California Air Resources Board

Technical Support Document

Proposed Identification of Inorganic Arsenic as a Toxic Air Contaminant

Part B
Health Assessment

State of California
Air Resources Board
Stationary Source Division

May 1990

HEALTH EFFECTS OF INORGANIC ARSENIC COMPOUNDS

Prepared by the

Air Toxicology and Epidemiology Section
Hazard Identification and Risk Assessment Branch
Department of Health Services
2151 Berkeley Way, Room 517
Berkeley, California 94704-9980

March 23, 1990

PART B
of the
REPORT TO THE AIR RESOURCES BOARD
ON INORGANIC ARSENIC

Made Available to the Public and
Submitted to the Scientific Review Panel on Toxic Air Contaminants
Pursuant to
Section 39661 of the Health and Safety Code

STATE OF CALIFORNIA

Acknowledgments

The following people played a major role in the preparation of this report:

David Holtzman, M.P.H., Associate Toxicologist
California Department of Health Services.

Irva Hertz-Picciotto, M.P.H., M.A., Ph.D., Assistant Research Epidemiologist
University of California, Berkeley. Consultant to:
California Department of Health Services.

The following persons provided in-house review of earlier drafts of this report:

George Alexeeff, Ph.D., Anna Fan, Ph.D., Peter Flessel, Ph.D., Robert Haas, Ph.D., Michael Lipsett, M.D., J.D., Dave Morry, Ph.D., Cullen Phillips, Ken Satin, Ph.D., David Siegel, Ph.D., Dan Smith, Ph.D., Calvin Willhite, Ph.D.

The following extramural consultant provided significant input to this report:

Allan H. Smith, M.D., Ph.D.

Literature searches performed by Sharon Brunzel, M.L.S., contributed to this report.

The document management skills of Laurie Bliss, Thelma Brown, Mary Erickson, Rose Findley, Gloria Harrell, Veah Keyes, Velinda Knowles, June Palmer, Rhonda Powell, and Mary Williams contributed to the production of this report.

TABLE OF CONTENTS

1.0 SUMMARY

The inorganic arsenic compounds usually associated with toxicity and carcinogenicity contain trivalent (As(III)) or pentavalent (As(V)) arsenic.[1]

Arsenic compounds may be absorbed from the lungs and the gastrointestinal tract. By ingestion, as little as 20 mg of arsenic may be life-threatening to man. Acute airborne exposure to high concentrations of arsenic (III) trioxide in occupational settings causes irritation of the eyes, nasal mucosa, and bronchi. Noncarcinogenic effects associated with chronic occupational exposure to high concentrations of airborne arsenic include nasal septum ulceration and perforation, respiratory tract irritation, and peripheral neuropathy.

The most sensitive noncarcinogenic endpoints are probably vascular disorders, neurological disturbances, and adverse reproductive effects. Occupational exposure of copper smelter employees to 50-500 μg As/m^3 was associated with blood pressure abnormalities, vascular constriction, and decreased nerve conduction velocity. Trends toward increasing numbers of skeletal malformations with increasing dose were observed in the offspring of mice exposed to 0, 200, 2200, or 21600 μg As(III)/m^3 for four hours per day over four days. While conclusive evidence of human reproductive

---

[1] Throughout this document, if not otherwise indicated, the word "arsenic" generally refers to inorganic compounds of arsenic. In discussions of nutritional essentiality, "arsenic" refers to the element and/or its compounds.

toxicity is lacking, adverse pregnancy outcomes have been observed among copper smelter employees and nearby residents; these included elevated spontaneous abortion rates, low birthweights, and elevated rates of malformed offspring.

These noncarcinogenic effects occur at concentrations greater than two orders of magnitude above a 24-hour maximum (0.392 $\mu g/m^3$) measured in 1986 near an industrial source and more than three orders of magnitude greater than the maximum 24-hour concentration away from industrial sources (0.020 $\mu g/m^3$). Therefore, the staff of the California Department of Health Services (DHS) concludes that it is unlikely that noncarcinogenic adverse health effects would be caused by the levels of arsenic compounds currently found in the ambient air.

Arsenic is genotoxic. Arsenic compounds induce chromosomal aberrations and sister chromatid exchange, and may inhibit DNA repair. Although arsenic compounds generally test negative in standard in vitro tests for mutagenicity, one assay in mammalian cells indicates that arsenic can inactivate genes by damaging chromosomes.

Animal studies using the oral or dermal route of arsenic exposure are consistently negative for carcinogenicity. The data from inhalation exposure are inadequate to evaluate the carcinogenicity of arsenic by this route in animals.

The carcinogenic effects of arsenic in humans are well documented in the epidemiologic literature. The International Agency for Research on Cancer

(IARC) evaluated arsenic in 1980 and classified "arsenic and arsenic compounds" into Group 1, which includes the "chemicals and groups of chemicals (which) are causally associated with cancer in humans." The staff of DHS agrees with this assessment, based on evidence summarized in the following paragraphs.

Ingestion of arsenic in drinking water and medicinal preparations is associated with skin cancer and precancerous skin lesions. Arsenic-associated skin cancers often occur on areas generally not exposed to sunlight.

Several studies of workers employed in the smelting industry and in insecticide manufacturing have found strong associations between respiratory cancer mortality and arsenic exposure. This association is a consistent, replicable finding of substantial magnitude with a clear dose-response relationship, and high statistical significance. The smelter studies involved primarily arsenic trioxide exposures, while in the insecticide manufacturing plants, significant exposures were to lead arsenate and calcium arsenate. The probability of such repeated and consistent findings being due to chance is extremely small.

The respiratory cancer standardized mortality ratios (SMRs)[2] for several entire study cohorts occupationally exposed to arsenic range from 165 to

---

[2] SMR = ([observed number of deaths]÷[expected number of deaths]) x 100. The expected number of deaths is typically based on age-, sex-, and calendar year-specific rates in the general population. An SMR of 200 would represent a doubling of mortality over expected rates, while an SMR of 1,000 would describe a ten-fold increase in mortality.

912, with many studies reporting an SMR of approximately 300. Heavily exposed workers experienced even higher SMRs (e.g., > 2000). These effects were unlikely to have been due to any systematic error in these occupational studies. The mean length of latency between the start of exposure to arsenic and the expression of cancer ranged from 20-40 years.

The large SMRs observed in these studies are unlikely to be explained by confounding variables. Occupational exposures to sulfur dioxide, nonarsenical pesticides, or asbestos do not explain the excess lung cancer deaths. Confounding from smoking was minimal. Arsenic-exposed nonsmokers in several cohorts had elevated rates of respiratory cancer deaths. In a study with quantified exposure data, a dose-response effect of arsenic was observed among nonsmokers and smoking rates did not vary by level of arsenic exposure. The staff of DHS concludes that confounding, either from smoking or from exposure to other workplace carcinogens, does not explain the strong association observed between arsenic and respiratory cancer.

The available data are inadequate to evaluate the possibility of interactions between arsenic and other chemicals. Interaction with smoking has been characterized; the effect on respiratory cancer rates of combining smoking and arsenic exposure appears to be greater than additive and at low doses may be as high as multiplicative.

The staff of DHS finds the evidence for human carcinogenicity due to inhaled arsenic to be strong. This conclusion is based on (1) the high relative risks (mortality ratios) seen in occupational studies, (2) the high

statistical significance of these findings, (3) the evidence of a dose-response effect using different indices of exposure and different measures of response, (4) the demonstration of increased risks due to arsenic after controlling for smoking, (5) the consistency of the arsenic-related effect among cohorts which are geographically dispersed (Japan, Sweden, China, and several states of the U.S.), (6) the consistency of the arsenic-related effect from at least two types of exposures: smelters and insecticide manufacturing, and (7) the failure of potential confounding from workplace exposures to explain the observed association.

Several mechanisms have been postulated for arsenic-related health effects, including reactions with sulfhydryl groups on enzymes and substitution of arsenate for phosphate groups in nucleotides and DNA. The precise mechanism of arsenic-related carcinogenicity is unknown, but may be related to effects on the immune system, effects on DNA replication and repair, or interference with some other system.

While some of these effects may be governed by a threshold, there is at present no way to determine where such a threshold might be. Furthermore, there is no evidence that arsenic acts by one mechanism only. The staff of DHS concludes that neither the epidemiologic evidence nor the toxicologic evidence supports a threshold-mediated mechanism for arsenic's carcinogenicity. In the absence of compelling evidence of a threshold, the staff of DHS treats the mechanism of arsenic's carcinogenicity as a nonthreshold process.

The staff of DHS has conducted a risk assessment to quantify the risk posed by ambient atmospheric levels of arsenic in California. The quantitative risk assessment is based on the assumption that cumulative lifetime exposure to arsenic determines the magnitude of carcinogenic effect. Risks were quantified by adjusting dose-response data from a cohort of smelter workers for interaction between arsenic and smoking, fitting a linear nonthreshold multiplicative model to the data, and then extrapolating to ambient exposures.

Risks were evaluated separately by sex and for four smoking categories: never, former, light (<1 pack/day) and heavy smokers. Unit risks for these categories, shown in Table 1-1, range from 400 to 8400 per million persons, with upper bounds ranging from 630 to 13,000 per million. The unit risk is the lifetime number of excess cancer deaths predicted to result from continuous exposure to arsenic at a concentration of 1 $\mu g/m^3$. This unit dose, which is within the range received by smelter workers who received low exposures, is fifty times greater than the maximum 24-hour concentration observed in the state away from industrial sources, and five hundred times greater than the population-weighted average concentration observed in the state away from industrial sources (1.9 ng/m^3).

The risk to residents of California from inhalation of atmospheric arsenic was estimated by applying the unit risk estimate to the population-weighted annual average arsenic concentration (1.9 ng/m^3) measured by Air Resources Board (ARB) staff in the state. For nonsmokers, the staff of DHS estimates the number of excess cancer deaths due to arsenic to be 0.8 to 2 per million persons exposed throughout their lives to the annual average ambient level

in California air. For former smokers, the risk ranges from 3 to 10 per million; for light smokers, from 5 to 14 per million, and for heavy smokers from 10 to 25 per million at the current average ambient levels of arsenic. The overall population-weighted average, based on current smoking levels, is estimated to be from 4 to 6 deaths per million. In each case, the lower figure is derived from a maximum likelihood estimate of unit risk and the higher figure is derived from an upper bound. Males generally exhibit higher rates of lung cancer mortality than do females. Therefore, the multiplicative model estimates the risks for males from arsenic exposure to be higher than those for females. The upper bound of excess cancer mortality risk from a lifetime of exposure to 1.9 ng As/m^3 ranges from 1 to 25 cases per million persons exposed (see Table 1-1).

Near industrial sites, however, the risk may be higher. During a one-month period in May-June 1986, one kilometer from a secondary lead smelter in California, an average concentration of 61 ng As/m^3 was measured. While emissions from this site were subsequently reduced, they may be indicative of potential exposures near point sources of arsenic. Exposure estimates for an area surrounding this site were therefore used in risk estimations. These estimations indicate that if arsenic emissions from that facility had continued unabated for a lifetime (75 years), 6 to 9 excess cancer deaths might have occurred among 725,000 persons residing nearby.

The staff of DHS emphasizes that the risk estimates derived in conducting a risk assessment are not exact predictions, but rather represent plausible estimates based on current scientific knowledge and methods. Uncertainty in this risk assessment stems from (1) extrapolation from occupational exposure

levels over two to three orders of magnitude to current average ambient arsenic concentrations, (2) limitations in the exposure data from which the assessment was derived, (3) potential inaccuracy and variability of ambient exposure measurements, (4) generalization from the mortality experience of adult white male workers in Tacoma, WA, to the general population of California, and (5) the use of current smoking data at a time when patterns of smoking are changing.

The staff of DHS recommends that for the purposes of California Health and Safety Code Section 39660(c), the range of risk for ambient exposures to arsenic be based on the maximum likelihood estimate and upper bound predicted from fitting a linear model to the human data adjusted for interaction with smoking. Therefore, the range of estimated excess cancer deaths from 24-hour-per-day lifetime exposure to the population-weighted annual average ambient airborne concentration in California, 1.9 ng As/m^3, is from 0.8 to 25 per million persons exposed. The width of this range is largely due to differences in risk by gender and smoking status. Among male heavy smokers, the range of risk is from 16 to 25 per million persons exposed; among female heavy smokers it is from 10 to 16 per million. The staff of DHS further recommends that the overall unit risk, 3.3×10^{-3} per $\mu g/m^3$, be considered the best estimate of the upper bound of risk.

Based on the findings of arsenic-induced carcinogenesis in humans and the results of the risk assessment, the staff of DHS finds that arsenic is an air pollutant which may cause or contribute to an increase in mortality or an increase in serious illness, or which may pose a present or potential hazard to human health.

TABLE 1-1

UPPER BOUND (AND MAXIMUM LIKELIHOOD ESTIMATES)
OF EXCESS LUNG CANCER RISKS
DUE TO AMBIENT ARSENIC EXPOSURE
IN CALIFORNIA

	MALES			FEMALES		
Smoking Category	% By Smoking Category	Unit Risk ($1\ \mu g/m^3$) Deaths per Million:	Risk at Average Ambient Level ($1.9\ ng/m^3$) Deaths per Million:	% By Smoking Category	Unit Risk ($1\ \mu g/m^3$) Deaths per Million:	Risk at Average Ambient Level ($1.9\ ng/m^3$) Deaths per Million:
Never	42	1200* (780)**	2 (1)	59	630 (400)	1 (0.8)
Former	32	5300 (3400)	10 (6)	15	2900 (1800)	5 (3)
Light (<1 pack/day)	19	7400 (4700)	14 (9)	21	4100 (2600)	8 (5)
Heavy (>1 pack/day)	7	13000 (8400)	25 (16)	5	8200 (5200)	16 (10)
	100			100		
Population-weighted average:		4600 (2900)	9 (5)		2100 (1300)	4 (2)

Overall unit risk (for males and females combined): 3300 (2100)

Overall risk at ambient levels: 6 (4)

* Upper bound estimate, based on upper 95% confidence bound on slope of dose-response data in epidemiologic study of Enterline et al. (1987).

** Numbers in parentheses are maximum likelihood estimates.

Based on data from Enterline et al. (1987) (Tacoma, WA, smelter employees), analyzed with follow-up starting at termination of employment, and adjusted for interaction with smoking.

TABLE 1-2

NAMES AND VALENCE STATES OF CERTAIN ARSENIC COMPOUNDS

Compound Name[1]	Chemical Formula	Valence State of Arsenic[2]	CAS Number[3]
Arsenic (metallic arsenic)	As	0	7440-38-2
Arsenic trioxide (arsenious oxide, white arsenic)	As_2O_3	+3	1327-53-3
Dimethylarsinic acid (DMA, DMAA, cacodylic acid)	$(CH_3)_2AsO(OH)$	+1	75-60-5
Methylarsonic acid (methanearsonic acid, MMA)	$CH_3AsO(OH)_2$	+3	
Potassium arsenite (Fowler's solution)	$KH(AsO_2)_2$	+3	13464-35-2
Sodium arsenate	Na_3AsO_4	+5	7631-89-2
Sodium arsenite	$NaAsO_2$	+3	7784-46-5

[1]Synonyms in parentheses.

[2]In the text, the +3 valence state is referred to as As(III), and the +5 valence state is referred to as As(V).

[3]Chemical Abstracts Service (CAS) Registry Number is a numeric designation assigned by the American Chemical Society's Chemical Abstracts Service and uniquely identifies a specific chemical compound.

Source: Adapted from IARC (1980).

