no evidence that bronchial tissue can reduce inhaled pentavalent arsenic, nor is there evidence it does not" and he concluded that he supports OSHA's regulation of both trivalent and pentavalent inorganic arsenic as a carcinogen.

Dr. Edwin Woolson (Ex. 218) presented his analysis and conclusion that the evidence available did not indicate that pentavalent arsenic converted to trivalent in vivo. He presented an evaluation of Yamauchi and Yamamura, and Vahter and the reasons he disagreed with those author's conclusions. Regarding Yamauchi and Yamamura, he commented that they had only accounted for a small percentage of the arsenic ingested. The percentage of trivalent was greater excreted than ingested, but the total excreted was less than that ingested.

Dr. Woolson also commented on Vahter's report, suggesting that the small amounts of trivalent arsenic found in the urine of the mice could be due to experimental conditions. Dr. Woolson stated that studies by Crecelius (1977), Peoples and Parker (1979) and Tam et al. (1979) do not support the conversion of arsenate to arsenite in vivo.

There remains uncertainty on the question of conversion of arsenate to arsenite. OSHA believes that this question is not determinative of any major issue before it. Other types of evidence available, namely, studies in humans, are more relevant for regulatory action.

E. Carcinogenicity of Pentavalent Arsenic

As discussed above there is little controversy about the carcinogenicity of trivalent arsenic. In the preamble to the final standard, OSHA concluded that it was necessary to regulate pentavalent arsenic as a carcinogen as well. OSHA based its position primarily on the Ott et al. study which provided epidemiologic evidence that pentavalent arsenic is a carcinogen, and a significant body of expert opinion including representatives of the National Cancer Institute and the National Institute for Occupational Safety and Health who recommended that pentavalent arsenic be regulated as on occupational carcinogen.

The CMA-Arsenic Panel (Ex. 202–3, 232, 250) strongly contended that inorganic pentavalent arsenic is not carcinogen. CMA criticized the Ott el al. study and questioned the reliability of the data for quantitative risk assessment. Dr. Marsh (Ex. 202–8) in a review of the Ott study concludes:

> The overall weakness of the study design, the uncertainties associated with exposure determination, and the probable biases related to the magnitude of the computed risk ratios do not support the utilization of these epidemiologic data for risk assessment purposes.

OSHA in the final standard's preamble concluded that the Ott et al. study provided strong evidence associating excess respiratory cancer with pentavalent arsenic exposure but it would not be used to demonstrate dose-response because of limitations in the exposure data.

Several witnesses at the recent hearing stated that the Ott et al. study, despite its limitations, could be a basis for risk estimation. Dr. Crump stated:

> Because of these shortcomings, I do not consider the Ott study to be as suitable for quantitative risk assessment as either the Pinto et al. study or the Lee and Fraumeni study. However, I do not consider these shortcomings severe enough to prevent its use in quantitative risk assessment (Ex. 206, p. 12).

Dr. Radford (Ex. 207) stated that the Ott et al. study provided a sufficient basis for risk assessment and a published paper by Dr. Blejer and Wagner (Ex. 237 I) takes this position as well.

NIOSH has stated:

> With relation to the paper by Ott et al. it seems to be a reasonably valid study of the results from exposure to arsenates. Although it is true that the employees involved were exposed to both arsenites and arsenates the authors state that 95 percent of the exposure was to arsenates and only 5 percent to arsenites. It seems not to be illogical or unjustified to attribute most, if not all, the excess of malignancies in the exposed group (incidence rate almost 60 percent greater than that in the control group) to the pentavalent arsenical compounds (Ex. 192A).

CMA argued that OSHA should place more reliance on the Nelson et al. study of Washington State orchardists who were intermittently exposed to pentavalent arsenicals, which did not observe excess lung cancer risk. CMA stated that there was an attempt to quantify exposures. OSHA agrees now that there was an attempt to quantify exposures in that study. Nevertheless, the study does have problems with ascription of exposure, especially since orchard work is seasonal. Also, the study by Nelson et al. is limited by the small number of persons studied, as noted by the authors (Ex. 1A–28).

A draft of a later study of orchardists in Washington, submitted by Milham (Ex. 237 FF), does suggest some excess risk for this group. Excess lung cancers were observed among orchardists. Milham noted that lead arsenate

insecticide, which is a pentavalent form of arsenic, was used heavily in the orchard areas. This study lacks exposure data.

As discussed in Section III, Koppers Company submitted studies performed by Tabershaw Occupational Medicine Associates of workers at two wood-preserving plants using chromated copper arsenate (Ex. 202–6B). Both studies were cross-sectional health surveys of workers exposed to very low levels of pentavalent arsenic (less than 6 $\mu g/m^3$). Because of several methodologic limitations characteristic of cross-sectional surveys which limit their usefulness for studying occupational cancer, as well as the small numbers of employees surveyed, OSHA judged that no conclusions could be drawn from these studies concerning cancer risk of workers exposed to the chromated copper arsenate wood preserving process.

OSHA continues to conclude that pentavalent arsenic should be regulated as a human carcinogen. The Ott et al. study strongly demonstrates an association between exposure to pentavalent arsenic and excess lung cancer risk. The study is not as strong a basis for risk assessment as some of the others, but the opinions of several experts presented at the hearings indicated that the study can be a basis for risk assessment. The mutagenicity studies have shown that both pentavalent and trivalent arsenic can produce positive results in a number of short-term tests. OSHA now concludes that the positive mutagenic responses with pentavalent arsenic compounds add support to epidemiologic data and expert opinion which support the conclusion that pentavalent inorganic arsenic is a human carcinogen.

F. Essentiality

Uthus, et. al. (1982) (Ex. 202–3A) reviewed the effects of arsenic deprivation in laboratory animals and concluded that "arsenic is an essential element for several animal species." The authors suggested that arsenic appears to affect arginine metabolism, and that the signs of arsenic deprivation may be influenced by arginine, zinc and manganese.

Anke, et al. (1976) described arsenic deficiency in goats and minipigs fed semisythetic diets containing less than 50 ppb of arsenic. They reported impaired reproduction, decreased birth weights, increased prenatal mortality, and lower weight gains in second generation animals, which they attributed to deficiency of arsenic in the diet. These birth defects were not noticed in control animals fed the semisynthetic diet supplemented with arsenic at 350 ppb. Nielson et al. (1975) fed rats only 30 ppb of arsenic in a specially formulated diet, and observed the following effects attributed to arsenic deficiency: rough hair coat, low growth rate, decreased hematocrit, and increased osmotic fragility of red blood cells. Nielsen and Shuter (1978) have reported that dietary arsenic has a physiological function in growing chicks. Dr. Frost (Ex. 202–2) reported that feeding arsenic stimulated growth, is believed to control diseases in poultry and swine, and to improve feed efficiency.

Mertz (202–7C) in 1981 reviewed the data concerning a number of essential trace elements. Mertz pointed out that deficiency studies of inorganic arsenic in animals suggest that inorganic arsenic may be an essential trace element in animals. Mertz also pointed out that essentiality is generally acknowledged when it has been demonstrated by more than one independent investigator and in more than one animal species. By these criteria, arsenic is now considered an essential element for several species. Mertz reports that no deficiency role for arsenic in man is known and that the functional role for arsenic is unknown.

Dr. Nielsen believes that arsenic is essential for animal life but stated "today, the majority of nutrition community does not regard arsenic as an essential nutrient for any animal" (Ex. 202–3A, p. 15–16). Harding-Barlow (Ex. 202–3E) suggested that arsenic is an essential element in animals, and that it seems highly likely that it is essential in humans. Harding-Barlow suggested that there may be a threshold for carcinogenicity for essential elements.

Dr. Rodricks (Ex. 226) stated that there is no direct evidence that arsenic is essential for humans. Dr. Rodricks commented that "assuming that arsenic plays a nutritional role (and this is only an assumption) there is no reason to maintain that the beneficial properties of the element are somehow related to its carcinogenic properties. These two biological properties could be completely independent, and display quite distinct dose-response relationships."

Dr. Crump stated,

> The fact that known carcinogens are necessary constituents of mammalian systems is also consistent with a non-threshold hypothesis. A non-threshold hypothesis does not imply that individuals exposed to a carcinogen must get cancer, but only that they must have some chance of getting cancer. Some individuals do get cancer and it is impossible to rule out the possibility that some of these cancers are due to naturally occurring and even essential body constituents. A slight elevation in cancer incidences might be a small biological price that mammalian species must pay for larger benefits derived from substances such as estrogens or trace metals (Ex. 212, p. 6).