1.1 Risk Assessment Highlights

I. National and International Evaluations (Other Agencies' Evaluations)

A. U.S. Environmental Protection Agency (EPA)

1. Short-Term Tests: Weak mutagenic potency compared to other known metal mutagens.

2. Animal Carcinogenicity Assays: Inconsistent.

3. Human Carcinogenicity: Sufficient evidence of lung and skin carcinogenesis.

4. Conclusion: Arsenic is in EPA's Group A (human carcinogen).

B. International Agency for Research on Cancer (IARC)

1. Animal Carcinogenicity Assays: Inadequate evidence.

2. Human Carcinogenicity: Sufficient evidence of lung and skin carcinogenesis. Inadequate evidence at other sites.

3. Conclusion: Arsenic and arsenic compounds are in IARC's Group 1 (causally associated with cancer in humans).

C. National Toxicology Program (NTP)

1. Animal Carcinogenicity Assays: Inadequate evidence.

2. Human Carcinogenicity: Sufficient evidence of skin carcinogenesis. Lung cancer risk increased in smelter workers who inhaled high levels of arsenic trioxide.

D. U.S. Occupational Safety and Health Administration (OSHA)

1. Human Carcinogenicity: "[I]norganic arsenic has been demonstrated to be carcinogenic to exposed workers" (OSHA 1983 at 1869).

2. Conclusion: OSHA set the permissible exposure limit (PEL) for occupational exposure to inorganic arsenic at 10 $\mu g/m^3$, the lowest feasible level.

II. Carcinogenic Mechanism

A Shape of the dose-response curve

1. Animal: NA

2. Human: Data from some occupational studies are consistent with a linear relationship between excess risk and cumulative lifetime dose of arsenic. The most recent and largest occupational studies are also consistent with a linear relationship between relative risk and cumulative lifetime dose of arsenic, although a supralinear relationship has also been reported.

B. Pharmacokinetic information: Pentavalent arsenic (As(V)) is reduced in vivo to the trivalent state (As(III)). As(III) is detoxified by methylation. After inhalation, ingestion or injection, significant amounts of As(III) and As(V) may be found unmethylated in the urine.

C. Information from short-term tests: Inorganic arsenic is clastogenic and elevates rates of sister chromatid exchange (SCE). It has not been demonstrated to cause point or frameshift mutations.

D. Conclusions: Proposed mechanisms of arsenic carcinogenesis include clastogenesis and chromosomal rearrangement. Occupational studies show an elevated risk even at the lowest category of occupational exposure when sufficient numbers of person-years are studied. The data are inadequate to evaluate the possibility of a threshold at lower levels of exposure. Therefore, arsenic should not be considered to have a carcinogenic threshold.

III. Exposure Sources

A. Air levels

1. Population-weighted annual average ambient level measured in California = 1.9 ng As/m^3. Maximum 24-hour average measured at an ambient monitoring station: 20.0 ng As/m^3.

2. Levels measured near a "hot spot": A month-long average of 61 ng As/m^3 and a maximum 24-hour average of 392 ng As/m^3.

3. Indoor Air: Not available.

B. Reported levels in water

1. National data: Most surface waters contain less than 0.010 milligrams of arsenic per liter. In the West, 86-87% of samples had concentrations below that level. Public

drinking water supplies containing up to 0.27 mg As/liter have been noted. Private groundwater wells may contain substantially higher levels of arsenic (see below).

2. California drinking water: Public water supplies in California generally contain ≤ 0.005 mg As/liter. In the Central Valley, levels may be higher: in Hanford, samples have contained from 0.05 to 0.01 mg As/liter. Household well water containing up to 1.4 mg As/liter was noted in Lassen County in the early 1970's.

3. Comment: The national maximum contaminant level (MCL) for arsenic in drinking water is 0.05 mg/liter. This was not based on carcinogenesis, however. California enforces the same standard.

C. Reported levels in food: Surveys indicate that a range of 8 to 104 μg, or an average of 50 μg, of elemental arsenic may be consumed in an ordinary daily diet. Certain seafood contains high levels of organic arsenic compounds.

IV. Quantitative Risk Assessment

A. Range of extrapolation: From occupational to environmental levels in equivalent lifetime daily exposures.

1. Occupational to ambient: 10^2 to 10^3.
2. Occupational to hot spots: 12- to 20-fold.

B. Range of unit risks: Using California background lung cancer rates, the estimated incremental risks of lung cancer mortality per million persons having a continuous lifetime exposure to 1 $\mu g/m^3$ of arsenic:

SMOKING STATUS	MALES		FEMALES	
	MLE[1]	UCL[2]	MLE	UCL
Never	780	1200	400	630
Former	3400	5300	1800	2900
Light	4700	7400	2600	4100
Heavy	8400	13000	5200	8200
Average	2900	4600	1300	2100

(Ratio of UCL to to MLE: 1.6)

---

[1] MLE - Maximum Likelihood Estimate.

[2] UCL - Upper 95% Confidence Limit.

C. Incremental risks at ambient levels (1.9 ng/m^3) in California (lung cancer mortality per million persons due to airborne arsenic) are as follows:

SMOKING STATUS	MALES		FEMALES	
	MLE	UCL	MLE	UCL
Never	1	2	0.8	1
Former	6	10	3	5
Light	9	14	5	8
Heavy	16	25	10	16
Average	5	9	2	4

2.0 UPTAKE, DISTRIBUTION, AND METABOLISM

The United States Environmental Protection Agency (EPA) has summarized much of the available information on the uptake and metabolism of arsenic compounds by humans (EPA 1984). The following discussion highlights information from the EPA's summary and other relevant data.

2.1 Absorption

The major routes of human exposure to arsenic compounds are inhalation and ingestion. The amount absorbed by inhalation has not been determined, while the amount absorbed following ingestion appears to be greater than 95% (EPA 1984).

2.1.1 Inhalation

Arsenic compounds are absorbed from the lungs (EPA 1984). However, the one available report on experimental human inhalation of arsenic (Holland et al. 1959) does not contain adequate data for estimating absorption (Piscator 1986a). For this experiment, each of eight lung cancer patients smoked a cigarette spiked with arsenic-74 radiolabeled sodium arsenite, and then stood with his chest 24 inches from a Geiger counter. This study does not provide an accurate estimate of deposition because a significant amount of arsenic may have been lost in sidestream smoke (smoke produced by the cigarette, but not directly inhaled). A small amount of arsenic from sidestream smoke may have been deposited onto the subjects' chests, however. Furthermore, data from this study are inappropriate for estimating

absorption from ambient exposure because smoking is unlike normal breathing, cancerous lungs are unrepresentative of normal lungs, and the residence time of arsenic compounds in the lung varies dramatically.

Absorption of arsenic appears to parallel the water solubility of the arsenic compound. After intratracheal instillation in the hamster, readily soluble compounds such as sodium arsenite and sodium arsenate are more rapidly absorbed than less soluble compounds such as lead arsenate or gallium arsenide (Marafante and Vahter 1987, Rosner and Carter 1987). Almost all (98%) of an administered dose of arsenic trioxide (containing about 2 mg As) disappeared from rat lungs 24 hours after intratracheal instillation, while only about 50% of a similar dose of calcium arsenate was lost after 162 hours (Inamasu et al. 1982). However, this study is not directly applicable to human exposure since intratracheal instillation is not a representive model of deposition produced by ordinary inhalation.

Several studies of workers at copper smelters have assessed correlations between airborne exposure levels and urine arsenic levels. Urinary measurements do not quantify the inhalation absorption of arsenic since it is excreted by several routes. Early studies found the correlation between arsenic intake and urinary levels to be poor (Smith et al. 1977, Pinto et al. 1977). However, Osborne (1984) and Enterline et al. (1987) used data from a wider range of exposures, including relatively high exposures of smelter workers and developed a mathematical relationship that could be used to estimate air levels (see Section 11.1.2a).

2.1.2 Ingestion

Arsenic is normally present in the human diet. A 1974 U.S. Food and Drug Administration (FDA) survey indicated that approximately 50 μg of arsenic is contained in the daily diet (EPA 1984). FDA scientists authored reports published in 1986 that put this figure at 45.9 μg in adult diets, 15.5 μg in toddler diets, and 1.26 μg in infant diets. Jelinek and Corneliussen (1977) reported a range of 8 to 104 μg of arsenic ingested daily. Soluble inorganic arsenic is almost totally absorbed from the human gastrointestinal tract (EPA 1984). Arsenic is concentrated in fish as well as aquatic plants and invertebrates (Fishbein 1981) and can be accumulated in aquatic food chains (McCabe et al. 1983). Ryegrass and spring wheat crops preferentially take up arsenic from fly ash (Andersson and Persson 1982). Thus, increased ingestion of arsenic compounds could result from their release into the air. Since ambient airborne levels of arsenic are generally less than 14 nanograms per cubic meter (See Part A) and 18 m^3/day is a normal breathing rate, the diet provides a larger exposure to arsenic than does ambient air. However, different routes of exposure present different toxicological concerns.

Inhalation of ambient arsenic may be more toxic than ingestion of an equivalent amount of dietary arsenic. Inhaled arsenic cannot be methylated (i.e., detoxified) before it reaches the lungs, whereas orally ingested arsenic ordinarily passes first through the liver. Furthermore, some arsenic in food, especially seafood, is found in organic compounds, which are less toxic than inorganic compounds.

2.2 Distribution

After ingestion, arsenic is distributed to blood cells and plasma (Winship 1984). As(III) is taken up by liver cells. As(V) is not readily absorbed by hepatocytes, but is quickly concentrated in the kidney (Marafante et al. 1985). In oral exposure studies, arsenic accumulated in the heart and lung (Schroeder and Balassa 1967, Bencko 1973). Within two to four weeks after ingestion by humans, arsenic is incorporated into hair, nails, and skin because of the large number of sulfhydryl groups (to which arsenic can bind) in keratin, the principal protein of these tissues (Schoolmeester and White 1980). Four weeks after ingestion, arsenic can be detected in bone, where it substitutes for phosphorus. Deposition of arsenic in bone coincides with a decrease in liver and kidney levels (Schoolmeester and White 1980). Most likely, As(III) binds to sulfhydryl groups, and As(V) replaces phosphorus.

Arsenic is distributed in a similar manner following inhalation (Bencko and Symon 1970). Mice exposed to a 1% arsenic aerosol (179.4 μg As(III)/m^3 for 6 hours/day and 5 days/week) accumulated arsenic in the skin, liver, and kidney in one week. From the second to fourth weeks of exposure, levels in liver and kidney declined markedly. A less marked decline in skin levels was observed after the fourth week (Bencko 1973, Bencko and Symon 1970).

Arsenic readily crosses placental brain barriers of rodents and humans (Gerber et al. 1982, Willhite and Ferm 1984). In fetuses, arsenic levels are highest in brain, bone, liver, and skin (Kadowaki 1960). In mice, levels of arsenic were elevated in the brain two hours after single oral administrations of arsenate or arsenite, but clearance from the brain was

nearly complete by 24 hours, indicating that little arsenic binds to brain tissue (Vahter and Norin 1980). There have been similar findings in rats (Kamkin 1982, Valkonen et al. 1983). However, rats concentrate arsenic in their red blood cells to an extent not seen in any other species (NAS 1977, EPA 1984).

2.3 Metabolism

2.3.1 Detoxification

Metabolism of arsenic is a detoxifying process of reduction and methylation. As(V) is first rapidly reduced *in vivo* to the more toxic As(III) intermediate (Marafante et al. 1985). Then As(III) is methylated to form the less toxic mono- and di-methyl metabolites, methylarsonic acid (MMA) and dimethylarsinic acid (DMA) (EPA 1984, Willhite and Ferm 1984). Data indicate that As(III) is a stable intermediate in the methylation of As(V) (Marafante et al. 1985). Marafante et al. (1985) speculated that the reduction of As(V) probably occurs in the blood. Nevertheless, As(V) is rapidly accumulated in the kidney (Marafante et al. 1985) and may possibly be reduced there. Only As(III) is methylated (Vahter and Marafante 1985), and the liver is the principal site for methylation (Schoolmeester and White 1980, Buchet et al. 1984, Marafante and Vahter 1984, Marafante et al. 1985, Buchet and Lauwerys 1985).

Some evidence indicates that the proportion of absorbed inorganic arsenic that is methylated decreases as exposure increases, suggesting saturation of this pathway. The arsenic methylation capacity of humans was saturated in some cases of acute intoxication (for example, ingestion of several hundred

mg As), but not at nontoxic doses (for example, 0.5 mg As) (Buchet et al. 1982, 1984). It has been suggested that cancer risk extrapolation for arsenic that is linear with dose may be inappropriate because of saturation of the detoxification pathway (Piscator 1981). However, although saturation of the methylation pathway may have occurred at the highest occupational exposure concentrations associated with lung cancer, the tumor of concern (lung cancer) occurs at the contact site (the lung), and the high end of the dose-response curve does not exhibit an inflection or curvature that would indicate saturation of detoxification (in fact, increasing cumulative exposure is associated with decreasing slope in this range) (see Chapters 9-11).

2.3.2 Oxidation and Reduction

In vivo, As(III) is not significantly oxidized to As(V). Early studies suggested otherwise, but it was later found that a flawed analytical technique identified methylated arsenic as As(V) (EPA 1984). In a well conducted study, Crecelius (1977) found relatively little As(V) in a human subject's urine after ingestion of wine containing 50 μg arsenite (As(III)) and 13 μg arsenate (As(V)), a ratio of 80% to 20%. After 61 hours, approximately 80% of the ingested arsenic was excreted; of this, about 80% was DMA or MMA, 10% was arsenite, and 10% was As(V). Presumably much of the the As(V) present was reduced to As(III) and methylated before excretion. Data from intratracheal instillation of hamsters with large doses of sodium arsenite (Marafante and Vahter 1987) indicate that some As(III) may be oxidized to As(V) in the lungs before absorption into the blood.

2.3.3 Interaction with Selenium

Selenium is an essential nutrient which is toxic in high doses. Arsenic may combine with selenium by reacting with selenol (-SeH) groups to form a conjugate that passes readily into the bile (NAS 1977). By this mechanism, arsenic may exert a protective effect against poisoning by high doses of selenium (NAS 1977). Independently, selenium and arsenic (As(III)) have some protective effects against the development of certain tumors (see Chapter 8), but one can antagonize the other's protective effects (Schrauzer et al. 1978).

2.4 Elimination

Inorganic arsenic compounds and their metabolites are eliminated primarily in urine, although some arsenic appears in the stool, hair, desquamated skin, and nails. In an experiment with hamsters, an As(V) compound was found to be more readily excreted in the urine while an As(III) compound was found in bile (Cikrt et al. 1980). Biliary transport data are not available for man (EPA 1984). Nevertheless, biliary excretion does not contribute significantly to elimination because bile-excreted arsenic is reabsorbed (EPA 1984). Clearance of arsenic in man and dogs has been estimated to fit a three-compartment model with half times of 1, 5, and 35 hours (EPA 1984 and Charbonneau et al. 1978). Rats retain arsenic for unusually long periods of time, which may affect interpretation of toxicological studies using this species. Whole-body retention of arsenic has been found to be 20 times greater in rats than in mice (Willhite and Ferm 1984). The half-time

for blood clearance of inorganic arsenic in the rat is about 60 to 90 days (EPA 1984).

Biliary excretion of arsenic is also quite different in rats than in other animals. Following i.v. administration of As(III), biliary excretion of As is much faster in rats than in rabbits and dogs (Klaassen 1974). This suggests that there may be an effective active transport mechanism for arsenic in rats (Klaassen 1974). However, due to arsenic's enterohepatic circulation in the rat, less than 10% of the administered dose appeared in the feces over a 7-day period (Klaassen 1974).

3.0 ARSENIC AS AN ESSENTIAL ELEMENT

Arsenic has been found to be an essential element of the diet of a few mammalian species, but there is disagreement about whether it is essential to the human diet (it has not been suggested that inhalation of arsenic is essential). An element is considered essential if a diet deficient in the element leads to an adverse health effect. Uthus and co-workers (1983) and the EPA (1984) have summarized studies demonstrating adverse effects of arsenic-deficient diets in goats, mini-pigs, chicks, and rats. In these studies arsenic deficiency affected manganese metabolism. Manganese is an essential element in humans. By inference, if a lack of arsenic were found to adversely affect human manganese metabolism, arsenic would be considered essential in humans, too. Further study of manganese-arsenic interaction is needed to resolve the issue. The interspecies concordance of the animal studies' findings and the lack of negative findings suggest that arsenic is likely to be an essential element in humans as well.

A trace element may also be classified as essential if the amount of the element in the body is maintained by biological processes (Liebscher and Smith 1968). By this criterion, arsenic is nonessential (Liebscher and Smith 1968). Neither a specific receptor nor a physiological role for arsenic or its compounds has been identified in humans (EPA 1984).

In an attempt to classify arsenic as essential for humans, arsenic tissue concentrations were examined from healthy adults who died as a result of violence (Liebscher and Smith 1968). The investigators found that these concentrations approximated a log-normal distribution, as did antimony and

mercury. However, the concentrations of known essential elements (copper and zinc) approximated a normal distribution. Liebscher and Smith proposed that this distinction could be used to predict the essentiality of trace elements because active maintenance of a particular tissue level of any substance would result in an interindividual normal distribution. Nevertheless, it has been noted that the arguments of Liebscher and Smith are "purely theoretical" (NAS 1977 at 143), and there may be some essential elements for which no active homeostatic mechanism exists. For arsenic, common ingestion levels may be high enough to eliminate any need for a homeostatic mechanism. Even so, this observation does not demonstrate that arsenic is indeed essential.

4.0 ACUTE TOXICITY

4.1 Human

High airborne concentrations of arsenic trioxide in occupational environments has caused irritation of the eyes, nasal mucosa, larynx, and bronchi (Pinto and McGill 1953). Nevertheless, acute exposure to the current ambient levels of airborne arsenic in California is not expected to produce any significant ill effects. The highest 24-hour average ambient concentration measured in California was 0.392 μg As/m^3, 1 km from a secondary lead smelter. Elsewhere in the state's two major industrialized air basins, measurements never exceeded 0.014 μg As/m^3 (See Part A).

The lethal oral dose of arsenic trioxide for humans is estimated to be approximately 70 to 180 mg (50 to 140 mg As or 0.8 to 2.3 mg As/kg for a 60 kg person), although toxic responses can result from much smaller quantities (Vallee et al. 1960, Thienes and Haley 1972). Based on lethality from oral exposure, humans are approximately an order of magnitude more sensitive to acute arsenic exposure than other animals (see Section 4.2).

Poisoning by ingestion of arsenic initially results in a metallic taste and garlicky breath. Victims may experience neurological symptoms as well as nausea, vomiting, gastrointestinal (GI) distress, fever, and sometimes shock. Small doses of arsenic can produce headache and muscle cramping; large doses can produce convulsions and death; the amounts that produce these symptoms vary with the particular compound ingested, its physical

form, and the inherent tolerance of the patient to arsenic (Schoolmeester and White 1980).

Acute oral arsenic poisoning may result in vascular and neurological damage. Capillary damage and dilation may occur in the gastrointestinal mucosa, leading to edema and vesicle formation, which may result in epithelial sloughing and loss of plasma into the GI tract. Cardiac muscle becomes weakened and blood pressure can fall to the point of shock (NAS 1977). Kidney damage, common in smaller animals as well as humans, involves dilation of glomerular capillaries, resulting in swelling and tubular degeneration (NAS 1977).

Accidental ingestion of a single dose of arsenic may result in peripheral neuropathy. In four such cases, each involving one or two teaspoonfuls of inorganic arsenic (powder or solution), the onset ranged from 10 days to 3 weeks after arsenic ingestion and recovery was slow and incomplete, even 6 to 8 years later. Electrophysiological studies showed reduced motor nerve conduction velocity and abnormalities of sensory nerve action potentials (Le Quesne and McLeod 1977). Biopsy and autopsy studies of poisoning victims have shown nerve damage, especially Wallerian degeneration of long-axon myelinated nerve fibers (EPA 1984). Central nervous system effects have also been seen after ingestion of toxic doses of inorganic arsenic; in approximately 5% of such cases, patients experience central depression without gastrointestinal symptoms (Klaassen 1985).

4.2 Animal

Oral LD_{50} values reported for various arsenic compounds range from 15 to 293 mg/kg in rats and from 10 to 150 mg/kg in other animals (EPA 1984). No mortality occurred in rats given up to 30 mg As/kg as dry arsenic trioxide mixed in their feed or in Swiss mice given 10.4 mg As/kg and C3H mice given 19.9 mg As/kg as arsenic trioxide in aqueous solution by oral intubation (NAS 1977).

Experiments to establish LC_{50} values and no-observed-effect levels (NOELs) for acute inhalation exposure to arsenic compounds have not been reported. Arsenic trioxide at 1500 $\mu g/m^3$ for 252 hours caused no changes in the behavior or appearance of 15 white rats, but whole blood cholinesterase activity, neurologic functioning, and sperm motility were disrupted (Kamil'dzhanov 1982).

5.0 CHRONIC AND SUBCHRONIC TOXICITY

Long-term exposure to arsenic compounds is associated with a variety of adverse effects, including neuropathies, vascular syndromes, hematological diseases, and decreases in immune response. Occupational exposure to approximately 50-500 $\mu g\ As/m^3$ (chiefly as arsenic trioxide) is associated with subclinical neuropathy and vascular disorders (see, e.g., Lagervist et al. 1986). The highest monthly average arsenic concentration measured in California, 0.061 $\mu g/m^3$ (one kilometer from a secondary lead smelter), is three orders of magnitude below this range. Also, the arsenic measured in California included a substantial quantity of As(V) (Shimp 1986), which is generally less toxic than As(III). Although there are few reliable data upon which to estimate a no-effect level, it is the opinion of the staff of the Department of Health Services (DHS) that noncarcinogenic chronic adverse health effects are not likely to be caused by exposure to ambient levels of arsenic.

5.1 Animal

Three months of inhalation exposure to 1.3 $\mu g/m^3$ arsenic trioxide (1.0 $\mu g\ As/m^3$) was reported by Rozenshtein (1970) as a NOEL in female albino rats where effects on the nervous system, brain tissue, and blood were noted at 4.9 $\mu g/m^3$ (3.7 $\mu g\ As/m^3$). This report lacks some important details, however (See Section 5.1.1 below). Several inhalation studies in hairless mice were concerned with tissue concentrations of arsenic rather than toxicologic

measurements (NAS 1977, Bencko and Symon 1969, 1970, Bencko 1973). Long-term studies examining reproductive effects are described in Chapter 6. Other effects are discussed below.

5.1.1 Central Nervous System. Rozenshtein (1970) reported that three months of exposure to arsenic trioxide aerosols at concentrations of 3.7 and 46 μg As/m^3 impaired conditioned reflex behavior and caused histopathological damage to brain tissue in rats. However, this report provides inadequate experimental detail to evaluate the validity of these findings: the number of animals was not noted and no procedure was given for either the behavioral experiment or monitoring the toxicant concentrations in the exposure chambers. Stomach intubation of rats with 2 or 10 mg arsenic trioxide (1.5 or 7.6 mg As) each day for 40 days impaired avoidance conditioning (a behavioral index thought to reflect central nervous system function) although no histopathological change in brain tissue was observed (Osato 1977). A variety of neurochemical effects, including an increase in the activity of lysosomal acid proteinase, were caused in rats by 0.77 mM sodium arsenite (As(III), 58 mg As/l) given in drinking water for 11 days (Valkonen et al. 1983).

5.1.2 Cardiovascular System. In one study (Carmingnani et al. 1983), chronic exposure to sodium arsenate in drinking water (50 mg As/l) increased rats' vascular response to β-adrenoreceptor stimulation, and decreased response to angiotensin I. After 320 days of exposure, however, no changes were noted in blood pressure, contractility of cardiac muscle, rate of contraction of the heart, or cardiovascular reactivity to various drugs.

In cats, electrocardiographic changes have been noted during several weeks of exposure to arsenate or arsenite in feed (0.5-1.5 mg As/kg feed). Blood concentrations associated with electrocardiographic abnormalities were as low as 0.03 mg As/l (Massman and Opitz 1954).

5.1.3 Blood. Hematological effects of arsenic in animals include decreased hemoglobin production, seen with arsenate and arsenite in rats and cats (Mahaffey and Fowler 1977, Byron et al. 1967, Massman and Opitz 1954) as well as with arsenite in rainbow trout (Oladimeji et al. 1984). Investigators have identified arsenic-induced disturbances of the heme biosynthetic pathway (Woods and Fowler 1977). The above-mentioned report by Rozenshtein (1970) noted significant depression of the number of circulating sulfhydryl groups in whole blood in rats exposed to 3.7 or 46 μg As(III)/m^3 for two or three months. The data cited to support this observation represent monthly samples of 10 animals per group compared to pre-exposure means based on 20 animals per group. Because of the unusual accumulation of arsenic in rat red blood cells, however, this observation may have little relevance to other species.

5.1.4 Immune system. Five or twenty daily 3-hour exposures to airborne arsenic trioxide ($\geq$76 μg As/m^3) inhibited pulmonary bacteriocidal activity in mice (Aranyi et al. 1985). Sodium arsenite inhibited the production of antibody-producing cells in mice at 0.5, 2.0, and 10.0 ppm in drinking water (Blakley et al. 1980). Furthermore, most studies have shown arsenic to increase susceptibility to infections (Vos 1977, Gainer and Pry 1972). However, in one in vitro experiment low concentrations of arsenite ($10^{-6.5}$

to $10^{-5.5}$ M) stimulated the viral plaque-inhibiting action of a certain concentration of mouse interferon (Gainer 1972).

5.1.5 Liver. Histopathological changes in liver tissue accompany arsenic exposure. In a study of mice, arsenite in drinking water (50 mg As/l, and roughly 6 mg/kg/day) caused an acute reaction characterized by enlargement of some membrane surfaces and loss of glycogen (Mohelská et al. 1980). Rabbits fed arsenates (lead, copper, and sodium, ≥0.3 mg As/kg/day) developed liver abnormalities including cirrhosis, with some protection afforded by alterations in diet (Von Glahn et al. 1938). Three months of airborne exposure of female albino rats to 4.9 mg/m^3 arsenic trioxide (3.7 mg As/m^3) produced fatty degeneration of hepatic cells (Rozenstein 1970). Dose-dependent structural changes in rat liver from exposure to arsenic trioxide in drinking water, and impaired mitochondrial respiration in rats injected with arsenite have been reported (Ishinishi et al. 1980, Ghafghazi et al. 1980).

5.1.6 Other Effects. Adverse effects on the skin after gastric exposure of rats to arsenic trioxide have been described (Osato 1977, see also U.S. Borax 1989). Drinking water exposure to sodium arsenate has adversely affected the kidneys of rats (Brown et al. 1976).

5.2 Human

Reports of chronic toxicity to humans of arsenic derive mainly from ingestion and inhalation exposure. The effects of high airborne exposures

to arsenic have been intensively studied in workplace environments at smelters. Other toxicants present in these environments may have contributed to some of the reported effects. Regarding ingestion exposure, many studies of chronic human exposure have been reviewed elsewhere (e.g., EPA 1984, NAS 1977).

5.2.1 Nervous System. Unilateral as well as bilateral neuropathy has been reported in humans (EPA 1984). A peripheral neuropathy with a "stocking-glove" distribution of dysesthesia is the most common arsenic-induced neurological lesion (Klaassen 1985). The predominant clinical features encountered in chronic arsenic neuropathy are paresthesia, numbness, and pain, particularly in the soles of the feet (Schoolmeester and White 1980). Encephalopathy, headache, convulsions, personality disturbance and/or coma have also been noted. Recovery from neuropathy induced by chronic exposure to arsenic compounds is generally slow, sometimes taking years. The degenerative changes consist of resorption of myelin and destruction of axonal cylinders; later, nerve atrophy and perineural fibrosis appear (Schoolmeester and White 1980).

Subclinical neuropathy manifested by decreased nerve conduction velocity was associated with occupational exposures at a copper smelter in Sweden to around 500 $\mu g\ As/m^3$ and below (Blom et al. 1985). Sweden's occupational standard, 50 $\mu g\ As/m^3$ (enacted in 1975) appears adequate to protect against the development of clinical neuropathies (Lagerkvist et al. 1986, Blom et al. 1985).

5.2.2 Cardiovascular System. Epidemiological evidence indicates that peripheral vascular diseases have often been associated with chronic arsenic exposure. The most significant vascular conditions are Blackfoot disease, Raynaud's phenomenon and acrocyanosis.[1] Administration of Fowler's solution (potassium arsenite) is associated with serious liver pathology, including portal tract fibrosis, an increase in the number of portal veins, and noncirrhotic portal hypertension (Morris et al. 1974).

Electrocardiographic changes have been noted prior to irreversible cardiac or vascular damage (Weinberg 1960).

Inhalation exposures of smelter workers to arsenic have been reported to be associated with Raynaud's phenomenon and blood pressure abnormalities (Lagerkvist et al. 1986). The exposures received by these workers were approximately 50-500 $\mu g\ As/m^3$ (See Section 5.2.1).

Blackfoot disease, which can involve gangrene of the extremities, was found to be associated with arsenic-contaminated groundwater in an area of Taiwan (Tseng 1977). The arsenic concentrations in the water ranged from 0.01 to 1.82 ppm (Tseng 1977). The prevalence of Blackfoot disease increased with increasing age and well-water arsenic concentration (Tseng 1977). It has been suggested that other known or potential vasoactive substances found in the contaminated water may have contributed to the Blackfoot disease (EPA 1984). In addition, arsenic's effects on the vasculature may also be due to effects on neural control of arteries, with Blackfoot disease secondary to arterial spasm in the legs (NAS 1977).

Raynaud's phenomenon and acrocyanosis were noted in a case of endemic chronic arsenic poisoning in Antofagasta, Chile (Zaldívar and Ghai 1980, Zaldívar et al. 1978, Zaldívar and Guillier 1977). The arsenic concentrations in this city's drinking water ranged from 0.05 to 0.96 ppm (average: 0.60 ppm) until three years before the initial clinical study, when a filter plant was installed; subsequently, the concentration ranged from 0.02 to 0.40 ppm (average: 0.08 ppm) (Zaldivar and Guillier 1977). Similar vascular disorders, as well as abnormal electrocardiograms, have been noted in vineyard workers exposed to arsenical insecticides (NAS 1977). Autopsies of children exposed to arsenic in Antofagasta revealed fibrous thickening of small and medium-sized arteries and a hypertrophic heart (Zaldívar and Guillier 1977).

5.2.3 Blood. Hematological effects are common with chronic arsenic poisoning. Anemia and leukopenia (low levels of red and white blood cells) are "almost universal" and are commonly accompanied by thrombocytopenia (low platelet count) and mild subacute eosinophilia (increased numbers of eosinophils, a type of white blood cell) (Schoolmeester and White 1980). Broken nuclei, elevated numbers of mitotic figures and anisocytosis (abnormal variation in red blood cell size) may also be observed in those chronically exposed to arsenic (Schoolmeester and White 1980, Klaassen 1985).

5.2.4 Nails. Nails, as well as hair and skin, are principally composed of keratin, to which trivalent arsenic readily binds. Transverse lines of whiter-than-normal nail (Mees' lines) are seen after acute and chronic exposure to arsenic (Schoolmeester and White 1980).

5.2.5 Skin. Chronic arsenic poisoning may cause a variety of skin lesions, some of which may be precancerous or cancerous (Klaassen 1985). Darkening of areas with little pigment, especially the palms of the hands and the soles of the feet, or multiple lesions of Bowen's disease, which can be a cutaneous marker for various systemic neoplastic processes, may occur (Schoolmeester and White 1980). Abnormal skin pigmentation was observed in 80% of the study population in Antofagasta, Chile (See Section 5.2.2), and 36.1% displayed hyperkeratosis (NAS 1977).