There is good evidence that arsenic in its organic form (which is not regulated by OSHA as a carcinogen and as for which there is no evidence indicating carcinogenicity) is a growth stimulant for poultry. Some experts believe that ingested arsenic is an essential nutrient for some species of animals and other experts have not been convinced. It should be noted that all of the essentiality experiments have utilized ingestion as the route of administration.

There is no evidence or tests that indicate that arsenic in any form is an essential element in humans though some experts have speculated on this. Humans do ingest some arsenic in organic form when eating some seafood. However, those metals, such as iron and manganese, for which there is proof of essentiality generally must be ingested to serve their physiologic function. They may be highly toxic when inhaled, however.

However, OSHA is regulating the inhalation of inorganic arsenic based on strong human evidence of carcinogenicity. There is no evidence available indicating that inorganic arsenic is an essential element in humans. In any case, a chemical can be essential and still be carcinogenic without a threshold. The very strong evidence associating inhalation of inorganic arsenic with excess risk of lung cancer and the well supported risk assessments are not affected by hypotheses that arsenic may be an essential trace element.

G. Mode of Action

CMA (Ex. 202–3, p. 90) contended that arsenic was not a genotoxic carcinogen and hence a no-threshold linear dose-extrapolation model was inappropriate for estimating risk from exposure to arsenic. As a basis for their statement that arsenic was not a genotoxic carcinogen, CMA maintained that arsenic had no effect on the accuracy of DNA synthesis, was an essential trace element, and that respiratory cancer risk declined 30 years after cessation of exposure.

Weisburger and Williams (1980) developed a classification system for carcinogenic agents placing them into two categories, namely, genotoxic agents and epigenetic agents. Genotoxic agents are those that are capable of causing DNA damage to cells that creates the potential for oncogenesis. In this category, Weisburger and Williams

included direct-acting carcinogens, procarcinogens and inorganic carcinogens. Epigenetic agents do not themselves damage the DNA but act through an indirect mechanism to increase the susceptibility of cells to genotoxic agents or to stimulate the carcinogenic action of a genotoxic agent. Promoters, co-carcinogens, immunosuppressors and hormonal mediators may be classified as epigenetic agents.

There is not consensus within the scientific community as to the criteria for distinguishing genotoxic from epigenetic carcinogens. Nor is there consensus as to whether genotoxic and epigenetic carcinogens should be regulated differently. OSHA does not have to decide if arsenic is a genotoxic or epigenetic carcinogen in order to determine whether arsenic poses a significant cancer risk to exposed workers. The epidemiologic evidence for the carcinogenicity of inorganic arsenic at relatively low exposure levels overrides theoretical arguments based on hypotheses of mode of carcinogenic action. As discussed in Section IV, Quantitative Risk Assessment, for many reasons, OSHA determined that a linear model was appropriate for predicting the risk of lung cancer mortality from inorganic arsenic exposure.

In addition, OSHA considers that CMA's contention that arsenic is not a genotoxic carcinogen is not supported by the available evidence. First, positive effects on DNA have been obtained when inorganic arsenic was tested for its mutagenicity and its ability to cause chromosomal aberrations. Second, as discussed in Section V–F, Essentiality, even if arsenic was definitely proven to be an essential trace element, which it has not been, a no-threshold model would not necessarily be inappropriate. Third, evidence for a decline in respiratory cancer risk after cessation of exposure is less than definitive, as discussed in Section III, Epidemiologic Studies. In summary, there is evidence that arsenic may affect the cell's genetic mechanism and damage DNA and consequently be genotoxic.

H. Power Plants

The Edison Electric Institute argued that significant risk was not demonstrated to power plant workers exposed to arsenic when cleaning boilers (Ex. 245). The Institute did not participate in any of the earlier stages of the proceeding, presented no evidence as to employee exposures, and only commented that exposures were intermittent. No information on processes was submitted either.

As in the smelter environment, power plant workers are exposed to arsenic released in a high temperature process with many other chemicals present. If the employees are exposed, as an example, to 100 $\mu g/m^3$ of arsenic for eight hours every two weeks, their cumulative exposures would be equivalent to an employee exposed every working day to 10 $\mu g/m^3$. The predicted level of risk of 8 excess deaths per 1000 exposed workers at this level would be significant. Further, the one study of power plant workers that OSHA is aware of does indicate excess lung cancer risk for employees working in a power plant utilizing coal containing arsenic as an impurity (Ex. 237H). Accordingly OSHA concludes a significant risk is presented to power plant workers and there is no basis for excluding them from the standard.

The Edison Electric Institute did not detail the cleaning process. If it is a maintenance operation with intermittent exposures, the arsenic standard indicates that a good respirator program with sign posting, training, and hygiene facilities to protect employees may be an appropriate control strategy. If exposures are continuous, additional control strategies would be appropriate.

VI. Summary of Evidence, Conclusions and Significant Risk

A. OSHA's Approach

OSHA's overall analytical approach for setting worker health standards is a four-step process consistent with recent court interpretations of the OSH Act and rational, objective policy formulation. In the first step, risk assessments are performed where possible and considered with other relevant factors to determine whether the substance to be regulated poses a significant risk to workers. Then, in the second step, OSHA considers which, if any, of the proposed standards being considered for that substance will substantially reduce the risk. In the third step, OSHA looks at the best available data to set the most protective exposure limit necessary to reduce significant risk that is both technologically and economically feasible. In the fourth and final step, OSHA considers the most cost-effective way to achieve the objective.

The Ninth Circuit's remand provides that OSHA consider the issues presented by the first two steps and some of the elements of the third step. This notice and rulemaking directly addresses those matters. A cooperative evaluation by technical experts from OSHA, the smelter companies and the United Steelworkers, which is not part of this rulemaking, gives additional consideration to the final steps.

It is appropriate to consider a number of different factors in arriving at a determination of significant risk with respect to inorganic arsenic. The Supreme Court gave some general guidance as to the process to be followed. It indicated that the Secretary is to make the initial determination of the existence of a significant risk, but recognized that "while the Agency must support its finding that a certain level of risk exists with substantial evidence, we recognize that its determination that a particular level of risk is 'significant' will be based largely on policy considerations." (*IUD v. API*, 448 U.S. 655, 656, n. 62). In order for such a policy judgment to have a rational foundation, it is appropriate to consider such factors as the quality of the underlying data, the reasonableness of the risk assessment, the statistical significance of the findings, the type of risk presented and the significance of the risk.

These factors were mentioned in the April 9, 1982 document as the basis to provide guidance for determining the significance of risk. No participant in the proceeding disagreed with this approach. OSHA continues to believe that those factors provide a good analytical framework for considering the issue of significant risk. OSHA's detailed analysis has been presented in the body of this document. The most important conclusions are summarized here.

B. Quality of Underlying Data

The first factor is the quality of the underlying data. The underlying data upon which the risk assessment for inorganic arsenic are based are high quality epidemiologic studies in an occupational environment. Three studies were available to OSHA and the other experts in published form for risk assessment purposes prior to the April 9, 1982 document. The studies by Lee and Fraumeni and by Pinto and Enterline involved workers exposed to inorganic arsenic in copper smelters. In the study by Ott et al., the workers studied were exposed to the pentavalent form of arsenic in a pesticide manufacturing plant. Subsequent to April, additional studies became available which could be used for quantitative risk assessment, including studies by Lee-Feldstein, Enterline and Marsh, and Higgins et al. All of the above studies are good epidemiologic studies. All clearly associated inorganic arsenic exposure with substantial excess risk of lung cancer, and their authors so conclude. All these studies have good follow-up,

generally reasonable exposure estimates and indicate that the risk was proportional to the degree of arsenic exposure.

There were also a number of studies in other chemical industries and smelters reported in the literature and discussed in the preamble to the final standard, which demonstrated an increase in lung cancer among workers exposed to inorganic arsenic but which are not as strong a basis for quantitative risk assessment. These studies included Baetjer et al., Kuratsune et al., Hill and Faning, and others.