5.2.6 Irritant and Immune System Effects. Subchronic arsenic exposure can cause a variety of irritating symptoms. Arsenic-contaminated beer has produced vomiting, diarrhea, conjuntivitis, rhinitis, laryngitis, and bronchitis; this beer was contaminated at a level such that a moderate drinker would receive a dose equivalent to only a fraction of the quantity of arsenic which would then (in 1900) have been prescribed as a treatment for epilepsy (NAS 1977). The beer contained as much arsenic as 15 ppm, and of some 6,000 people who became ill, 70 died (Vallee et al. 1960). Many arsenic compounds cause allergic skin sensitization (NAS 1977).

Dusts of arsenic trioxide dissolve in the moisture of skin folds and mucus membranes, causing inflammation (Dinman 1960). Exposure of workers to high levels of airborne arsenic (up to 7 mg As/m^3) has been associated with nasal septum perforation, rhinopharyngolaryngitis, tracheobronchitis, and pulmonary insufficiency (EPA 1984). In general, data associating specific concentrations of specific arsenical compounds with irritant effects are lacking. A recent review by the American Conference of Governmental Industrial Hygenists (ACGIH 1986) found no reports of industrial or

experimental exposure containing criteria on which to base an industrial threshold limit value (TLV).

Notes

[1]Raynaud's phenomenon consists of intermittent vasoconstriction, marked by severe pallor, in the fingers or toes (and sometimes the ears or nose). Acrocyanosis is a condition marked by bluish discoloration of the extremities with persistent, uneven, mottled blue or red discoloration.

6.0 REPRODUCTIVE TOXICITY

Arsenic compounds are fetotoxic and teratogenic in several laboratory animals. Specific effects on reproductive biology have been summarized and reviews of reproductive toxicity experiments are available (EPA 1984, Willhite and Ferm 1984, Hood 1983). Most of the experiments were not designed to determine no-observed-effect levels (NOELs). Although some experiments appeared to demonstrate NOELs for arsenic at specific stages of pregnancy, at other stages these same doses were teratogenic or fetotoxic (Willhite 1985). Highlights of relevant studies are presented below and in Appendix G.

Three inhalation studies have been reported. The lowest-observed-adverse-effect level (LOAEL) in these studies is 0.76 μg As(III)/m^3; reduced fertility and delayed fetal ossification were reported in rats exposed to this level (Kamkin 1982). The validity of this report cannot be evaluated, however, because key experimental details were not reported. In another study, cytological and structural damage to murine fetuses was observed after four hours of exposure to 200 μg As(III)/m^3 on each of days 9-12 of gestation in mice (Nagymajtenyi et al. 1985). Also, exposure of male rats to 360 μg As(III)/m^3 for 800 hours decreased the period of motility of spermatozoa (Kamil'dzhanov 1982).

Common terata seen after administration of arsenic compounds to pregnant mammals include malformations of the brain, genitourinary abnormalities, skeletal malformations, micropthalmia or anopthalmia (small or missing eyes), and ear deformities (Willhite and Ferm 1984, Winship 1984). Although

arsenic has repeatedly been demonstrated to be a teratogen in animals, there is a lack of such data in humans (Schoolmeester and White 1980). A single case of premature birth and neonatal death associated with deliberate arsenic ingestion has been reported in humans (Lugo et al. 1969). Decreased birth weight and increased frequencies of spontaneous abortion and malformed offspring have been found in arsenic-exposed smelter workers (Nordstrom et al. 1978a,b; 1979a,b). Although at high doses arsenic may pose a risk of reproductive toxicity in humans, there are inadequate data to evaluate whether any such risk is created by exposure to current ambient levels of arsenic.

6.1 Human

Studies in Sweden associated reduced birthweight and increased rates of spontaneous abortion with employment at a smelter, the types of employment at the smelter, and distance of residence from the smelter. The association between employment at the smelter and spontaneous abortion was even more pronounced when both parents were employed there (Nordstrom et al. 1978a,b, 1979a,b; Beckman 1978). For mothers who were employed at the smelter during pregnancy, malformed offspring appeared at twice the expected rate and the risk of multiple malformations was about four times as high as expected. There was no statistically significant association between congenital malformations and distance of residence from the smelter (Nordstrom et al. 1979b). Interpretation of these findings is confounded by the presence of toxicants other than arsenic, including lead, in the smelter processes (Nordstrom et al. 1978a, 1979b; Beckman 1978). The studies did not report the arsenic concentrations associated with the adverse effects.

6.2 Animal

6.2.1 Rats

Given the unusual pharmacokinetics of arsenic in rats (see Chapter 2), the relevance of studies in rats must be assessed cautiously. Arsenic research conducted with rats is difficult to apply to man (NAS 1977).

Kamkin (1982) reported delayed fetal ossification and a statistically significant increase in preimplantation mortality after five months of exposure to concentrations as low as 1 $\mu g/m^3$ of arsenic trioxide (0.8 μg As/m^3). Key details are missing from this report, however: no data are presented to substantiate the claim of delayed ossification; no details are given of the method used to assess preimplantation mortality or of the procedures used in biochemical assays. Thus, the significance of this report cannot be adequately evaluated.

The most sensitive effect noted in an airborne exposure study of male rats and arsenic trioxide was a decrease in the period of motility of the spermatozoa (Kamil'dzhanov 1982). At an arsenic concentration of 32.4 mg/m^3, motility was decreased after 48 hours; at 7.95 mg/m^3, after 120 hours; at 1.45 mg/m^3, after 252 hours; and at 0.36 mg/m^3, after 800 hours.

Intraperitoneal injection of pregnant rats with various doses of sodium arsenate ($\geq$ 7 mg As/kg) caused a variety of soft-tissue and skeletal malformations in their offspring (Beaudoin 1974, also see Appendix G). Thirty mg/kg of sodium arsenate (11 mg As/kg) was found to be the "optimum" dose when administered on day 8, 9, or 10 of gestation. Similar results

were observed in a later study (Burk and Beaudoin 1977), which examined renal agenesis.

6.2.2 Hamsters

The hamster has been widely studied as a model for arsenic-induced teratogenesis and is the most sensitive mammalian species tested. Details of hamster teratogenesis induced by intravenous exposure to sodium arsenate have been reported by Ferm and Saxon (1971) and Willhite (1981).

The subcutaneous implant method used by Ferm and Hanlon (1985) closely approximates the near-constant-rate exposure which may result from air pollution. Sodium arsenate (As(V)) produced teratogenic effects at the lowest dose tested, 5.1 mg As/kg/day delivered throughout the critical period of embryogenesis. This daily dose would correspond to an ambient air concentration of 17 mg As/m^3 for a 60-kg person who inhales 18 m^3 of air per day and absorbs all of the arsenic in that air.

Hyperthermia (induced by high ambient temperature to simulate fever) acts synergistically with intraperitoneal injection of arsenate in inducing teratogenesis and fetal mortality (Ferm and Kilham 1977). Therefore, human fetuses of mothers who run fevers during pregnancy may be especially sensitive to As(V).

6.2.3 Mice

In mice, an inhalation study using arsenic (III) trioxide found teratogenic effects at three dose levels (200, 2200, and 21600 μg As/m^3 for 4 hrs/day for 4 days, days 9-12 of gestation) (Nagymajtenyi et al. 1985, also see Appendix G). The investigators examined 50 fetuses from each dose level and a control group. The effects were not statistically significant at the two lowest doses, but these doses are not NOELs. Significant trends (increasing response with increasing dose) are apparent throughout the data in specific ossification defects (e.g. skull and limbs) as well as in the number of fetuses with skeletal malformations. The lowest dose was less than occupational exposures of many workers, but was four orders of magnitude higher than ambient air concentrations. Other reproductive studies of mice exposed to arsenic by gavage, drinking water and intraperitoneal injection are noted in Appendix G.

6.3 Discussion

Trivalent arsenic compounds are generally more toxic than As(V) compounds, but arsenate (As(V)) has been more frequently teratogenic in animals than arsenite (As(III)) (Hood 1983). The optimal teratogneic dose of As(V) for a particular route of exposure may be higher than that of As(III), however. In mice, arsenate As(V) produced more severe malformations than arsenite As(III); the two valence states produce characteristic patterns of malformations (Hood 1983 at 137).

Although in some animal experiments the optimal doses used to produce malformations were near doses which are associated with maternal toxicity and mortality (Hood 1983), this was not always the case (Willhite 1986a,b). Studies showing clear evidence of malformations without maternal toxicity include those of Willhite (1981) in hamsters and Morrisey and Mottet (1983) in mice. In the experiment by Morrisey and Mottet (1983), intraperitoneal injection with 45 mg/kg of sodium arsenate produced exencephaly in 65% of the offspring without producing signs of maternal toxicity. Furthermore, to discount the teratogenicity of arsenic compounds on the basis of maternal toxicity would be inappropriate because the compounds appear to have specific targets in developing organisms (Hanlon and Ferm 1974). Arsenic may have teratogenic or other adverse reproductive effects at high doses in humans. Such effects would be unlikely to occur at ambient arsenic levels because in animals they have only been observed at much higher levels (more than three orders of magnitude higher). However, existing data are inadequate to rule this possibility out definitively.

7.0 GENOTOXICITY

Arsenic compounds are genotoxic in assays of chromosome damage and inhibition of DNA repair. Data from mammalian cell cultures suggest that arsenic may induce mutations by its effects on chromosomes, but no inorganic arsenic compound consistently tests positive as a mutagen in specific-locus tests. Inorganic arsenic has been negative in most bacterial assays testing for mutagenicity. This chapter presents highlights of the gentoxicity research with arsenic; more comprehensive summaries may be found elsewhere (e.g., EPA 1984, IARC 1987, U.S. Borax 1989).

7.1 Bacteria

Arsenic compounds have tested negative in bacterial systems for the ability to induce mutations (Table 7-1). However, some arsenic compounds enhance mutation induced by ultraviolet (UV) radiation. Inorganic arsenic compounds have tested negative in the Ames assay.

Nishioka (1975) found that sodium arsenate induced mutations in *Escherichia coli*, but Rossman and colleagues (1980) were unable to replicate this result and offered several reasons why the positive finding might have been spurious: in particular, Nishioka used an inappropriate denominator for calculating mutation frequencies.[1] Rossman and co-workers also observed negative results for sodium arsenite using the same strain of *E. coli* in a fluctuation test, a procedure which is more sensitive than standard agar plate assays (Rossman et al. 1980; see also Luria and Delbrück 1943). Nunoshiba and Nishioka (1987) reported that sodium arsenite inhibited

certain spontaneous and induced mutations in E. coli; they suggested that this was mainly due to inhibition of induction of a particular gene (umuC) involved in error-prone ("SOS") DNA repair.

Certain organic arsenical pesticides, such as thiacetarsamide sodium (TAA) and cacodylic acid, have tested positive for mutation in E. coli assays (Piper et al. 1979, Simmon et al. 1977).

Inorganic arsenic tested positive in the rec assay (Kanematsu et al. 1980). When a chemical inhibits cellular growth in recombination repair-deficient (rec^-) bacteria more than in wild-type (rec^+) bacteria, it is presumed that the test chemical damages cellular DNA. A chemical does not have to produce mutations to be considered positive in the rec assay: the DNA damage may be lethal rather than mutagenic. Relatively high concentrations (0.05 to 0.1 M) of arsenic compounds (including arsenic trioxide and sodium arsenate) were used in this assay.

Arsenic is unusual among carcinogenic metal elements in that it has not been shown to decrease the fidelity of DNA synthesis. Of ten metals which are known carcinogens or mutagens, arsenic is the only one that does not increase misincorporation of bases into DNA (Zakour et al. 1981).

7.1.1 Interactions with UV Radiation

Low concentrations of arsenite (0.1 mM) inhibit DNA repair in bacteria in which mutations have been induced by UV light (Rossman 1981a).[2] Arsenate (up to 0.5 mM) had no effect on DNA repair. Slightly higher concentrations

of both arsenite (2 mM) and arsenate (10 mM) diminished UV-induced mutation in excision repair-competent strains of E. coli (Okada et al. 1983).[3]

In these two experiments, arsenic demonstrated different effects at different dose levels. At the higher doses (Okada et al. 1983) DNA synthesis was slowed, prolonging the period for excision repair. At lower doses, the rate of DNA synthesis was not affected: thus, the effect of the excision repair inhibition was more pronounced (Rossman 1981a). Two conclusions can be derived from these experiments: (1) arsenite can inhibit excision repair, and (2) both arsenite and arsenate can slow DNA replication and synthesis.

7.2 Yeast

Sodium arsenite (As(III)) was reported to give a "weak positive response" for reverse mutation in the yeast Saccharomyces cerevisiae (Singh 1983), but inadequate details were provided to interpret this result (EPA 1984). Also, the concentration of arsenite used, 0.1M, was high.

7.3 Mammalian Cells

Many arsenic compounds induce chromosomal abnormalities in mammalian cells but have not been shown to cause base-sequence mutations in the absence of chromosomal abnormalities. Arsenic exposure is associated with elevated levels of sister chromatid exchange (SCE) in numerous studies (EPA 1984). Increased SCE has been observed in individuals with Blackfoot disease (see

Chapter 5) (Wen et al. 1981). Zanzoni and Jung (1980) demonstrated a dose-related increase in SCE in cultured human lymphocytes exposed *in vitro*, and Wan et al. (1982) observed this effect in Chinese hamster ovary (CHO) cells. Sodium arsenite injected intraperitoneally in male mice was active in the micronucleus test, though negative in the dominant lethal test and an assay of sperm abnormalities (Deknudt et al. 1986).

Inhalation exposure of arsenic trioxide by pregnant mice produced chromosomal aberrations in liver cells of fetuses (Nagymajtényi et al. 1985). Exposure was 4 hours/day on days 9 to 12 of gestation. The number of cells with aberrations among 200 cells increased from 6 in the control group to 10, 13, and 24 in the low, medium, and high dose groups, respectively. This number reached statistical significance ($p < 0.05$) at the high dose, 28.5 mg/m^3 (21.6 mg As(III)/m^3).

Both sodium arsenite As(III) and sodium arsenate (As(V)) induced morphological transformation of cultured Syrian hamster embryo cells. Clear dose-response relationships were observed; arsenite was more potent than arsenate. These effects were associated with chromosome aberrations and other cytogenetic effects (Lee et al. 1985b).

Chromosomal aberrations may explain the weak positive response observed in a forward mutation assay in mouse lymphoma cells (Oberly et al. 1982). Although As(III) was negative in a hypoxanthine guanine phosphoribosyl transferase (HPGRT) locus assay (Rossman et al. 1980), Oberly and co-workers (1982) observed increased mutation frequencies with compounds of As(III)

and, after metabolic activation, As(V)[4] in the L5178Y mouse lymphoma cell thymidine kinase (TK) locus assay.

Amacher and Paillet (1980) reported negative results with As(V) in the TK assay (Table 7-1). They observed increased mutation frequencies but they did not observe increased absolute numbers of mutants.

Arsenic may affect gene expression as well as chromosomal structure. Exposure to sodium arsenate (As(V)) at concentrations as low as 1.3×10^{-5} M induced transformation of Syrian hamster embryo cells (DiPaolo and Casto, 1979). The karyotype of the transformed cells was not reported.

Arsenic also affects mitogenesis. In an experiment by McCabe and co-workers (1983), very low concentrations of arsenite (As(III), 2×10^{-6} M) or arsenate (As(V), 5×10^{-6} M) increased the rate of mitogenesis, as measured by the rate of incorporation of [^{3}H]-thymidine into DNA in human lymphocytes stimulated to divide by phytohemagglutinin (PHA). Higher concentrations (4×10^{-6} M arsenite or 5×10^{-5} M arsenate) inhibited mitogenesis. Stimulation of mitosis may be a mechanism by which arsenic induces epidermal hyperkeratosis, a potentially precancerous lesion. Any increase in skin cell mitosis increases the opportunity for the introduction of errors in the DNA replication process (McCabe et al. 1983). The maximum contaminant level set by the U.S. Environmental Protection Agency for arsenic in drinking water is 0.05 mg/l, or 6.7×10^{-7} M (NTP 1985, 40 CFR 141.11).

Tsutsumi and colleagues (1980) found inhibition of [^{3}H]-thymidine uptake with exposure to dissolved arsenic trioxide (As(III)) in murine lymphocytes.

The lowest As(III) concentration tested was about 5×10^{-6} M, which may explain why these investigators saw no stimulation of mitogenesis.

7.3.1 Human Cells

Sodium arsenite (As(III)) at concentrations (7.7×10^{-7} to 3.1×10^{-6} M) comparable to the arsenic levels found in the urine of smelter workers caused chromosomal aberrations in human lymphocytes exposed in vitro (Nordenson et al. 1981). The low concentration produced a statistically significant increase in gaps, and at 1.5×10^{-6} M, chromatid breaks became significant. Arsenite-induced chromosome breaks, although not statistically significant, were also apparent. Sodium arsenate (As(V)) tested negative at these same concentrations.[5] This study did not employ metabolic activation.

Researchers observed statistically significant increases in the frequency of aberrations (gaps, chromatid breaks, and chromosome breaks) in lymphocytes cultured from smelter workers (without in vitro exposure). The exposure concentrations producing these effects were not available (Nordenson et al. 1978, Nordenson and Beckman 1982).

7.3.2 Interactions with UV Radiation and Other Mutagens

Arsenic compounds have been shown to potentiate the genotoxic effects of UV light in mammalian cells as well as in bacteria. In cultures of CHO cells exposed to UV light, sodium arsenite increased the frequency (per 10^6 viable cells) of forward mutations to 6-thioguanine resistance, but did not increase the number of 6-thioguanine resistant cells (Lee et al. 1985a).

This suggests that the reported elevation of mutation frequency may be an artifact of differential killing of 6-thioguanine sensitive (nonmutant) CHO cells versus 6-thioguanine resistant cells. Lee et al. (1985a) also reported synergism between arsenite and UV light in producing chromosome aberrations and cytotoxicity. Arsenite was also found to be negative for forward mutation to ouabain resistance.

Sodium arsenite caused a synergistic increase in chromosome aberrations caused by ethyl methanesulfonate in dividing CHO cells, human fibroblasts, and human lymphocytes, but not in cultures of these cells that were in stationary phase (Huang et al. 1987). Based on these findings, the experimenters suggested that sodium arsenite might selectively kill cancer cells when used in combination with some cancer drugs (Huang et al. 1987).

7.4 Immune Suppression and Viral Transformation

Inorganic arsenic enhances the susceptibility of mice to infection by pseudorabies, encephalomyocarditis, and Rauscher leukemogenic viruses (Vos 1977). Arsenic may promote carcinogenesis and tumor growth by suppressing the immune system (NAS 1977). As(III) compounds are in the group of metal salts showing the most synergism with virally induced morphological transformation (Casto et al. 1979).

7.5 Conclusions

Arsenic compounds are clastogenic and induce both SCE and chromosome aberrations but have not been shown to cause base-pair substitutions or

frame-shift mutations. They may inhibit DNA repair. They inhibit the immune system and may play a role in the transformation of mammalian cells by viruses. As(V) required metabolic activation to induce a positive response in a mammalian cell forward mutation assay, and appears to be less potent than As(III) in several assays.

Notes

[1]For the denominator, Nishioka used the size of the initial inoculum rather than the final size of the plated population. Rossman and co-workers also pointed out that Nishioka's control values (number of mutants per plate) were lower than theirs, that Nishioka's experimental values (mutants per plate in the arsenite-treated sample) were not very different from their controls, and that the survival rate reported by Nishioka at an arsenite concentration of 0.8 mM for 15 min was comparable with the survival rate they found after treatment at 25 mM for 1 hour. These inconsistencies cast serious doubt on the positive finding of Nishioka.

[2]Low concentrations of arsenite (0.1 mM), but not arsenate (up to 0.5 mM), enhanced UV-induced reverse mutagenesis at the trp locus in WP2 *E. coli* strains which can carry out excision repair of UV-damaged DNA. This effect was not seen in excision-repair deficient strains, so Rossman (1981a) proposed that arsenite interferes with excision repair.

[3]Again, no marked genotoxic effect was seen in an excision-repair deficient strain. In this investigation, arsenite and arsenate also had cell-protective effects in a rec$^-$ strain exposed to UV-radiation. Arsenite, and to a lesser degree, arsenate, inhibited uptake of thymidine. From these results, the authors hypothesized that the arsenic compounds enhanced the error-free excision repair of UV-damaged DNA by retarding DNA replication and prolonging the period of time for excision repair.

[4]Although sodium arsenite (As(III)) did not require metabolic activation in order to show a positive response, sodium arsenate (As(V)) required activation by a S9 liver homogenate. It is likely that the S9 fraction contained enzymes which reduced the As(V) to As(III) and that As(III) was the active species in this assay.

[5]This result is not consistent with the hypothesis that As(V) can substitute for phosphorous and weaken DNA structure. However, higher concentrations of arsenate may be required to produce a clastogenic effect.

TABLE 7-1 SUMMARY OF MUTAGENICITY OF ARSENIC: GENE MUTATIONS

Reference	Test system	Chemical Information	Results	Comments
Nishioka, 1975	Reverse mutation in E. coli Strains: WP2 (trp^-) WP2 uvrA ($uvrA^-$, trp^-) CM571 ($recA^-$, trp^-)	$NaAsO_2$ 8.0×10^{-4} M in WP2 1.6×10^{-4} M in WP2 uvrA 1.6×10^{-4} M in CM571 Source: Nakarai Chemical LTD (reagent grade) Solvent: H_2O	$NaAsO_2$ positive for mutations in WP2 and WP2 uvrA but not in CM571. Increases were approximately 10x background.	1. Doses of arsenite were selected to kill 60-70% of cells. 2. Lack of mutagenesis in CM571 suggests that a rec function is required for mutagenesis in E. coli. 3. Rossman et al. (1981) were unable to reproduce these mutation studies. They claimed (a) that the induced mutation frequencies observed by Nishioka were within the normal range of background, (b) that they observed a 31-fold difference in cytotoxicity studies compared to Nishioka, and (c) that Nishioka used an incorrect method for determining mutation frequency.

Source: EPA 1984 and Oberly et al. 1982

TABLE 7-1 (continued)

Reference	Test system	Chemical Information	Results	Comments
Rossman et al., 1980	Induction of reverse mutations in *E. coli* at the trp locus. Assays: Spot test, Plate test, Fluctuation test Strains: WP2 (trp^-), $WP2_S$ (trp^-, uvrA-), WP6 (trp^-, $polA1^-$), WP10 (trp^-, $recA1^-$), $WP44_S$-NF (trp^-, $uvrA^-$, tif-1/sti^-). tif-1 mutation confers a thermally inducible SOS repair system resulting in normal mutation at 30°C and a 20-fold increase in mutation at 42°C.	$NaAsO_2$: 50 µl of 0.1 M in spot tests with $WP44_S$-NF (30°C), WP2, WP6, and WP10. $NaAsO_2$: 10 µl of 0.01 M in spot test $WP44_S$-NF, 10 µl of 0.1 M in spot test $WP44_S$-NF. $NaAsO_2$: 25 mM in plate tests WP2. $NaAsO_2$: 0.4, 1, 2, mM in fluctuation test WP2.	Arsenic did not increase the mutation frequency in any of the assays. Arsenic showed a dose-dependent decrease in mutations in $WP44_S$-NF at 42°C.	1. Results indicate that arsenic may inhibit SOS repair.
Lofroth and Ames, 1978 (abstract only)	*Salmonella* microsome assay	Arsenite and arsenate	Negative	1. No data available since information comes from an abstract.

TABLE 7-1 (continued)

Reference	Test system	Chemical Information	Results	Comments
Singh, 1983	Gene conversion at the trp locus and reverse mutation at the ilv locus in S. cerevisiae. Strain D7 = $\frac{a\ ade\ 2\text{-}40\ \ trp\text{-}5\text{-}12\ \ ilv\ 1\text{-}92}{a\ ade\ 2\text{-}119\ \ trp\ 5\text{-}27\ \ ilv\ 1\text{-}92}$	$NaAsO_2$ (0.1 M added to well, volume not indicated) Solvent: H_2O	Negative for conversion. Weak positive for mutation.	1. Study lacking sufficient experimental details.
Amacher and Paillet, 1980	Forward gene mutation at the thymidine kinase (TK) locus in mouse L5178Y cells.	Na_2HAsO_4 Doses tested: (0.83×10^{-4}, 1.1×10^{-4}, 1.47×10^{-4}, 1.96×10^{-4}, 2.26×10^{-4} M) Source: Fisher Solvent: Normal saline	Negative	1. Exposed 3 hrs at 37°C. 2. Survival ranged from 66% at the low dose to 35% at the high dose. 3. Other metals such as cadmium, nickel, and trans-platinum were positive.
Rossman et al., 1980	Induction of forward mutations in Chinese hamster cells in vitro at HGPRT locus and the sodium-potassium ATPase locus.	$NaAsO_2$ (0.5×10^{-6} M, 2 days) ouabain resistance (5.0×10^{-6} M, 1 hour) ouabain resistance (20×10^{-6} M, 1.5 hours) thioguanine resistance (100×10^{-6} M, 25 min) thioguanine resistance	No increased mutation	1. UVC and MNNG used as positive controls. 2. Doses of arsenite used varied from slightly inhibitory to cell growth to fairly toxic.

TABLE 7-1 (continued)

Reference	Test system	Chemical Information	Results	Comments
Oberly et al., 1982	Forward gene mutation at the thymidine kinase (TK) locus in mouse L5178Y cells.	$NaAsO_2$ (3.8×10^{-6}, 7.7×10^{-6}, 11.5×10^{-6}, 15.4×10^{-6}, 19.2×10^{-6} M) Na_2HAsO_4 (7.5×10^{-5}, 9.7×10^{-5}, 11.8×10^{-5}, 14.0×10^{-5} M) Source: Mallinckrodt	$NaAsO_2$ was positive for the three highest doses tested in the absence of S-9 mix; Na_2HAsO_4 was negative in the absence of an Aroclor-induced rat S-9 mix; Na_2HAsO_4 was positive at the three highest doses tested in the presence of an S-9 mix.	1. Chemical exposure was for 4 hours. 2. Only positive data were shown; negative results were only mentioned in the text. 3. The spontaneous mutation rate varied a great deal between experiments; between 2.5 and 17.9 mutants per 10^5 survivors. Most of the arsenic-induced mutant frequencies were between or just slightly above this spontaneous range. 4. The increases in mutant frequencies occurred at very low survival levels for both compounds; the highest doses caused 97% lethality. 5. At survivals above 10% none of the mutant frequencies exceeded the limits of the control mutant frequency range.

8.0 CARCINOGENICITY -- ANIMAL DATA

Arsenic is unique in that it is a human carcinogen for which carcinogenicity has not been conclusively demonstrated in animals. Arsenic produces tumors in animals, but these tumors are rarely malignant. The few reports of carcinogenic effects of arsenic compounds in animals are seriously flawed. The National Toxicology Program (NTP) has not conducted a standard bioassay of inorganic arsenic carcinogenesis. A recent compilation of carcinogenesis studies (EPA 1984) is reprinted here as Table 8-1; the most important studies are discussed below. In 1980, the International Agency for Research on Cancer (IARC) found that there was "inadequate evidence" for the carcinogenicity of arsenic compounds in animals (IARC 1980). There is currently not sufficient evidence of such carcinogenicity.

8.1 Inhalation

Two animal studies of arsenic carcinogenicity used inhalation exposure. The results of this research were negative. Results of these experiments have been published only as abstracts or interim reports. Berteau et al. (1977, 1978) tested 60 female mice of a tumor-susceptible strain with 30 cagemates and 30 controls housed separately. The test mice were exposed to a respirable aerosol of As(III) (containing approximately 27 mg As(III)/m^3) for 40 minutes/day for 26 days and 20 minutes/day thereafter. Inhaled doses were approximately 1.3 mg As/kg/day and 0.69 mg As/kg/day (Berteau et al. 1977). At 55 weeks into the exposure regimen, no evidence of neoplasia had been encountered grossly or in histological studies of a few sacrificed animals (Berteau et al. 1978). From the fifth week of exposure onward, the

experimental animals consistently weighed less on average than their cagemates who, in turn, weighed less on average than the controls. This was the only treatment effect noted.

Glaser and co-workers presented negative results from an inhalation study of arsenic trioxide at a recent conference (Glaser et al. 1986). For 18 months, 20 rats inhaled approximately 60 μg As/kg/day and 40 rats inhaled approximately 20 μg As/kg/day (assuming a breathing rate of .10 liter/min and 0.5 kg rats). The rats were subsequently housed in clean air. These researchers presented a tabulation of their results, but did not mention important methodological details, including the method of housing the animals, randomization of animals to dose groups, and sampling to verify exposure levels. Furthermore, as discussed in Chapter 2, rats are probably an inappropriate animal model of arsenic toxicity. Also, while the daily dose in the study by Berteau and colleagues was adequately representative of occupational exposure associated with cancer (see Chapter 9), the daily doses employed by Glaser and co-workers were at least an order of magnitude lower, representative of only the low end of the range of concentrations to which smelter workers were exposed. Finally, the researchers tested fewer animals than required by standard cancer bioassay protocols, thereby limiting the power of the study to observe statistically significant effects. These factors suggest that the negative result reported by Glaser and co-workers is not surprising.

8.2 Intratracheal Instillation

Intratracheal instillation typically involves anesthetizing animals and introducing a suspension into the trachea with a special syringe. From the trachea, the suspension can flow into the lungs and the test substances may be absorbed. Compared with inhalation studies, intratracheal instillation may allow larger doses of suspected carcinogenic substances to be deposited and retained in the lung. However, irritation produced by particles in the suspension may confound tumorigenicity testing.

In several animal bioassays that used intratracheal instillation, arsenic induced tumors. In an arsenic (III) trioxide-treated group of 47 male hamsters, Pershagen and colleagues (1984) found three carcinomas (versus none in 53 controls): two of bronchi or lungs (an adenocarcinoma, and an anaplastic carcinoma) and one of larynx or trachea (a squamous cell carcinoma). These carcinomas were not statistically significant when considered in relation to the concurrently treated controls. However, considering additional controls (49 male hamsters from the same colony that had been identically treated one year earlier), causes the carcinomas to become statistically significant ($p \approx 0.01$, one-tailed test) (Pershagen et al. 1984). Without considering the additional controls, the experimenters found a statistically significant ($p < 0.01$) increase in the incidence of papillomas and adenomas and adenomatoid lesions in the treated group. These researchers concluded that "[t]aken together, the data provide strong evidence that arsenic trioxide can induce lung carcinomas" (Pershagen et al. 1984 at 227). In female hamsters, Ishinishi and Yamamoto (1983) induced benign lung tumors (adenomas) by instillation of a suspension of solid

arsenic trioxide in a phosphate buffer. Ohyama et al. (1988) induced alveolar cell hyperplasia, but no lung tumors, in male hamsters, by 15 weekly instillations of arsenic trioxide or gallium arsenide; gallium arsenide markedly decreased survival of the animals.

As(V) has also induced pulmonary tumors by intratracheal instillation. Calcium arsenate induced lung adenomas in male hamsters in a recent experiment (Pershagen and Björklund 1985) which used an exposure regimen nearly identical to that used by Pershagen and colleagues in their 1984 study of arsenic trioxide.