Subsequent to 1977, new studies in this category have been completed which reach the same conclusion, that exposure to inorganic arsenic is associated with increased risk of lung cancer in the occupational setting. These studies, discussed above, are Mabuchi et al., Wall, and Axelson et al. However, the dose data were not quantified in these studies and therefore they do not constitute as good a basis for quantitative risk assessment as the other studies which provide better quantification of exposure.

The two studies which showed no excess risk, authored by Cooper and Tabershaw Occupational Medicine Associates, included small numbers of employees exposed to arsenic. In the study by Cooper, no attempt was made to analyze the mortality of employees known to be exposed to arsenic and the study by Tabershaw was a cross-sectional survey with extremely limited ability to detect any excess of cancer.

Based on both the high quality new human data and the high quality earlier human data associating arsenic exposure with increased risk of lung cancer, OSHA concludes, as discussed in detail above, that inorganic arsenic is a carcinogen in the occupational setting. These are the conclusions of the National Institute of Occupational Safety and Health, the International Agency for Research on Cancer, the Environmental Protection Agency Carcinogen Assessment Group, the World Health Organization-Arsenic Working Group, and many scientists whose views are discussed in this preamble, the data in the record and in the preamble to the final standard.

The Chemical Manufacturers Association-Arsenic Panel in their prehearing comment indicated that they might disagree with the conclusion that inorganic arsenic was carcinogenic in the occupational setting. However, Dr. Lederer, representing the CMA stated:

> I would like to make clear that I do not dispute that there is an association between arsenic exposure and respiratory cancer. Likewise, the evidence indicates that reducing arsenic exposure apparently reduces the carcinogenic risk (Tr. p. 356, 7/15/82).

In response to a question he stated that this was the CMA's view as well, though the CMA "feels there are various factors that also have to be considered" in addition. (Tr. p. 356, 7/15/82).

Several other factors, previously discussed in depth, will be briefly reviewed here. OSHA believes that the strong human data associating inorganic arsenic with excess lung cancer risk are much more important than the following factors.

The first factors concern experimental studies of arsenic. OSHA agrees with the position of CMA, IARC and others that there is no clear animal model demonstrating excess malignant tumors in test animals resulting from arsenic exposure. OSHA believes that the weight of the evidence now indicates that inorganic arsenic in both its trivalent and pentavalent forms is mutagenic in most types of short term tests. CMA's judgment to the contrary is based principally on negative results in "Ames" type tests. But a number of other kinds of mutagenicity tests indicate positive results.

Dr. Harding-Barlow (Ex. 202–3E) and Dr. Frost (Ex. 202–2) generally believed that arsenic is not carcinogenic. In addition to the above factors they refer to the presence of various other chemicals in the human studies, to the fact that organic arsenic is a growth stimulant for some animals and to the possibility that arsenic may be an essential nutrient for humans.

As discussed above, work by Brown and Chu, Lubin et al., Mabuchi et al., Enterline and Marsh and Higgins et al. provide clear evidence that smoking and other contaminants such as sulfur dioxide present in the work environment are not major factors in the carcinogenesis seen. These studies analyzed the effects of these potentially confounding factors and the results indicated that inorganic arsenic was likely to be the major contributing factor to the excess risk. There is no evidence that arsenic is an essential element for humans. It is also likely that an element can be essential at low levels and still be carcinogenic with no threshold.

OSHA also concludes as discussed above that pentavalent forms of inorganic arsenic are carcinogenic. The Ott et al. study clearly associates pentavalent arsenic exposure with substantial excess risk of lung cancer. In addition, the short term tests of pentavalent arsenic are mostly positive, a number of experts view pentavalent arsenic as carcinogenic, and considering the totality of evidence on inorganic arsenic leads to this conclusion.

To reiterate, there are strong data indicating that inorganic arsenic is carcinogenic in humans. Some of the human studies provide an excellent basis for quantitative risk assessment. Other issues do not call into question these conclusions, and in most cases support them.

For purposes of risk analysis, the data base for inorganic arsenic is of unusually high quality. The April 9, 1982 proposal regarding significance of risk stated that the studies relied upon for risk analysis "provide a sound data base for performing risk assessments because of their excellent follow-up, reasonable exposure estimates, and strong dose-response relationship. They provide considerably more than the minimum data necessary for attempting risk assessment" (47 FR 15364). OSHA also characterized the quality of the available data as "higher than that needed to place reasonable confidence in the risk assessment predictions" (47 FR 15365).

Most potential occupational carcinogens have not been studied with regard to their effects in humans. Even if there are epidemiologic studies of the effects of a carcinogen, such studies usually lack historical exposure data and may not be designed and conducted as well as the epidemiologic studies of populations exposed to inorganic arsenic. In the future, it is likely that OSHA will be determining the significance of risk from exposure to carcinogens and regulating carcinogens based on data that are not as strong as the arsenic data and based on animal studies. Therefore, OSHA's significant risk determination for inorganic arsenic should be viewed as having an exceptionally strong basis.

OSHA wishes to make clear that its determination as to the strong association between inorganic arsenic exposure and increased risk of lung cancer is in the occupational setting. As discussed above, it is reaching no conclusions about the effects of arsenic on drinking water or airborne exposure to the general (not occupationally exposed) population.

OSHA reiterated in the April 9th document its determination in the preamble to the final standard that the inorganic arsenic standard covers only occupational exposure to inorganic arsenicals. The estimates of risk would not be applicable to organic arsenicals for which OSHA has not data indicating carcinogenicity. In addition, OSHA pointed out at 43 FR 19613 that arsenic in preserved wood has substantial

chemical differences from other arsenicals, after the reaction, and therefore, based on the existing record, it did not believe it appropriate to regulate preserved wood. These matters were not specifically addressed by the parties in this proceeding and therefore OSHA is not reexamining this position.

C. Reasonableness of the Risk Assessment

The second factor to be considered after the strength of the underlying data, is the reasonableness of the risk assessment. In the April 9th document OSHA presented three risk assessments (47 FR 15362.) OSHA then stated its preliminary judgment that:

> * * * reasonable confidence can be placed in the estimates of the risk presented. In addition to the good exposure and response documentation, as discussed above the dose-response curves demonstrate a good fit of the linear model to the measured data, increasing confidence that a linear model through the origin is the appropriate model to use. It should be emphasized that the risk analyses are based on human data and not on animal data. Therefore, they do not have the uncertainties associated with extrapolating animal data to man (47 FR 15365).

OSHA stated as its preliminary estimate of risk that:

> OSHA believes that those estimates with Dr. Chu's high side estimates excluded (which were based on his estimates of exposure levels) are preferable for the reasons stated. These are the estimates presented above by OSHA as its preliminary analysis. * * * The(se) estimates from the risk analysis which OSHA believes are most reasonable based on the data now before it are (therefore) the following: The excess risk of lung cancer for a working lifetime of exposure is 500% to 620% (375 to 465 excess deaths per 1000 employees) at 500 $\mu g/m^3$, 50–68% excess risk (38 to 51 excess deaths per 1000) at 50 $\mu g/m^3$, and 10–14% excess risk (7.7–10 excess deaths per 1000 employees) at 10 $\mu g/m^3$ of inorganic arsenic based on the linear model (47 FR 15364–5).

OSHA's final estimates of risk for a working lifetime of exposure of 45 years range from 2.2 to 29 excess deaths per 1000 workers at 10 $\mu g/m^3$, 11.2 to 146 excess deaths per 1000 to 50 $\mu g/m^3$ and 148 to 767 excess deaths per 1000 at 500 $\mu g/m^3$. Within this range, OSHA's preferred estimates for a 45-year working lifetime are approximately 400 excess lung cancer deaths per 1000 exposed employees at 500 $\mu g/m^3$; 40 excess deaths per 1000 at 50 $\mu g/m^3$ and 8 excess deaths per 1000 at 10 $\mu g/m^3$. OSHA wants to make clear that these single point estimates are approximations and are not to be thought of as exact numbers. The science of risk assessment is not certain enough to permit exact estimates and the April 9 document made clear that OSHA's estimate was a range and that a range of estimates was reasonable. See also the discussion in section IIA.

The April 9th document discussed three specific questions about the risk assessments. The first was whether a linear or quadratic model was more appropriate. OSHA in the April 9th document preliminarily concluded that the linear model was preferred because it fit the data better but that a quadratic model would also be reasonable in the case of inorganic arsenic. Subsequent evidence strongly confirms that a linear model is more preferable to a quadratic model in the case of inorganic arsenic. Dr. Crump demonstrated by using a Chi-squared statistic that a linear model fits the data much better than a quadratic model. Dr. Crump stated "these analyses indicate that it is reasonable to use a linear model to assess risk from occupational exposure to arsenic, but it would not be reasonable to use a quadratic model" (Ex. 206, p.5).