In the report of that study, Pershagen and collegues (1984) noted a positive interaction between arsenic trioxide and benzo[a]pyrene (B[a]P) in the induction of adenomatous lung tumors in hamsters.

8.3 Other Routes of Exposure

8.3.1 Subcutaneous injection. Osswald and Goerttler (1971) produced an increased incidence of leukemia and lymphoma by subcutaneously injecting sodium arsenate (As(V)) into pregnant mice and, postnatally, their offspring. Effects were seen in both the mothers and the offspring. However, there was no control group exposed to the appropriate vehicle solution (EPA 1984). The report of lung tumors produced in CFLP mice by subcutaneous injection of arsenic trioxide (Table 8-1) did not note whether the tumors were malignant (Rudnai and Börzsönyi 1981, EPA 1984).

8.3.2 Oral. Among many studies to use the oral route of exposure (Table 8-1), only one reported positive findings. Tumors, including adenocarcinomas of the skin, lung, and lymph nodes, were noted in mice given Fowler's solution (potassium arsenite), but the report lacks experimental details necessary for critcal assessment (Knoth 1966, as reviewed in EPA 1984).

8.3.3 Drinking water. Rather than inducing tumors, arsenite at 3 μg As/l in drinking water reduced the total tumor incidence in male and female white Charles River CD mice. The reduction was statistically significant: from 32% of 170 controls to 10.7% of 103 treated mice. A small reduction of malignant tumor incidence (from 8.8% to 5.8%) was not significant, however (Kanisawa and Schroeder 1967).

In another study, arsenic in drinking water enhanced the growth rate of "spontaneous" (common) mammary tumors in female inbred C3H mice (Schrauzer and Ishmael 1974, Schrauzer et al. 1978). In this research, which also investigated the protective effect of selenium, all of the tumors in the arsenic-treated group appeared before the tumors in the selenium-treated group, all of which appeared before the tumors in the control group. Two parts per million As (2 mg As/liter) (arsenite) abolished the tumor-protective effect of 2 ppm Se (selenite).[1]

8.3.3 Drinking water exposure after pretreatment. Sodium arsenite (As(III)) promoted kidney tumors in a bioassay designed by Emmelot and Scherer (1980) to increase the rate of liver tumors. Rats fed arsenite after partial hepatectomy and intraperitoneal injection with diethylnitrosamine had more kidney tumors than rats treated with partial hepatectomy and the nitrosamine

alone (7 in 10 treated rats compared to 1 in 7 untreated, $p < 0.03$) (Shirachi et al. 1983). It is unclear whether the partial hepatectomy affected formation of the kidney tumors. The relevance of this study is questionable because the test animals were rats, and rat metabolism of arsenic is anomalous (See Chapter 2). Additionally, As(III) treatment significantly lowered the body weights of the rats.

8.4 Arsenic as a Tumor Promoter

The hypothesis that arsenic may act as a tumor promoter has been tested but not proven in animals. Arsenic trioxide in drinking water given to three strains of mice (at 80 mg As/liter) failed to promote grafted skin tumors initiated by methylcholanthrene (Milner 1969). In one of the strains tested arsenic had a protective effect. Neither arsenic trioxide (80 mg As/liter in drinking water) nor sodium arsenate (by skin application in a 1.58% aqueous solution) tested positive for promotion of 7,12-dimethylbenz(a)anthracene (DMBA)- or urethan-initiated tumors in Swiss mice (Baroni et al. 1963). Potassium arsenite in chow (1.2 mg As over a 5-day period) did not affect the incidence of DBMA-induced tumors or DBMA-induced and croton oil-promoted tumors in female, skin tumor-susceptible mice (Boutwell 1963). The arsenite did inhibit weight gain. Milner (1969) has suggested that at the doses employed in some animal studies, arsenic, as a weak poison, may inhibit tumor promotion.

Notes

[1]The 1974 paper (Schrauzer and Ishmael 1974) reported that all of the exposed mice that developed tumors were hyperactive. Under normal maintenenance, hyperactive mice of this strain do not develop spontaneous mammary tumors (Schrauzer and Ishmael 1974). The tumors in controls must have been in nonhyperactive mice. In humans, no similar behavioral correlate to arsenic tumorigenesis has been reported.

TABLE 8-1 SUMMARY TABLE OF EXPERIMENTAL STUDIES OF ARSENIC CARCINOGENESIS

Route	Species (Strain)	Compound	Vehicle	Results	Reference	Remarks
Oral	Mice (C57B16)	As_2O_3	Tap water or 12% aqueous ethanol	-	Hueper and Payne, 1962	Shortened life span of treated (aq. ethanol) vs. control.
Oral	Mice (Swiss)	As_2O_3	Drinking water	-	Baroni et al., 1963	
Oral	Mice (Swiss)	$NaAsO_2$	Drinking water	-	Kanisawa and Schroeder, 1967	Shortened life span, low dose.
Oral	Mice (NMRI)	As_2O_3	Drug (Psor-Intern) or Fowler's solution	+(?)	Knoth, 1966	Significance cannot be determined, uncomplete reporting by author.
Oral	Mice (C3H/St, female)	$NaAsO_2$	Drinking water	-	Schrauzer and Ishmael, 1974	
Oral	Rats (not specified)	$Pb_3(AsO_4)_2$ $Ca_3(AsO_4)_2$	Not specified	-	Fairhall and Miller 1941	Poor survival in treated. As reviewed by IARC (Vol. 23, 1980)
Oral	Rats (Bethesda Blacks)	As_2O_3	Tap water or aqueous ethanol (12%)	-	Hueper and Payne, 1962	
Oral	Rats (Osborne-Mendel)	$NaAsO_2$ Na_3AsO_4	Diet	-	Byron et al., 1967	Reduced survival at highest dose.
Oral	Rats (Long Evans)	$NaAsO_2$	Drinking water	-	Kanisawa and Schroeder, 1969	Low dose.
Oral	Rats (Wistar)	$Pb_3(AsO_4)_2$ Na_3AsO_4 $Pb_3(AsO_4)_2$ + NDEA Na_3AsO_4 + NDEA	Diet Diet Diet Diet	- - - -	Kroes et al., 1974	High mortality and 2 tumors (incidence not reported observed in lead arsenate group).

TABLE 8-1 (continued)

Route	Species (Strain)	Compound	Vehicle	Results[a]	Reference	Remarks
Oral	Dog	$NaAsO_2$ or Na_3AsO_4	Diet	-	Byron et al., 1967	Weight loss, early mortality, short duration of experiment.
Inhalation	Mice (not specified)	$NaAsO_2$	Aqueous aerosol	-	Berteau et al., 1978	Reported in an abstract form, high incidence in controls.
Intratracheal instillation	Rats (Wistar King) male	(1) As_2O_3 (2) Copper ore (3.95% Arsenic) (3) Flue dust	Not specified	- - -	Ishinishi et al., 1977	One tumor observed in treated, not significant.
Intratracheal instillation	Rats (Wistar King) male	As_2O_3	Aqueous solution	-	Ishinishi et al., 1976	One tumor observed in treated, not significant.
Intratracheal instillation	Rats (BDIX)	$Ca_3(AsO_4)_2$	Bordeaux mixture (contains $CuSO_4$ and $Ca(OH)_2$)	+	Ivankovic et al., 1979	Results cannot be attributed to arsenic alone.
Intratracheal instillation	Golden Hamsters (males)	As_2O_3 ± BP	Carbon carrier + dilute H_2SO_4	+	Pershagen et al., 1983	Adenomas significantly greater than controls ($p < 0.01$). Carcinomas in 3 treated animals vs. 0 in controls.
Intratracheal instillation	Golden Hamsters (female)	As_2O_3	Phosphate buffer	+	Ishinishi and Yamamoto, 1983	As_2O_3 was tumorigenic in a dose-response fashion.

TABLE 8-1 (continued)

Route	Species (Strain)	Compound	Vehicle	Results[a]	Reference	Remarks
Intratracheal instillation	Rats	Ore dust containing As at two levels of content	Not specified	+	Chung and Liu, 1982	Possible confoun ing effects of other element sent, unknown. apparent differences in lung ce cer with differe As levels in dus
Skin painting (application)	Mice (not specified)	$KAsO_2$ and As_2O_3	Ethanol	-	Leitch and Kennaway, 1922	Neubauer (1947) failed to confir this observation
Skin painting (application)	Mice (S)	$KAsO_2$ followed by croton oil in acetone	Methanol	-	Salaman and Roe, 1956	As reviewed by IARC (Vol. 23, 1
Skin painting (application)	Mice (Rockland all-purpose)	(1) $KAsO_2$ followed by croton oil in benzene	80% ethanol	-	Boutwell, 1963	As reviewed by IARC (Vol. 23, 1
Skin painting (application)	Mice (Rockland all-purpose)	(2) DMBA followed by $KAsO_2$ in 80% ethanol	acetone	Not carcinogenic	Boutwell, 1963	
Skin painting (application)	Mice (Swiss)	(1) Na_3AsO_4	Water containing Tween 60	-	Baroni et al., 1963	
		(2) Na_3AsO_4 followed by croton oil and DMBA	Water containing Tween 60	No promotional activity observed		
Subcutaneous injection	Mice (Swiss) female Progeny	Na_3AsO_4 Na_3AsO_4	Water Water	+ +	Osswald and Goerttler, 1971	

TABLE 8-1 (continued)

Route	Species (Strain)	Compound	Vehicle	Results[a]	Reference	Remarks
Subcutaneous implant	Rats (random-bred) male albino	$Ca_3(AsO_4)_2$	Paraffin pellets	-	Arkhipov, 1968	As reviewed by IARC (Vol. 23, 1980).
Subcutaneous injection	Rats (random-bred) male albino	$Ca_3(AsO_4)_2$	Sunflower oil	-	Arkhipov, 1968	
Subcutaneous injection (pre-natal + post-natal)	Mice (CFLP)	As_2O_3	Aqueous solution	+	Rudnai and Borzsony, 1981	Histological description of tumors poor.
Intravenous injection	Mice (Swiss) female	Na_2AsO_4	Water	+	Osswald and Goerttler, 1971	
Intramuscullary injection	Rats (Osborne-Mendel)	Arsenic	Metallic	-	Hueper, 1954	
Intramuscullary injection	Rabbits	Arsenic	Metallic	-	Hueper, 1954	
Oral	Mice (Swiss)	As_2O_3 and croton oil, DMBA or urethan	Drinking water	-	Baroni et al., 1963	
Oral	Mice (STS)	Arsanilic acid or $KAsO_2$ followed by DMBA (skin) then croton oil (skin) in benzene	Diet	-	Boutwell, 1963	As reviewed by IARC (Vol. 23, 1980).

([a]) + statistically significant excess tumors observed over controls

\- no statistically significant excess tumors of treated vs. control or no tumors observed

Source: EPA 1984

9.0 CARCINOGENICITY -- HUMAN DATA

The carcinogenic effects of arsenic in humans are well documented in the epidemiologic literature. The International Agency for Research on Cancer (IARC) evaluated arsenic in 1980 and classified "arsenic and arsenic compounds" in Group 1, which includes the "chemicals and groups of chemicals (which) are causally associated with cancer in humans." Since this document evaluates health effects of airborne arsenic, only those human studies involving exposure via inhalation are considered for use in the quantitative risk assessment. Ingestion of arsenic is associated with cancer at sites different from those associated with arsenic inhalation: ingestion is associated with skin cancer, while inhalation results in lung neoplasms.

Ingestion of arsenic in drinking water and medicinal preparations is associated with skin cancer and potentially precancerous skin lesions (keratosis and hyperpigmentation) (EPA 1984). Arsenical medications (chiefly Fowler's solution, potassium arsenite) were mainly prescribed for skin conditions such as psoriasis and eczema, both of which may predispose one to develop arsenical-induced cancer, thus confounding the study of the relationship between arsenic and skin cancer (Neubauer 1947, EPA 1984). Nevertheless, arsenical skin cancer has also occurred subsequent to treatment for conditions such as anemia, asthma, epilepsy, and rheumatism (Neubauer 1947, Schoolmeester and White 1980).

Positive associations between the level of arsenic in drinking water and the prevalence of skin cancer have been observed in particular areas of Poland, Argentina, Chile, and Taiwan (Tseng 1977). High drinking water levels of

arsenic have been measured in Lassen County, California (where well water from 72 households contained from ≤ 0.1 to 1.4 mg/ℓ) and in counties of Oregon (range: 0-2.15 mg/ℓ, avg.: 0.008 mg/ℓ) and Idaho (averages for two communities: 0.18 and 0.27 mg/ℓ). Epidemiological studies in these areas failed to disclose any significant relationships between arsenic levels in drinking water and cancer (Goldsmith et al. 1972, NAS 1977b, EPA 1984).

Levels of arsenic in California's public drinking water supplies are generally as low as 0.005 mg/ℓ and are often not detectable (Spath 1987). However, certain localities in the central valley have higher levels in their drinking water; for example, levels in Hanford have ranged from 0.05 to 0.1 mg/ℓ (Spath 1987).

Arsenic-associated skin cancer often occurs on areas with little pigmentation, including palms and soles; in this regard it differs from skin cancer associated with exposure to the sun or ultraviolet radiation (EPA 1984). Skin cancers associated with arsenic exposure are mainly of two histopathological types: squamous carcinomas in keratotic areas and basal cell carcinomas (EPA 1984).

Table 9-1 (EPA, 1984) presents a synopsis of the human cancer studies which involve either occupational or environmental exposures to airborne arsenic. Most of the table is reproduced directly from the EPA document and is organized by: (1) occupational smelter studies, (2) studies involving environmental exposure to smelter emissions, and (3) studies involving nonsmelter exposures to arsenic. The fifth through last page of the table were produced by DHS to include studies not in the original EPA table.

Table 9-2 (Lee-Feldstein 1983) is a summary of the occupational studies through 1981 concerned with respiratory cancer mortality. More recent occupational studies are discussed in the text.

This report presents an overview of the evidence from the occupational studies only, with an emphasis on the most recent studies. For a more detailed summary of other studies on airborne exposure to arsenic, see EPA 1984. For a review of studies of communities exposed to arsenic-producing industries, see Hughes et al (1988), who noted (p. 407) that such studies "had insufficient statistical power to detect the small increases in risk that may occur. Even the most powerful studies were not designed to detect relative risks less than about 1.2 and the majority of the studies had little power to detect risks under 2.0." These authors conclude that "null findings do not rule out the possibility of excess risks that may be significant from a public health viewpoint."

Following the overview of the occupational studies is a discussion of potential confounding from other carcinogenic chemicals and from smoking. The possible interaction between arsenic and smoking is also addressed. Exposure assessment is discussed in Chapter 11, "Carcinogenic Risk Assessment", because this topic is particularly relevant to the derivation of an exposure-response relationship.

9.1 Overview of the Occupational Studies

The major industries in which the carcinogenic effects of arsenic exposure have been studied are copper and other types of smelting, mining, and

insecticide manufacturing or application. An increase in respiratory cancer is consistently associated with occupational exposure to arsenic. In most instances the increase has been large in magnitude and of high statistical significance.

9.1.1 Smelter and Mining Exposures

Cancer mortality has been studied among workers employed in three major smelters in the U.S., in (1) Tacoma, Washington, (2) Anaconda, Montana, and (3) Garfield, Utah. Smelter workers in Sweden (Ronnskarverken) and in Japan (Sagnoseki-Machi) and cohorts of both miners and smelter workers in China have also been studied. For all of these arsenic-exposed workers, a significantly increased risk of respiratory cancer was observed. Five other small smelters with relatively lower concentrations of arsenic have also been examined.