A second question discussed was the correct estimates of dose at the Tacoma smelter in the past. Dr. Chu utilized estimates indicating that exposures were twice as high pre-1948 than in 1973, leading to higher estimates of risk than Clement Associates who utilized estimates by Pinto and Enterline that exposures were 5 to 10 times higher pre-1948 than in 1973. OSHA preliminarily concluded in the April 9th document that both estimates were reasonable but preferred Clement's. However, a table of urinary arsenic levels published in Enterline and Marsh (1982) (Ex. 201–9, p. 4) indicates that levels were roughly twice as high in 1948, tending to support Chu's higher estimates of risk. Dr. Enterline still believes exposures were 5 to 10 times higher pre-1948.

A third question presented was use of the Ott et al. study for risk assessment purposes. The Ott study clearly showed an association between pentavalent arsenic exposures and excess risk of lung cancer. OSHA indicated in the April 9th document that it was reasonable to utilize it, but preferred the estimates which did not incorporate it and used only the stronger studies. OSHA had stated in the preamble to the final standard that because of some analytic difficulties it would not use the Ott et al. study as a basis for a determination of whether dose-response existed. CMA in its prehearing brief argued the Ott et al. study was not adequate for risk assessment purposes because of the analytic difficulties and because it claimed that the excess risk might have been due to other chemicals. Dr. Crump and Dr. Radford, however, stated in this hearing that the Ott et al. study characterizes both dose and response well enough for it to be a basis for a quantitative risk assessment. Blejer and Wagner concluded this as well. The risk estimates based on the Ott et al. data are not very different than those based on the other studies. Based on these experts' views and the similarity of results, OSHA concludes that there is sufficient characterization of dose for the Ott et al. data to be utilized for risk assessment.

OSHA requested Dr. Crump, a leading expert in risk assessment and biostatistics, to perform risk assessment on the three studies available to OSHA before the April 9th document, which were the basis of the three risk assessments presented in that document. Dr. Crump included some refinements in his assessment discussed in his statement (Ex. 206) and above. His estimates of risk presented in Table 2 were 8.7 to 29 excess deaths per 1000 exposed employees at 10 $\mu g/m^3$, confirming the estimates of the three earlier assessments and OSHA's preliminary conclusion in the range of 7.7 to 25 per 1000.

OSHA also requested Dr. Crump to perform risk assessments on the studies which became available after the April 9th document. The first was the Enterline and Marsh cohort study of employees at the Tacoma smelter. This was an expansion and update of the earlier Pinto and Enterline study of Tacoma retirees. The Pinto and Enterline study showed clear dose-response. See 43 FR 19594. However, the dose-response relationship of the Enterline and Marsh study was not so clear upon initial inspection, though the authors considered that it exhibited some dose response relationship. Table 8 and 9 of the study (Ex. 201–9) indicated that while there were statistically significant excess risks for most exposure levels, the excess risks did not clearly increase with increased exposure.

Dr. Crump pointed out that when SMR's are used for analysis, age differences can sometimes confound the results if the disease in question (like lung cancer) increases with age and if the groups being compared have different age distributions. The retirees of the Pinto and Enterline study had similar ages; therefore, age confounding would not be a problem and indeed dose-response was clear for the retirees. Dr. Crump pointed out that since the Enterline and Marsh study included active employees as well as retirees, there were probably substantial age differences among the various dose

groups, and the high exposure cohorts would likely be older.

Dr. Crump also pointed out that an absolute risk model, another well-established statistical technique, could partially control for age confounding. Dr. Crump applied an absolute risk model to the Enterline and Marsh data. The following chart taken from Dr. Crump's Table 3, 10 year lag (Ex. 206) demonstrates a dose-response relationship.

TABLE 5.—SMR AND ABSOLUTE RISK BY CUMULATIVE EXPOSURE

Cumulative exposure μg As/l uirine-years	SMR	Absolute risk × 104
Under 500	155	1,28
500 to 1,500	176	5.80
1,500 to 3,000	226	12.9
3,000 to 6,000	177	10.0
7000+	246	26.2

The excess risk shown by the absolute risk model (partially addressing age confounding) quite clearly increases with increases in cumulative exposure to arsenic while the dose-response relationship is not as clear when risk is measured by SMR. Crump characterized the linear fit as adequate. Using the risks presented in Table 5, Dr. Crump predicted at 10, 50 and 500 $\mu g/m^3$, 7.6, 37.3 and 303 excess deaths per 1000 exposed employees—estimates very similar to OSHA's estimate of 8, 40 and 400 at those levels respectively.

Dr. Crump also performed a risk assessment on the Lee-Feldstein study. He predicted at 10, 50 and 500 $\mu g/m^3$ excess risks of 8.3, 40.6, and 310 excess deaths per 1000 respectively using a relative risk model, and 3.2, 16 and 148 excess deaths per 1000 using an absolute risk model. These estimates are very similar to earlier predictions. However, in this particular case there was not a close fit between the data and model. Dr. Crump hypothesized that the poorer fit in the Lee-Feldstein data might result from the way exposure was characterized which would tend to overestimate total dose.

The exposure classification system of Higgins et al. included average exposures and cumulative exposures, as well as ceiling exposures. The risk assessment performed by Dr. Crump utilizing the cumulative exposures estimated by Higgins et al. indicated at 10, 50, and 500 $\mu g/m^3$ respectively, an excess risk of 9.4, 45.8 and 342 per 1000 using a relative risk model and 5.2, 25.9 and 228 per 1000 utilizing an absolute risk model. The data fit the model well and the predictions of risk again were very similar to OSHA's risk estimates. This tends to support Crump's conclusion that there is linearity in the Anaconda data and the poorer fits seen with the Lee-Feldstein data result from less precise estimates of cumulative exposure.

Dr. Radford also submitted estimates of risk. Dr. Radford, who is an expert in epidemiology, was Chairman of the National Academy of Science Advisory Committee on Ionizing Radiation (BEIR III) where he was involved in estimating risk from radiation exposure. Dr. Radford's estimates of 19 to 38 excess deaths per 1000 employees at 10 $\mu g/m^3$ were on the high side of the range OSHA considered reasonable. The basis for his higher estimate was that the Lee-Feldstein data led to overestimates of dose and consequently underestimated risk per unit of exposure. He made various adjustments to correct for this. He also believed that the Chu high side estimates of risk were better supported because the 1948 urinary arsenic levels (see above) tended to confirm Chu's estimate of exposure. Finally, his estimates based on Ott et al. were about the same as Chu's high side estimate. Dr. Radford believed that the fact that data from three independent locations indicated very similar levels of excess risk strengthened confidence that these estimates were reasonable.

Dr. Enterline, an expert in epidemiology, submitted estimates of risk somewhat lower than the other estimates of risk (2 to 3 excess deaths per 1000 at 10 $\mu g/m^3$). He believed that the high level of risks that the raw data from his studies indicated should be reduced because of three factors. He believed that exposures were higher in the past than his urinary data indicated. He also believed that a somewhat higher smoking rate existed for smelter workers and that there was the possible existence of other carcinogens in smelters which would be cause of some of the excess risk.

OSHA's conclusion is that the substantial body of additional data and analyses submitted during the hearing process confirms the estimates of risk which OSHA preliminarily presented in the April 9, 1982 document. In that document OSHA indicated that estimates of risk for a working lifetime exposure were in the range of 7.7 to 25 excess deaths per 1000 employees at 10 $\mu g/m^3$, 38 to 51 at 50 $\mu g/m^3$ and 375 to 465 at 500 $\mu g/m^3$ and that these were reasonable estimates. OSHA believed that the most reasonable were estimates towards the lower end of the range.

The new data expand the range of reasonable estimates somewhat from about 2.2 to 29 excess deaths at 10 $\mu g/m^3$ and 148–767 excess deaths at 500 $\mu g/m^3$. OSHA considers the preferred point estimates for a working lifetime to be approximately 8 excess lung cancer deaths per 1000 exposed employees at 10 $\mu g/m^3$ exposure, 40 excess deaths per 1000 exposed employees at 50 $\mu g/m^3$ and 400 excess deaths per 1000 exposed employees at 500 $\mu g/m^3$. (It should be kept in mind that these estimates are an approximation of a range of estimates).