The Tacoma, Washington cohort has been the subject of numerous published reports; among these, Enterline and Marsh (1982) and Enterline et al. (1987a) examined the longest follow-up period. The 1982 report used cumulative doses based on urinary As measurements. Standardized mortality ratios[1] (SMRs) for respiratory cancer ranged from 170 for those receiving the lowest intensity and shortest duration of exposure, to 578 for those with the highest intensity and with 20-29 years duration of exposure[2]. A strong dose-response relationship was evident only when the analysis was limited to the 582 retired workers in the cohort (see Table 9-3). Cumulative doses (measured as As in urine) ranged from <2000 $\mu g/\ell$ -years to >15,000 $\mu g/\ell$ -years, and the corresponding SMRs ranged from 142 to over 300.

Effects were strongest in the decade after exposure ceased, with SMRs as high as 833 in the first five years following termination for workers with high intensity exposure for 20-29 years. The implications of this pattern of effect are discussed in Appendix B.

In the 1987 reanalysis, Enterline and colleagues improved their exposure measurements by incorporating newly available historical air sampling data (Enterline et al. 1987a). This allowed recalculation of the conversion from urinary arsenic concentrations to airborne exposure levels. The findings differ from the earlier analysis in that the dose-response relationship appears more clearly (see Table 9-4). The authors fitted models which allowed for nonlinearities in the data and found that a concave-downward curve (decreasing slope with increasing dose) provided the best fit between the SMRS and cumulative exposure based on air concentrations. A linear relationship worked best when exposure was expressed in urinary measurements. To explain the nonlinearity when air measurements were used, the authors suggested that the bioavailability of arsenic may be dose-dependent (Enterline et al. 1987a) or that workers in areas with high air concentrations may have taken steps to reduce their exposures (Enterline 1986).

The Anaconda, Montana cohort was also the subject of numerous publications. The earliest report was by Lee and Fraumeni (1969), and a follow-up through 1977 was conducted by Lubin et al. (1981). Follow-up from 1938 through 1977 was reported by Welch et al. (1982) and Lee-Feldstein (1983, 1986, 1989). Higgins et al. (1985) extended follow-up through January 1, 1981.

Lee-Feldstein (1983, 1986) divided the 8,045 men of the full study group (with 196,000 person-years of follow-up) into nine subcohorts based on arsenic exposure and year of first employment. The two women in the study group were excluded from the analyses. Year of first employment was divided as follows: prior to 1925, between 1925 and 1947, and between 1948 and 1955. The work areas at the smelter had been classified as having heavy, medium, or light exposure based on measurements of As_2O_3 levels which had been ranked on a 1 to 10 scale. Person-time of follow-up was divided into arsenic exposure categories (heavy, medium, or light) based on the heaviest exposure area in which each individual had worked for that time period. When considering only those men who had been in their maximum exposure category for at least 12 months, each of the nine subcohorts, except for one subgroup which had a very small sample size, showed significantly elevated respiratory cancer rates relative to the combined male population of Idaho, Montana and Wyoming (Lee-Feldstein 1983). In the earliest-employed cohort, heavy or medium arsenic exposure was associated with higher SMRs than light arsenic exposure. In the second employment date cohort, a dose-response trend was observed (increasing exposure was associated with increasing SMR). No dose-response trend was observed in the latest-employed cohort; this may have been due to a general decline in As_2O_3 concentrations in the smelter atmosphere over time or insufficient time for the observation of many respiratory cancer deaths (Lee-Feldstein 1983).

Lee-Feldstein (1983) also investigated the association of sulfur dioxide (SO_2) with respiratory cancer in this cohort. Industrial hygiene measurements had also been made for sulfur dioxide. As with arsenic, members of the study group who had worked less than 12 months in their

maximum exposure category were excluded from the analysis. In the earliest-employed cohort, the highest SMRs were observed in the medium As_2O_3-heavy SO_2 and heavy As_2O_3-medium SO_2 groups. Among those employed later, the greatest excess respiratory cancer mortality was in the heavy As_2O_3-medium SO_2 group. From these findings, one could not conclude that arsenic trioxide was the primary environmental agent causing the excessive respiratory cancer seen in the study group (Lee-Feldstein 1983). Nevertheless, Lee-Feldstein (1983) pointed to two other studies, those of Ott et al. (1974) and Mabuchi et al. (1979), as evidence suggesting that As_2O_3 was the primary agent; these studies, she noted, reported on nonsmelter groups exposed to arsenic without concurrent exposure to SO_2.

A separate analysis by Lee-Feldstein (1986) incorporated quantitative exposure estimates based on industrial hygiene data collected between 1943 and 1958.[3] Her analysis used the measurements of airborne arsenic concentrations (Morris 1978) but not the estimates of the proportion of a workday spent in each area by men employed there (Lee-Feldstein 1986). Arsenic exposure was assumed to be "light" where employment records listed work areas as "unknown." Each calendar year of follow-up for each worker was divided into seven categories of cumulative exposure. In all but the latest-employed cohort, a statistically significant linear dose-response relationship was observed between arsenic exposure and the directly standardized death rate (DSDR) for respiratory cancer. Nevertheless, the shape of the dose-response curve is not clearly linear, and actually resembles the concave-downward curve observed for the Tacoma cohort (Enterline 1987a, Hertz-Picciotto 1989). A similar analysis using exposures

estimated by taking geometric rather than arithmetic means revealed no significant trends.

In the report of this quantitative analysis, Lee-Feldstein (1986) reiterated that the latest-employed cohort may not have been followed long enough to display a dose-related mortality pattern. In addition, she noted that the men in this cohort tended to be older than those in the previous cohort when hired and may have experienced prior exposures which confound the relationship between arsenic exposure and respiratory cancer mortality. Statistically significant SMRs were observed in this study in some of the groups with the lowest cumulative exposures: in the second employment-date cohort, even the group with the lowest cumulative exposure levels (less than 10 mg/m^3-months [833.3 $\mu g/m^3$-years]) experienced a statistically significant SMR (183, 15 deaths observed vs. 8.2 expected) (see Table 9-5).

The most recent analysis by Lee-Feldstein used a nested case-control study to compare five indices of exposure: maximum category, time-weighted average (TWA) based on arithmetic or geometric means, and cumulative dose based on arithmetic or geometric means. Each was a significant predictor of lung cancer risk. Lee-Feldstein also found that men who were younger at the start of employment were at greater risk for lung cancer than those who began employment later in life.

Welch et al. (1982) analyzed records for 1800 men from this same cohort (100% of the heavily exposed and a random sample of 20% of the remainder) and used three separate indices of exposure: time-weighted average (TWA),

30-day ceiling, and cumulative. A strong dose-response relationship was observed regardless of which index of exposure was used (see Table 9-6).

Using the same methods as were used by Welch et al., Higgins et al (1985) confirmed these results in an analysis which extended the follow-up for four additional years and included the full cohort of 8,044 men (see Table 9-7). In the full cohort, there was sufficient statistical power for the low-exposure workers to show a significantly elevated lung cancer death rate. Results were essentially unchanged when exposure was lagged 20 years (i.e. a 20-year latency was assumed) or when alternative exposure assumptions were made.

The Garfield, Utah smelter was studied by Rencher et al. (1977), who found a three- to five-fold increase in the proportion of deaths due to lung cancer among smelter workers when compared to workers in the mine or concentrator. The data from this study are examined in greater detail elsewhere (see Appendix A).

Similar results, albeit with higher SMRs, were reported by Tokudome and Kuratsune (1976) who studied 839 copper smelter workers in Japan. A dose-response effect on respiratory cancer was observed using either duration of employment or intensity of exposure. SMRs rose from 563 to 735 to 1905 for <10, 10-20, and >20 years exposure, respectively. The p-values for every subgroup were less than 0.01. SMRs were 635, 1250 and 1485 for light, medium and heavy exposures, respectively. These investigators observed that, for the same duration of employment, risks were greater among those employed in earlier periods.

Wall (1980) examined workers at the Ronnskarverken smelter in Sweden. The lung cancer SMR for the cohort consisting of all males employed for 3 months or longer was 288, using Swedish national population rates for standardization; but because local lung cancer rates were about half the national rates, these workers actually experienced lung cancer mortality at about five times the rate of residents of the county. For workers in the high exposure areas of the plant, rates were two to three times higher still. No quantified exposure data were reported.

Pershagen et al. (1981) conducted a nested case-control study within the cohort at Ronnskarverken, focusing on the interrelationship of smoking, arsenic and lung cancer. For smokers and nonsmokers, the age-standardized rate ratios (SRRs) were 3.0 and 2.9. Among roaster workers, the most heavily exposed in this plant, the SRRs were 4.4 and 4.5. This paper is discussed further in Appendix A. Exposures were not quantified in this analysis.

Another study of cancer incidence and mortality among workers at the Ronnskar smelter confirmed the excess lung cancer risk using 3 different reference populations (Sandstrom et al. 1988): all males in Sweden, males in the same county, and males in the same municipality. Nonsignificant increases were also observed in the incidence rates of cancer of the digestive organs, and of the urogenital organs. An analysis of age-adjusted rates by calendar year showed a decline in lung cancer starting in the mid-1970s, possibly due to lower exposures, earlier notification of health problems, and/or changing smoking habits (in view of the smoking-arsenic synergism -- see below). However, even among the most recently hired

cohort, lung cancer incidence was greater than expected. No quantified exposure data were evaluated.

Jarup et al. (1989a) conducted further follow-up of the Ronnskar cohort studied by Wall (1980). They observed 3,916 male workers through 1981, and obtained complete follow-up for over 99% of the cohort, covering over 125,000 person-years. Lung cancer deaths were examined in relation to quantified estimates of arsenic exposure. Exposure estimates were based on measurements taken since 1945, and for earlier periods, on an assessment that utilized production figures, changes in production methods, and records of sick leave specific to each workplace and time period.

The SMRs for lung cancer increased with cumulative arsenic exposure whether or not a 10-year latency period was assumed, and whether or not exposure was lagged by 5 years (Jarup et al. 1989a). These results were unchanged when a weighting procedure was used to adjust for different age distributions in the different exposure groups. Elevated risks were also found in every level of cumulative exposure when the analysis was stratified by year of hire. The effect of intensity of exposure appeared to be greater than that of duration.

The shape of the dose-response curve, using cumulative exposures, was either curvilinear, or linear with an elevated intercept. The latter could occur if smelter workers tended to smoke more than the general population used for standardization, however, no smoking data were available in this analysis. Subsequent analyses in which smoking data were collected in a nested case-control design (Jarup 1989b) appear to show "negative" confounding,

particularly at the higher dose levels. That is, the estimated relative risks are larger after controlling for smoking. A curvilinear relationship is supported by the fact that the confidence intervals for the SMRs at each dose point include the concave-downward function fit to the data of Enterline et al. (1987a).

Taylor et al (1989) conducted a case-control study among tin miners in China to examine the relationship between arsenic exposure and lung cancer. Living cancer cases (N=107) and age-matched controls were interviewed to obtain employment and smoking histories. Cumulative arsenic exposure was quantified using industrial hygiene data. After adjusting for tobacco use and radon exposure, the risk of lung cancer for subjects in the highest quartile of arsenic exposure was 22.6-fold higher than for those in the lowest quartile. As in the studies by Lee-Feldstein (1986), Enterline et al (1987a), and Jarup et al (1989a), the data appear to be consistent with a concave-downward dose-response relationship. Duration but not intensity of exposure appeared to be a predictor of lung cancer risk. Also, those with only smelter experience had a higher risk than those with only mining experience, but there were too few cases in the former group to draw any definitive conclusion.

Another report from China covers a cohort consisting of workers employed at two copper smelters, one arsenic smelter and a mine (Wu 1988). It is not clear whether the arsenic smelter and the mine were the same ones in which the case-control study of Taylor et al. (1989) was conducted. Wu reported that nearly 19,000 person-years were followed, resulting in 40 lung cancer deaths. The overall SMR was 678 (95% confidence interval = 511,882). A

strong dose-response was observed but exact figures were not published in the report.

Enterline et al. (1987b) analyzed data from eight smelters with fairly low levels (relative to the Anaconda, Tacoma, and Ronnskar smelters) of arsenic. One of the smelters lacked data to estimate individual exposures, and another had arsenic levels too low to estimate individual exposures. Of the remaining smelters, one was the Garfield plant studied by Rencher et al. (1977). The years of follow-up covered 1949 to 1980. The relationship of lung cancer mortality to arsenic exposure was evaluated using a cohort analysis, and also by means of a nested case-control study which simultaneously adjusted for sulfur dioxide exposure and cigarette smoking.

When examined by smelter in the cohort analysis, only the Garfield smelter had a significantly elevated SMR. When data from the six smelters were combined, the results suggested an increasing trend in risk with increasing exposure ($p=.06$). Results of the case-control analysis were based on fitting a logistic regression model. A significant effect was observed for cumulative exposure to arsenic (expressed as a continuous variable) and for smoking, regardless of whether these exposures were measured in their original units or transformed to their square roots. The effect of sulfur dioxide was either not significant, or protective, after controlling for arsenic and smoking.

The exposure level at the Garfield plant corresponded to the lowest 2 exposure levels in the Tacoma smelter (Enterline 1987a). The other 5 smelters examined in this study (Enterline 1987b) each had exposures less

than 1/5th the level of the Garfield plant, and had fewer than 1/2 as many workers or person-years. Thus the power to detect an increase in lung cancer mortality in these smelters separately was low. Using the dose-response relationship observed for the Tacoma smelter, DHS staff calculated the power to detect effects in each of these studies to range from .05 to .28.

9.1.2 Insecticide Manufacturing Exposures

Major reports on cancer and insecticide manufacturing exposures to arsenic were by Ott et al. (1974), Baetjer et al. (1975b), Mabuchi et al. (1979), and Sobel et al. (1988). A recent study of orchardists who potentially sprayed arsenic-containing pesticides is also reviewed (Wicklund et al. 1988).

The report by Mabuchi et al. (a more extensive follow-up of the same cohort Baetjer analyzed) found a sharp increase in the lung cancer SMR with increasing duration of employment among those predominantly exposed to arsenic, although no increase was observed for those with exposure to arsenic only. However, more than 99 percent of this latter group were employed for five years or less.

Ott et al. (1974) observed a marked increase in respiratory cancer mortality with increasing cumulative dose (see Table 9-8). This analysis used the proportion of deaths due to respiratory cancer, rather than the actual death rates. Expected deaths were calculated based on a regression line fit to the data on nonexposed decedents. In this regression, predictor variables

were age and calendar year of death; the outcome variable was the proportion of deaths due to respiratory cancer. The ratio of the observed proportion to the expected proportion is a proportionate mortality ratio, or PMR. In this cohort the PMR rose from 0.6 for those exposed to <1 mg As cumulative dose, to 7 for those exposed to ≥ 96 mg As. Losses to follow-up were high in this study: 20%.

Sobel et al. (1988) updated the study by Ott et al. on insecticide manufacturing workers by ascertaining deaths for 9 additional years of follow-up and by tracing more than 99% of those who had been lost to follow-up in the study by Ott et al. During the 9 follow-up years, 7.8 lung cancer cases were expected, using U.S. mortality rates, while 9 were observed. This yielded a non-statistically significant SMR of 116 for the recent period. The authors did not use local, regional, or statewide rates for comparison. In this study, a measure of individual cumulative dose in mg/m^3 - months was constructed using information from area monitoring data and interviews with veteran personnel. However, these exposure estimates were not used to analyze dose-response relationships. Instead, the investigators showed that increasing duration of exposure produced no trend in lung cancer mortality. No explanation was given for not utilizing the quantified exposure data. Elevated SMRs were observed among workers with short-term employment whose employment terminated even as long as 45 or more years previously.