The preferred estimate of 8 excess lung cancer deaths per 1000 exposed workers was the median of all the estimates presented in this document. The estimates of 40 excess deaths per 1000 at 50 $\mu g/m^3$ and 400 excess deaths per 1000 at 500 $\mu g/m^3$ are derived by using a linear model assuming that 8 excess deaths per 1000 was the best estimate at 10 $\mu g/m^3$. Estimates of risk presented in this document clustered around 8 excess deaths at 10 $\mu g/m^3$. It should be noted, however, that the best-fitting dose extrapolation curve yielded an estimate of 19 excess deaths per 1000 exposed workers. Also, there is now greater support for Chu's high side estimates. See also the discussion in the April 9, 1982 document.

Estimates in this range are supported by a number of experts in the field, Drs. Chu, Crump, Radford, Enterline, Rodricks, EPA–CAG, Clement Associates, NIOSH and others. Estimates in these ranges are derived both from the earlier epidemiology studies and the later studies available after the April 9 document. In general the underlying studies are of high quality and well suited for risk assessment. The linear model fits the data well, in some cases exceedingly well. (It should be recalled that fit is a statistical concept which indicates how close the measured data is to the curve or line which the dose extrapolation model predicts as the one best quantifying the risk).

The risk assessments performed by Dr. Crump quite clearly demonstrate that the linear model is much more appropriate than the quadratic model for arsenic risk assessment purposes. Based on this OSHA does not believe at this time that a risk assessment based on a quadratic model would be reasonable for inorganic arsenic.

These estimates of risk are appropriate for all inorganic forms of arsenic. The Ott et al. study is an adequate basis for risk assessment and risk assessments based on it predict risk towards the higher end of the range. However, in view of the similarity of results, it is most appropriate to treat all the studies together and utilize the same estimates for both trivalent and pentavalent forms.

The range of estimates from 2.2 to 29 excess lung cancer deaths per 1000 at 10 $\mu g/m^3$ and similar ranges at higher exposure levels is a remarkably narrow range of estimates in the context of risk assessment. These estimates are derived from 6 separate studies at 3 separate work places. They are dependent on estimates of exposures taking place 20 to 50 years ago which are somewhat uncertain. Therefore a variation of one order of magnitude is quite narrow and lends additional support to the validity of these estimates.

Further supporting OSHA's conclusion are measured data in the record indicating statistically significant excess risk at levels well under 500 $\mu g/m^3$. Lee and Fraumeni showed a statistically significant 114% excess risk for employees whose average exposure was 290 $\mu g/m^3$ for an average of approximately 5 years (Ex. 201–2B) and a 150–210% excess risk for long term employees. Lee-Feldstein demonstrated a statistically significant 131% excess risk for employees who averaged 290 $\mu g/m^3$. Pinto and Enterline indicated a statistically significant excess risk of 173% for long term employees who averaged 68 $\mu g/m^3$. Enterline and Marsh demonstrated a statistically significant excess risk of 168% for employees whose exposure averaged 49 $\mu g/m^3$ for a period of employment of 10–19 years.

Consultants in Epidemiology and Occupational Health, Inc. (CEOH represented by Dr. Lamm) took the position that there was little or no excess risk for workers who had never been exposed to peak exposures over 500 $\mu g/m^3$. The principal basis for its view were findings from the Higgins et al. study that employees whose average exposure was less than 500 $\mu g/m^3$ and who had no peak exposures over 500 $\mu g/m^3$ did not have statistically significant excesses of lung cancer. Dr. Lamm also referred to a "plateau" effect in some of the other studies which he felt indicated that there was not a clear dose-response relationship for lower exposure workers with short or medium term employment. He believed his conclusions were based on the latest and best data. Dr. Higgins, the CMA-Arsenic Panel, ASARCO and Kennecott supported CEOH's analysis.

The CEOH conclusions are not nearly as well supported as the risk assessments by the other experts and the estimates OSHA accepts. The results from the Higgins et al. study upon which CEOH relied had very low statistical power because of the small numbers of workers included. Higgins et al. studied only 22% of the cohort at risk. They only had a 16% to 37% chance of demonstrating a 50% excess risk which actually existed (Method I analysis). Also, the workers who had no peak exposure over 500 $\mu g/m^3$ probably had relatively low average exposures. A reasonable estimate would be 150 $\mu g/m^3$ for 15 years. Methods OSHA considers reasonable would predict about 150 SMR for this group.[6] That risk is close to the actual SMR's of 116 to 129 which were observed in the study by Higgins et al. (Method I analysis). The statistical power of the Higgins results is so low the results can neither support nor refute the hypothesis that there is no excess risk below 500 $\mu g/m^3$ in the Anaconda cohort.

The Brown and Chu analysis, which was more statistically robust, indicated that duration of exposure and not intensity was the more important factor contributing to the excess risk. This contradicts the CEOH and others' contention that duration of exposure and hence cumulative exposure had little effect on excess risk. Also, as just discussed, measured data of excess risk down to 49 $\mu g/m^3$ tends to refute the CEOH conclusions.

Most importantly, Lee and Fraumeni, and Lee-Feldstein showed a statistically significant excess risk ranging from 86% to 213% for their low exposure groups who averaged 290 $\mu g/m^3$. These studies excluded from the low exposure group employees who ever had short term exposures in higher categories (that is, excluding employees who had average exposures over approximately 500 $\mu g/m^3$). Therefore, these data indicated that workers with no peak exposures over 500 $\mu g/m^3$ had statistically significant excess risk. The Lee and Fraumeni and Lee-Feldstein results were for all the Anaconda employees, not just a 22% sampling as the Higgins et al. study was. Consequently, the Lee and Fraumeni and Lee-Feldstein data are better for purposes of analysis of risk from low exposures.

Dr. Lamm argues that the Higgins et al. study does a better job of describing an individual's exposures than can be done from the Lee and Fraumeni and Lee-Feldstein data. The Higgins et al. study in some of its analyses estimates year by year exposures for employees and that does permit better estimates of average and cumulative exposures. However, the study does not necessarily do a better job of ascribing dose classifications to particular work areas than can be done by utilziging the Lee and Fraumeni and Lee-Feldstein classifications in conjunction with the Morris data in the OSHA record. The much larger size of the Lee and Fraumeni and Lee-Feldstein studies in conjunction with their reasonable dose ascription entitles their findings to much greater weight.

The risk assessments of most of the experts and which OSHA generally relies on utilize regression analysis which is a standard technique for this kind of analysis. When appropriate, fit of the regression line is then tested using correlation coefficient squared (R^2) or Chi-squared. CEOH did not use regression analysis. CEOH concluded there was a "plateau" effect by selecting data points from several of the epidemiologic studies and stating that risks did not increase substantially between those points. Regression analysis is a more reliable approach and permits, when appropriate, one to statistically test the fit of the data to the predicted risk. There are circumstances where regression analyses are not appropriate, but the arsenic data clearly permit it.

In addition CEOH and CMA argue that the Higgins et al. study was the best and latest study and should be given more weight because of this. But as discussed elsewhere that study, Pinto and Enterline, Lee and Fraumeni, Enterline and Marsh, and Lee-Feldstein are all good studies giving reasonable estimates of risk for the time frame covered and the latter two are just as recent and more complete than the Higgins et al. study. The studies, like all studies, have relative strengths and weaknesses, and the Higgins et al. study does not negate the earlier studies. All of those studies need to be considered together along with all relevant information in estimating the risk presented by inorganic arsenic.

Finally, Dr. Crump and Dr. Radford point out that there is not a well established biologic model to support the ceiling hypothesis. Dr. Lamm and Dr. Higgins briefly speculate on possible mechanisms. However, the Higgins result is a single result. At the present time, there are not other epidemiologic studies to support the hypothesis that ceiling exposures can be the major determinant of risk.

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[6] In Lee and Fraumeni, short term workers averaged 5.4 years, medium term 18.1 years and long term 31.7 years for an overall average slightly over 15 years (Ex. 201–2B). Workers towards the low end of the medium group include converter workers at 240 $\mu g/m^3$ and zinc roaster workers at 111 $\mu g/m^3$. Workers towards the high end of the low exposure group include ferromanganese workers at 82 $\mu g/m^3$ and casting workers at 74 $\mu g/m^3$. Workers in these categories would be included in the low end of the medium exposure group and 150 $\mu g/m^3$ is a reasonable overall estiamte for them (Ex. 202–3B, p. 78). 150 $\mu g/m^3$ for 15 years is equivalent to 50 $\mu g/m^3$ for 45 years. A reasonable estimate for the latter is 50% excess risk or an SMR of approximately 150 (47 FR 15362, Table 1, EPA–CAG).

D. Further Research

The Chemical Manufacturers Association in its post-hearing brief suggested an extension of the Higgins et al. study. (Ex. 250, pp.21–22). ASARCO also suggested this in its post hearing brief. In several meetings with OSHA staff after the close of the period for post-hearing comments (minutes of which have been placed in the Docket Office), CMA recommended that OSHA delay a final decision on the degree of risk presented by inorganic arsenic (and make an appropriate request of the Ninth Circuit for an extension) until the Higgins et al. analysis could be extended to the entire cohort of Anaconda employees. CMA estimated that the study would take 12–18 months and, if so, the entire process would take approximately 24–30 months including time for public comments and OSHA review. CMA suggested they would be willing to have the standard remain in effect with existing stays and variances for that period.

OSHA has carefully considered this suggestion, but it has decided not to request the Ninth Circuit for a further extension. An expanded analysis using the methods of Higgins et al. might provide additional useful information. However, it would not be determinative or definitive on the question of low-dose risk from arsenic exposure. For the reasons discussed, the expanded study fits in the category of "sophisticated research [which] could be attempted but might not shed new light on the subject." *American Petroleum Institute* v. *OSHA*, 581 F. 2d 493, 507 (5th Cir. 1978).

First, as just discussed above, the already completed Lee-Feldstein and Lee and Fraumeni studies have analyzed the entire Anaconda cohort, not just 22%, and indicate statistically significant excess risks of between 86% and 213% for employees who had no peak exposure over approximately 500 $\mu g/m^3$. Second, there is measured excess risk for workers whose average exposure was as low as 49 $\mu g/m^3$, which also tends to refute a threshold at 500 $\mu g/m^3$.

Third, while expanding the Higgins analysis to the entire cohort would increase its statistical power and would permit further exploration of the low end of the dose response curve, it would not definitively resolve whether the ceiling hypothesis is correct. The results might support the Lee-Feldstein and Lee and Fraumeni results and the cumulative dose model, or the results might be inconclusive or they might provide greater support for Higgins et al.'s ceiling hypothesis. In the latter case, it would be results of one study inconsistent with the results of two studies of high quality of the same population.

Fourth, any differences between an expanded Higgins study and the Lee and Fraumeni and Lee-Feldstein studies would probably be attributable to how different experts estimated exposures for work areas taking place 20 to 50 years ago. The divergence in exposure ascription could not be definitively resolved, particularly since there are no air measurements to determine which exposure estimates are correct in some areas. The Lee and Fraumeni and Lee-Feldstein studies in conjunction with the Morris data (Ex. 28b) provide reasonable estimates of early exposures. Higgins et al. changed some of the Lee-Feldstein classifications. One of the changes Higgins et al. made—moving the masons into a higher category—is probably justified. However the change Higgins et al. made by moving the slag workers into a higher category was probably not justified since the high smelter temperatures would remove the arsenic before the stage in the process that the slag workers became involved. In addition, hooding or respirators would be used because of the sulfur dioxide, which would also decrease arsenic exposure. Mr. Nelson of ASARCO, a leading expert, indicated exposures are low in slag tapping (Tr. p. 304–305). Some other changes Higgins et al. made were based on assumptions about the nature of exposure rather than actual air measurements.

Fifth, a cumulative dose model has generally been used in risk assessments and has considerable scientific acceptance. The ceiling exposure hypothesis for carcinogens has not been widely explored and one result supporting it would not validate it because of the possibility of uniqueness at that one location. Replication of findings at several other workplaces probably would be necessary before this hypothesis would gain general acceptance in the scientific community. This would take a number of years. There is not now a widely accepted biologic model supporting the ceiling hypothesis.

One further observation is relevant to the question of expanding the study by Higgins et al. Enterline and Marsh expanded the study of Pinto and Enterline. Pinto and Enterline studies only 526 retirees whereas Enterline and Marsh studies all 2802 workers with one year or more of exposure during 1940-1964. Based on a SMR below 100 observed in the 99 workers who had 50–199 μg As/l with less than 25 years of exposure, Pinto and Enterline suggested that there may be a threshold for arsenic—induced lung cancer (See Table 2, 43 FR 19594). However, Enterline and Marsh observed elevated SMRs ranging from 169.9 to 268.2 for workers with an average exposure of 163 μg As/l with 1–19 years of employment. Therefore, expanding the study cohort and increasing the statistical power was associated with detecting an increased risk at an exposure level previously hypothesized to be a threshold.

For all these reasons OSHA concludes it should not delay submitting its estimates of risks, while waiting the approximately 24–30 months for completion and review of an expanded study by Higgins et al.

E. Statistical Significance and Type of Risk

The April 9th document referred to a third factor to be analyzed in a risk assessment, that is, statistical significance. That document pointed out that the first time that statistical significance is important is the determination in the individual studies that an excess risk from exposure to inorganic arsenic exists in the observed population. The statistical significance of the results are discussed in the preamble to the final standard, in the April 9th document and in this document. In general there is a high degree of statistical significance in the underlying epidemiologic studies which are the basis for the risk assessments with exceptions which are also discussed above.

The next stage at which statistical significance is important is the determination of the statistical significance of the dose-response relationship. The April 9th document pointed out that using a standard statistical test (Student's t-test), the dose-response relationships for the Lee and Fraumeni and for the Pinto and Enterline studies are highly significant (approximately the 0.0001 level). While the p value for the Ott et al. study is not as significant as it is for the other two studies, there is still less than a 0.10 chance that the dose-response relationship seen would occur by chance.

The April 9th document and this document also discuss the statistical concept of the fit of data to a regression line either with a R^2 or Chi-squared statistic. The above discussion indicates when fits are good and when they are not. Several of the risk assessments which are the basis for OSHA's estimates of risk have very good fits.

The fourth factor in risk assessment discussed in the April 9th document is the type of risk presented. The

epidemiological evidence has clearly demonstrated that inorganic arsenic is strongly associated with increased risk of lung cancer in humans. Lung cancer is usually a fatal disease. It evades early detetion and, according to the American Cancer Society, only about 9% of lung cancer patients live five or more years after diagnosis. No one at the hearing contested the seriousness of the risk of lung cancer. Inorganic arsenic is also associated with other diseases which are discussed above.

F. Significance of Risk

1. *Significance of Risk at 500 μg/m³.* The fifth factor in OSHA's approach to regulation is determination of the significance of the risk. OSHA stated in the Federal Register notice of April 9, 1982 as its preliminary analysis that:

> Briefly, measured data already in the inorganic arsenic record from the Lee and Fraumeni study show for long term employees (cohort 1 and 2, 15 or more years of exposure) a 455–567% excess risk (334–425 excess deaths from arsenic exposure per 1000 exposed employees) at 580 μg/m³ [and] a 150–210% excess risk (112–158 excess deaths per 1,000 employees) at 290 μg/m³. * * *
>
> OSHA concludes that exposure to inorganic arsenic clearly presents a significant risk of harm at the 500 μg/m³ level. As noted, the risk assessments estimate 375 to 465 excess deaths per 1,000 exposed workers for a working lifetime exposure (45 years) at 500 μg/m³. These estimates indicate a very high risk of death at the level of the old standard and comport with the conclusion of the Ninth Circuit Court of Appeals in the case that "it is undisputed that exposure to inorganic arsenic at the level of 500 μg/m³ poses a 'significant' health risk (*ASARCO* v. *OSHA*, 647 F. 2d 1 (1981) (47 FR 15365).

Much new data have been entered into the record to support the preliminary analysis. First, additional data points indicate substantial excess risk in the 500 μg/m³ range. For example, Lee-Feldstein demonstrates an excess risk of 346% (446 SMR) for employees who averaged 580 μg/m³, the medium exposure group. Higgins et al. indicate a 203% (303 SMR) excess risk for employees who averaged between 100–500 μg/m³.

In addition as discussed above OSHA's estimate of the excess risk at 500 μg/m³ from the risk assessments is approximately 400 excess deaths per 1000 employees. Dr. Crump made estimates of excess deaths per 1000 employees at 500 μg/m³ of between 321 and 578 based on the studies available before the April 9th document and from 148 to 342 based on the 3 updated studies.

Third, supporting the conclusion of excess risk at 500 μg/m³ is the substantial excess risks measured at levels well below 500 μg/m³. Dr. Chu estimated earlier that excess risk existed at the 68 μg/m³ level among the Pinto and Enterline retirees (Ex. 201–2B, p. 5). The Lee-Feldstein study covering 8045 men and 39 years of observation shows a statistically significant excess risk of 131% (231 SMR) for 4448 employees exposed to an average of 290 μg/m³, the light category (Ex. 203–3 A, p. 20–6). The Enterline and Marsh data indicates that employees with between 10 and 19 years employment at or below 290 μg/l with a mean level of 163 μg/l (or an average airborne exposure of 163 × 0.3=49 μg/m³) had a statistically significant 168% excess risk (268.2 SMR). There are also other measured data of excess risk at and well below 500 μg/m³ discussed in section III above.

All the above data very strongly confirms OSHA's original judgment that a significant risk exists at 500 μg/m³. However an alternate analysis has been presented by Dr. Lamm supported by the CMA-Arsenic Panel and others that 500 μg/m³ might be a threshold, and that there would be little or no excess risk for employees whose exposures were kept below 500 μg/m³. This conclusion was based principally on the peak exposure analysis of Higgins et al. showing no statistically significant excess risk for employees who did not have peak exposure over 500 μg/m³. Based on this result several participants recommended that OSHA set an exposure limit of 50 to 100 μg/m³ to provide a safety factor.

If these particular data in the Higgins et al. study were stronger and if they were not contradicted by other epidemiologic evidence, OSHA might have to reconsider its 10 μg/m³ PEL. However, as discussed above, this particular result of Higgins et al. had very low statistical power, not enough statistical power to support its conclusion. The Lee-Feldstein and Lee and Fraumeni studies of much greater size and statistical power indicate that employees in the low exposure group who had no peak exposures over approximately 500 μg/m³ had a statistically significant excess risk ranging from 86% to 213% depending upon study and length of employment. In addition, there is the evidence of measured excess risk at levels at and well below 500 μg/m³ in other studies and the clear dose-response relationship in many studies. The cumulative dose risk assessments generally have very good fit indicating additional confidence in the cumulative dose model, that excess risk is linearly proportional to the amount of arsenic to which an employee is exposed.

For all the above reasons and others discussed in Section VI–D, the hypothesis that excess risk is low if peak exposures are kept under 500 μg/m³ is not well supported. By far, the weight of evidence indicates that a very high and significant excess risk exists at 500 μg/m³ which can be reduced by lowering exposures.

2. *Substantial Reduction in Significant Risk.* The Second significant risk question discussed in the April 9th document is whether reducing exposures to 10 μg/m³ would substantially reduce risk. OSHA stated in that document:

> There appears to be little doubt that reducing exposures to inorganic arsenic from 500 μg/m³ to 10 μg/m³ will substantially lessen the level of risk of development of cancer. The most reasonable estimates predict that the reduction would be from 375–465 excess deaths per 1,000 exposed employees to 7.7–10 excess deaths per 1,000 exposed employees over a working lifetime. Confidence can be placed in the predicted lessening of risk since both the Lee and Fraumeni study, and the Pinto and Enterline study demonstrated dose-response relationships. (See the tables at 43 FR 19549–5). For example, measured data from the Lee and Fraumeni study indicate substantially less excess risk at 290 μg/m³ than at 580 μg/m³. Clearly lower exposure substantially reduces risk (47 FR 153656).

Substantial additional evidence supports that conclusion. The newer studies continue to show dose-response. The Lee-Feldstein study shows a 512 SMR for high exposure employees, 446 for medium exposure employees and 231 SMR for low exposure employees. The Enterline and Marsh study did not show quite so clear dose-response, but, when corrected for potential age confounding through use of an absolute risk model, indicated clear dose-response. The studies by Lubin et al. and Higgins et al. also showed a clear dose-response based on average exposure. Dr. Crump's risk assessment had very good data fits with the models indicating that excess risk is reduced directly proportional to reductions in exposure. OSHA's estimate of 400 excess lung cancer deaths per 1000 exposed employees at 500 μg/m³, 40 excess deaths at 50 μg/m³ and 8 excess deaths at 10 μg/m³ demonstrates a very substantial 98% reduction in risk by reducing exposures to 10 μg/m³. The great weight of the evidence indicates that reducing exposures from 500 μg/m³ to 10 μg/m³ will very substantially reduce significant risk.

3. Risk at 10 μg/m³.

In the April 9, 1982 document, OSHA preliminarily concluded as follows concerning the predicted remaining risk

of 7.7 to 10 excess deaths per 1000 exposed workers at 10 $\mu g/m^3$.*

The linear model estimates a risk level of 7.7 to 10 excess cases of cancer per 1,000 exposed workers at the 10 $\mu g/m^3$ limit. OSHA's preliminary conclusion is that significant risk is not eliminated at this risk level and that a reasonable person would take steps to reduce it if feasible.*

Some guidance for this conclusion is presented by an examination of other occupational risk rates and legislative intent. For example in the high risk occupations of fire fighting and mining and quarrying the average risk of death from an occupational injury or an acute occupationally related illness from a lifetime of employment (45 years) is 27.45 and 20.16 per 1000 employees respectively. Typical risk in occupations of average risk are 2.7 per 1000 for all manufacturing and 1.62 per 1000 for all service employment. Typical risks in occupations of relatively low risk are 0.48 per 1000 in electric equipment and 0.07 per 1000 in retail clothing. (These rates are derived from 1979 and 1980 Bureau of Labor Statistics data from employers with 11 or more employees adjusted to 45 years of employment for 46 weeks per year.)

There are relatively little data on risk rates for occupational cancer as distinguished from occupational injury and acute illness. The estimated cancer fatality rate from the maximum permissible occupational exposure to ionizing radiation is 17 to 29 per 1000. (47 years at 5 rems; Committee on the Biological Effects of Ionizing Radiation (BEIR) III predictions.) However, most radiation standards (unlike OSHA standards) require that exposure limits be reduced to the lowest level reasonably achievable below the exposure (the ALARA principle). Approximately 95% of radiation workers have exposures less than one-tenth the maximum permitted level. The risk at one-tenth the permitted level is 1.7 to 2.9 per 1000 exposed employees. (BEIR I estimates are 30 to 60 per 1000 at 5 rem per year and 3 to 6 per 1000 at one-tenth that level.)

The linear model predicts a 7.7 to 10 per 1000 excess death rate from arsenic at 10 $\mu g/m^3$. This ¼ to ½ the death rate in the riskiest occupations, 2 to 5 times higher than the risks in occupations of average risk, and 10 to 100 times the risk of the low risk occupations. It is also ⅛ of the maximum permitted radiation cancer risk but about 3 times higher than the cancer risk which 95% of the radiation workers are under. It must also be noted that this risk of 7.7–10 excess deaths per 1000 employees due to lung cancer is in addition to the risk of accidental death in copper smelters of 8.69 per 1000 (1978–80 BLS data).

Congress passed the Occupational Safety and Health Act of 1970 because of a determination that occupational safety and health risks were too high. Based on this it is clear that Congress gave OSHA authority to reduce risks of average or above average magnitude when feasible. Therefore OSHA believes that the 10 $\mu g/m^3$ standard for arsenic, which should reduce risk from several hundred per thousand to approximately ten per thousand is carrying out the Congressional intent within the limits of feasibility and does not attempt to reduce insignificant risks.

Under the both Congressional intent and the Supreme Court rationale, OSHA could if it were feasible, seek to reduce risks below those estimated by the linear model at 10 $\mu g/m^3$. However, OSHA expects that there will be reduction of risk beyond that estimated using the mathematical model. The estimates do not take into account the other protective provisions (protective clothing, showers, clean lunch rooms, etc.) that will reduce exposure to arsenic in nonwork areas and during nonwork hours, reduce the possibility of arsenic ingestion and ensure proper respiratory and bodily protection. With the 10 $\mu g/m^3$ level and these protective provisions lowering risks below the predicted level, OSHA concludes that its arsenic standard is protecting employees and that employers who fulfill the provisions of the standard will have taken all reasonable steps to protect their employees from the hazards presented by occupational exposure to inorganic arsenic (47 FR 15366).

This analysis still remains applicable. After reviewing all the comments and new data OSHA's preferred estimate of risk for a working lifetime of exposures is approximately 8 deaths from respiratory cancer per 1000 exposed employees at 10 $\mu g/m^3$, with a range of reasonable estimates from 2.2 to 29 per 1000. This estimate is very similar to the estimate which was the basis of the above discussion on significance of risk.

Relatively little comment and no detailed analysis was submitted on the above discussion of significance of risk. The Chemical Manufacturers' Association—Arsenic Panel stated that,

OSHA drew inappropriate comparisons between acute risks, such as those in the 'hazardous occupations' OSHA lists, and chronic risks such as carcinogenesis. The appropriate comparison therefore is not to occupational mortality rates for firemen, but to the rate for radiation workers, who also are exposed to a chronic health hazard, As OSHA notes in the Federal Register, the risk of increased mortality at maximum permissible occupational exposure under the radiation standard is 17–29 per 1000. Thus this risk level should be considered acceptable by OSHA in setting a standard to protect workers against other long-term health risk (Ex. 202–3, pp. 101–102, fn. 50).

One of the arguments that Kennecott Minerals Company made in support of a 50 $\mu g/m^3$ level is that,

Dr. Enterline's new data show that the excess risk at 50 $\mu g/m^3$ is approximately the same as that found by the OSHA assessments at 10 $\mu g/m^3$ [Dr. Enterline's estimate is 11.2 to 13.4 excess cases per 1000 employees at 50 $\mu g/m^3$] * * * Thus, Dr. Enterline's new data show that a PEL of 50 $\mu g/m^3$ would provide approximately the same level of protection deemed adequate by OSHA under the current 10 $\mu g/m^3$ PEL (Ex. 202–8, p. 38).

The United Steelworkers of America specifically addressed this argument, pointing out that OSHA had stated that its "preliminary conclusion is that significant risk is not eliminated at this risk level" and further noting that "Enterline's risk at 50 $\mu g/m^3$ is an order of magnitude higher than the risk considered significant by the Supreme Court in *IUD* v. *API*." (Ex. 249, p. 14, fn. 24). The United Steelworkers stated with regard to OSHA's analysis of significant risk:

OSHA's risk assessments used human studies, with relatively good estimates of dose compared to most epidemiological studies. These data permitted the use of quantitative methods. OSHA then compared its derived risk of arsenic-induced lung cancer at the PEL to the risk of death from other occupations concluding that the risk is significant because it is higher than average. This procedure works very well for arsenic, but we would caution against generalizing it to other toxic substances considered for regulation. Human studies are not always available. When they are, they may not include adequate information of exposure. The risk in question may not be death. . . . Reliable quantitative risk assessment may not be possible, nor do we believe the Supreme Court's benzene decision requires their use. Nor do we believe a risk is significant only if it exceeds the average risk of death from occupational causes. Congress intended OSHA to reduce the rate of injury, death, and disease throughout American industry, not just to flatten out the peaks. Indeed, the average risk of death from occupational causes in manufacturing of 2.7/1000 is considerably higher than the risk of 1/1000 the Supeme Court considered significant in the benzene decision. OSHA's risk comparisons clearly demonstrate that the risk of arsenic-induced cancer is significant even at the 10 $\mu g/m^3$ level. But they should not be used in the future to demonstrate that a given risk is insignificant (Ex. 231, p. 5–6).

The National Institute for Occupational Safety and Health stated that "NIOSH accepts the OSHA conclusion of significant risk to 10 μg arsenic/m^3" (Ex. 227, p. 2). Dr. Radford,

*This level of risk is also above the level at which the Supreme Court indicated a reasonable person might well consider the risk significant and take steps to decrease it. The Court stated: "It is the Agency's responsibility to determine in the first instance what it considers to be a "significant" risk. Some risks are plainly acceptable and others are plainly unacceptable. If for example the odds are one in a billion that a person will die from cancer by taking a drink of chlorinated water the risk clearly could not be considered significant. On the other hand, if the odds are one in a thousand that regular inhalation of gasoline vapors that are two percent benzene will be fatal a reasonable person might well consider the risk significant and take appropriate steps to decrease or eliminate it" (*IUD* V. *API* 448 U.S. 655) The Supreme Court's language indicates that the examples given were of excess risk over a lifetime. It speaks of "regular inhalation" which implies that it takes place over a substantial period of time and refers to the "odds * * * that a person will die," obviously a once in a lifetime occurrence.

who had been actively involved as chairman of BEIR III in considering questions of acceptable levels of risk in the context of ionizing radiation stated:

> I conclude that the risk estimates presented in the OSHA April 9 summary must be raised in the light of the new information. Whether the above risk estimates for the standard are acceptable is problematic. Certainly on the basis of the assumptions made they are significant, even if the current standard (10 $\mu g/m^3$) is retained (Ex. 207, p. 13).

After reviewing these comments, OSHA concludes that its analysis in the April 9, 1982 document is correct. By setting the PEL at 10 $\mu g/m^3$ OSHA is very substantially reducing the risk of lung cancer for employees within the limits of feasibility and it is not reducing risk to the level of insignificance. The risk assessments and significant risk analysis clearly demonstrate that the 10 $\mu g/m^3$ level should not be raised.

In response to the comments, OSHA believes it is appropriate to reduce both acute and chronic risks of deaths. OSHA also believes, as stated in the April 9th document, that Congress did not intend OSHA to limit reductions in death to the highest existing levels, but intended OSHA to reduce significant risk to the extent feasible.

In addition the NRC regulations which cover employees exposed to higher levels of radiation require employers to reduce each employee's exposure below the level stated in the regulation to as low a level as is reasonably achievable. This is not the case with OSHA regulations.

Finally, Dr. Enterline's estimates of risk of 11 to 13 at 50 $\mu g/m^3$ and 2 to 3 at 10 $\mu g/m^3$ are lower than OSHA's estimates although they are reasonable estimates. His estimate of 11 to 13 excess deaths per 1000 at 50 $\mu g/m^3$ is still an above average level of risk and his 10 $\mu g/m^3$ estimate of 2 to 3 excess deaths per 1000 is an average level of risk. Therefore Dr. Enterline's risk estimates are not a basis to raise the exposure level to a level which would result in above average risks.

Those participants who advocated a 50 or 100 $\mu g/m^3$ level generally did not do so because they believed that OSHA's predicted level of risk at those levels would be acceptable or insignificant. Rather, based on the CEOH analysis, they argued that a "threshold" existed at higher levels. As stated above the great weight of the studies and evidence supports the estimates of risk presented by OSHA, and therefore that very substantial body of high quality evidence must be the basis of OSHA's significant risk determinations.

VII. Regulatory Analysis

This supplemental statement of reasons for the final rule was issued pursuant to a court order limiting the issues to estimates of risk, analysis of its significance and any changes to the permissible exposure limit resulting from analysis of those factors. The analysis indicates that no changes in the PEL are justified and accordingly no changes are being made to the standard. A limited time was granted by the Court for this review. Accordingly, as the remand limited OSHA to specified issues and as all required reviews occurred at earlier stages in the rulemaking, this is not an action for which a further environmental impact statement, regulatory flexibility analysis or regulatory impact analysis is required.

VIII. Authority

This notice was prepared under the direction of Thorne G. Auchter, Assistant Secretary for Occupational Safety and Health, Frances Perkins Labor Department Building, 200 Constitution Avenue, N.W., Washington, D.C. 20210.

List of Subjects in 29 CFR Part 1910

Arsenic, Occupational safety and health, Chemicals, Cancer, Health, Risk assessment.

(Secs. 6, and 8, of the Occupational Safety and Health Act of 1970 (29 U.S.C. 655, 657, Secretary of Labor's order 8–76 (41 FR 25059); 29 CFR Part 1911))

Signed at Washington, D.C. this 6th day of January 1983.

Thorne G. Auchter,

Assistant Secretary of Labor.

[FR Doc. 83–759 Filed 1–7–83; 9:10 am]

BILLING CODE 4510–26–M