A recent case-control study of deaths among orchardists (Wicklund et al. 1988) found no association between exposures to arsenic-containing pesticides and respiratory cancer, after controlling for smoking. All

exposure information was obtained from next-of-kin proxies. If the informant could not recall what pesticide was used by the deceased, but was able to recall the years of orchard work, exposure or lack of exposure was presumed based on the years when lead arsenate was used. The percent of exposures which were presumed based on such information was not reported. If informant information was inaccurate, and these inaccuracies were not associated with the cause of death of the deceased, then the results would be biased towards the null. Given that outdoor spraying could lead to exposures that are considerably lower than those of smelter workers, it is not clear how large the predicted risk would be, and therefore how great the discrepancy between the findings in orchardists as compared with other occupationally exposed groups.

9.1.3 Summary of Findings

For smelter workers, the association between respiratory cancer mortality and arsenic exposure is a consistent, replicable finding of substantial magnitude with a clear dose-response relationship, and high statistical significance. The mortality data on workers employed in the manufacturing of insecticides provide further evidence that arsenic acts as a respiratory tract carcinogen. The probability of such repeated and consistent findings being due to chance is vanishingly small. The lack of association between lung cancer deaths and arsenic exposure in the study of orchardists could have been due to low power, misclassification bias, chance, or unusual properties (solubility, particle size, retention in lungs) of lead arsenate. It should be noted that the smelter studies involved primarily arsenic trioxide exposures, while in the insecticide manufacturing plants,

significant exposures were to lead arsenate and calcium arsenate, as well as arsenic trioxide.

There is a bias toward underestimating risk because of the healthy worker effect, i.e. self-selection into the workforce of healthy individuals, with sick individuals either leaving or not entering the workforce. However, bias from most other sources is likely to be small. Selection criteria usually included some minimum period of employment to ensure a minimum level of exposure for those included in the study. Classification of exposure was based on employment records and therefore, was blind to outcome and not subject to the differential biases that occur in interview studies. Any misclassification of exposure would have been nondifferential (independent of outcome status) and could result in an underestimate of the true risk, but not an overestimate.

As seen in Table 9-2, the range for the overall respiratory cancer SMR from studies of occupational cohorts exposed to arsenic is 160 to 912, with many studies reporting an SMR of around 300. As described above, heavily exposed workers experienced much higher SMRs. With relative risks this large, any confounder would have to carry risks of the same magnitude (i.e. about 3) and be found among the exposed about three times as frequently as in the general population (Cornfield 1959). Furthermore, where a dose-response relationship was observed between arsenic exposure and outcome, the confounder would have to increase in prevalence as arsenic exposure increased.

The staff of DHS concludes that the association between arsenic and respiratory cancer is not explained by confounding and that the results of these studies provide ample support for the conclusion of IARC that arsenic and/or arsenic compounds are carcinogenic in humans. The following sections discuss the evidence for confounding due to (1) other chemical carcinogens in the workplace, and (2) smoking.

9.2 Confounding

Occupational exposure to arsenic is almost always accompanied by exposure to other potential or known carcinogens. The staff of DHS concludes that other "suspect" chemicals do not appear to have confounded the relationship between arsenic and respiratory cancer in these studies. The staff of DHS also concludes that the potential effect of smoking as a confounder in these studies was too small to explain the strong association observed between arsenic and respiratory cancer.

9.2.1 Confounding by Other Workplace Carcinogens

Several studies addressed the potential for confounding due to other exposures at the workplace.

In the smelter studies, concern over the role of SO_2 was raised by several investigators. Among workers with very high arsenic exposures, Enterline and Marsh (1982) compared those with essentially no sulfur dioxide exposure to those with low to moderate exposures and found the SMRs to be similar. Rencher et al. (1977) conducted a crude analysis, and therefore could not

separate the effects of As from those of SO_2 because of the high correlation between these exposures (correlation = .87).

In a more extensive follow-up of the Garfield smelter workers a crude analysis showed a dose-related effect of sulfur dioxide exposure expressed as years of peak exposure (Enterline et al. 1987b). However, after controlling for smoking and arsenic exposure, the effect of sulfur dioxide was not significant, and when the exposure variables were transformed to their square roots, sulfur dioxide appeared to significantly "protect" against lung cancer. When data from the 5 other smaller smelters were also included in the model fitting, SO_2 was not a significant predictor of lung cancer mortality.

To control for the high correlation between As and SO_2 exposures, Lubin et al. (1981) and Welch et al. (1982) fitted a multivariate model to the Anaconda smelter data. After controlling for heavy or medium arsenic exposures and for length of employment, there was no significant increase in risk for heavy or medium SO_2 exposure. After controlling for SO_2 and length of employment, the effects of arsenic remained. The authors reported that the studies lacked statistical power to detect interactions.

Pershagen et al. (1981) conducted a case-control study of lung cancer deaths among male smelter workers. Among smokers the small increases in risk among those with high sulfur dioxide exposure could have been due to arsenic exposure. There appeared to be too few nonsmokers to draw any conclusions regarding an effect of SO_2 in this group.

In the most recent cohort study of the Ronnskar smelter workers (Jarup et al. 1989a), elevated risks were found at all levels of exposure to sulfur dioxide, but there was no evidence of a dose-response. Since the analysis of sulfur dioxide did not control for arsenic exposure, an independent effect of sulfur dioxide could not be established.

Welch et al. (1982) noted that 436 workers were potentially exposed to asbestos in their arsenic-exposed cohort of 1800. Exclusion of these workers from the analysis did not alter the SMRs for respiratory cancer.

Taylor et al. (1989), after adjusting for smoking, stratified their analysis by both arsenic and radon exposure among tin miners in China. While the radon effect may have been stronger, a large independent effect of arsenic exposure was still apparent.

In their study of insecticide manufacturing workers, Mabuchi et al. (1979) found no dose-response relationship between lung cancer and the duration of high exposure to nonarsenicals. In contrast, a steep dose-response was seen for duration of high exposure to inorganic arsenicals (rising from <100 to 1365 and 2750 for <4 months, 15-24 years, and >25 years, respectively).

The staff of DHS conclude that other chemicals are not likely to explain the sharp increase in respiratory cancer deaths that has been observed. Studies involving workers at four smelters (Tacoma, Anaconda, Garfield, Ronnskar) consistently fail to find an independent effect on lung cancer from SO_2 exposure. The absence of consistent dose-response relationships for SO_2 and for nonarsenical pesticides is noteworthy. Similarly, an effect of arsenic

is seen independent of asbestos or radon exposures. As noted above, the sheer magnitude of the observed associations between arsenic and lung cancer, particularly among those heavily exposed, is strong evidence against confounding. The possibility that interactions between arsenic and other chemicals enhanced the carcinogenic response cannot be excluded, but since the other exposures alone cannot explain the excess cancers, this, in fact, strengthens the evidence for the role of arsenic in the etiology of cancer.

9.2.2 Confounding by Smoking

If more or heavier smokers were represented among the arsenic-exposed cohorts than among the comparison population, the observed relationship between arsenic and respiratory cancer might be spurious, i.e., the increased cancer rate might actually have been due to smoking. Several authors have addressed this possibility.

Two nested case-control studies collected smoking information for workers exposed to arsenic. Taylor et al (1989) examined living lung cancer cases and age-matched controls from a cohort of tin miners in China who were interviewed about smoking, residence, diet, prior medical conditions, etc. Significantly elevated odds ratios for arsenic exposure were seen at all levels of smoking. Enterline et al. (1987b) also conducted telephone interviews with relatives of workers at 6 smelters in the U.S. who had died of lung cancer; these researchers found a significant arsenic effect in a logistic regression model which included terms for years smoked and years since start of smoking.

Among cohort studies, the most detailed information on workers' smoking habits was presented by Welch et al. (1982), who obtained data on 82% of their sample. While these smelter workers included more smokers than the U.S. adult male population, the differences in smoking habits among workers in different exposure categories were very small (Table 9-9). The SMRs for respiratory cancer among smokers and nonsmokers were calculated separately, and each group showed an increasing trend with increasing exposure to arsenic (Table 9-10).[4] While smoking could be responsible for some of the elevation in respiratory cancer mortality for this cohort, differences in risk between exposure groups cannot be explained by smoking.

Several other studies of respiratory cancer mortality collected information on smoking habits of arsenic-exposed workers. In all, the nonsmokers who were exposed to arsenic experienced elevated death rates from respiratory cancer. Nonsmoking smelter workers in Utah had four to five times the percentage of deaths due to lung cancer as nonsmoking workers in other sites of the same copper corporation (Table A-1, Appendix A) (Rencher et al. 1977). Nonsmoking smelter workers in Washington had a relative risk five times that of nonsmoking males in the state as a whole (Table A-3, Appendix A) (Enterline 1983). Nonsmoking arsenic-exposed workers in Sweden had an age-adjusted relative risk of three compared to nonsmoking workers in the same plant with no arsenic exposure (Table A-4, Appendix A) (Pershagen et al. 1981), and 8.4 compared to nonsmoking residents of an unexposed region of Sweden (Table A-5, Appendix A) (Pershagen 1985).

Other epidemiologic studies lack data on smoking habits of arsenic-exposed workers, but present indirect evidence that the arsenic-exposed cohort under

study did not include an excess of smokers. If the SMRs are not elevated for causes of death (other than lung cancer) which are usually associated with smoking, then the likelihood of smoking explaining the excess in lung cancer deaths is lower. Mabuchi et al. (1979) presented SMRs for bronchitis, emphysema and cancers of the oral cavity, pharynx and esophagus, none of which was elevated. Lubin et al. (1981) found no significant increases in deaths from other smoking-related cancers, but did find a significant increase in deaths from other respiratory diseases. This was the same cohort from which Welch et al. (1982) took a random or total sample in each exposure group and found an excess of smokers. Ott et al. (1974) reported no significant excess of deaths due to emphysema or chronic bronchitis. Although no smoking data were presented in the published report, these authors stated that smoking habits of a cross-section of arsenic-exposed workers did not differ from those of the general population in that area, nor did smoking habits differ by arsenic exposure level.

While the distribution of smokers among workers exposed to arsenic may, in some instances, have had a small confounding effect on the association between arsenic and respiratory cancer, the staff of DHS concludes that the observed association between arsenic and respiratory cancer is not a spurious one due to such confounding. This conclusion is based on: (1) the high relative risks observed among the arsenic-exposed workers, (2) the data of Welch et al. (1982) showing an arsenic-related dose-response effect unaccompanied by any increase in the proportion of smokers in the higher arsenic exposure categories, (3) the results of Pershagen et al. (1981), Rencher et al. (1977), and Enterline (1983), who all found elevated rates of respiratory cancer deaths among nonsmokers, (4) the stratified analysis by

Welch et al. in which smokers and nonsmokers separately exhibited a dose-related effect of arsenic exposure, and (5) the finding of a significant arsenic effect after adjustment for smoking in two case-control studies, one of tin-miners in China (Taylor et al. 1989), and one of workers at 6 smelters with relatively low occupational exposure to arsenic (Enterline et al. 1987b).

9.3 Interactions with Other Carcinogens

Before evaluating the interactions if arsenic with other carcinogens, some definitions of terms are provided.

(a) The "measure" of effect must be selected. From studies on arsenic and smoking the "measures" which could be calculated were risk ratios,[5] the proportion of deaths, and risk differences.

(b) Interaction is present when the effect from one exposure (e.g. arsenic) changes in the presence of another exposure (smoking).

The measure of effect determines a reference scale which is either additive (if measure of effect = risk difference) or multiplicative (if measure of effect = risk or rate ratio). As an example, the following table shows lung cancer mortality risk relative to that of nonsmokers unexposed to arsenic:

	Controls	Arsenic Exposure
Nonsmokers	1.0	5.1
Smokers	7.2	??

On an additive scale, arsenic exposure increases risk by 4.1 (risk units), and smoking increases risk by 6.2. With reference to an additive scale, the fourth cell should have 1 + 4.1 + 6.2 = 11.3 (= background + arsenic effect + smoking effect). On a multiplicative scale, arsenic multiplies risk by a factor of 5.1, and smoking multiplies it by 7.2. Therefore, on a multiplicative scale, the fourth cell would have a risk of 1 x 5.1 x 7.2 = 36.7. The calculated risk for the arsenic-exposed smokers in this study was actually 20.7, which was between the additive and multiplicative risks (see Appendix A, Table A-3).

Note that an interaction which is less than multiplicative implies that nonsmokers will have higher risk ratios due to arsenic than smokers. In the table above, using 20.7 in the fourth cell, the arsenic risk ratio is five for nonsmokers, but three for smokers; however, the excess risk or risk difference for arsenic is 4.1 (5.1 - 1.0) for nonsmokers, but 13.5 (20.7 - 7.2) for smokers. For addressing public health concerns, the risk difference is considered to be more relevant than relative risk (Rothman et al. 1980, Kleinbaum et al. 1982, p. 411). There is much debate as to which measure is appropriate for evaluating interaction.

A few reports addressed the potential for interaction between arsenic and sulfur dioxide. For the Anaconda cohort, Lubin et al. (1981) reported that the power of their study was insufficient to detect such an interaction. This was related to the lack of an independent SO_2 effect. A similar situation appears to apply to the data of smelter workers in Sweden (Pershagen et al. 1981), in Tacoma, Washington (Enterline and Marsh 1982), and in the six smaller U.S. smelters. The one case where an interaction was

observed involved a "protective" main effect of SO_2 at the Garfield plant that was less protective in the presence of arsenic. Interactions with other compounds such as aromatic hydrocarbons or process additives could not be evaluated as there were no appropriate data available.

Numerous reports either addressed the interaction of smoking and arsenic, or presented data that allow such an analysis: Rencher et al. (1977), Welch et al. (1982), Enterline (1983), Pershagen et al. (1981), Pershagen (1985), Enterline et al. (1987b), Taylor et al. (1989), and Jarup et al. (1989b). Five of those presenting stratified analyses are discussed in detail in Appendix A, which also includes tables summarizing the separate and joint effects of arsenic and smoking observed in each of five studies.

The results from the five studies are summarized in Table 9-11. Using four different measures of effect, three studies indicate the joint effects of occupational arsenic exposure and smoking to be greater than additive but less than multiplicative. One occupational and one environmental comparison indicate a joint effect that is multiplicative.

Three recent studies also address the arsenic-smoking interaction. Taylor et al. (1989) reported finding no evidence of a synergistic interaction between arsenic and smoking. The data actually were not adequate to evaluate this interaction because (1) there were almost no nonsmokers, and (2) there appeared to be no main effect from smoking alone.

Jarup et al. (1989b), and Pershagen (1990) conducted a nested case-control study in the cohort of Ronnskar smelter workers and found that the

interaction between arsenic and smoking is intermediate between additive and multiplicative.

Enterline et al. (1987b) used logistic regression to analyze lung cancer cases and controls at the 6 smaller U.S. smelters. The two-way and three-way interactions between arsenic exposure and smoking variables were not significant; that is, a multiplicative interaction of arsenic and smoking could not be rejected. (Since the logistic model assumes multiplicative effects for two separate variables, the test of interaction terms is a test for deviation from a multiplicative relationship.)

It appears, therefore, that the joint effects of smoking and arsenic are not additive. They may be as high as multiplicative, though they may be less. None of the currently available evidence suggests more than a multiplicative effect. The finding of an interaction which is greater than additive, referred to as synergism, constitutes further evidence of a causal role for arsenic in the etiology of respiratory cancer.

9.4 Conclusion

The staff of DHS finds the evidence for carcinogenicity due to inhaled arsenic to be strong. This conclusion is based on (1) the high relative risks seen in these occupational studies, (2) the high statistical significance of these studies, (3) the evidence for a dose-response using different indices of exposure, and different measures of response, (4) the data of Welch et al. (1982) showing a dose-response effect of arsenic while the proportion of smokers remained constant from one level of arsenic

exposure to the next, (5) the data of Welch et al. (1982), Enterline et al. (1987b), Jarup et al. (1989b), and Taylor et al. (1989) showing strong dose-related effects of arsenic after controlling for smoking, (6) the four studies showing increased risks among nonsmokers, (7) the seven studies indicating a synergistic interaction between smoking and arsenic exposure, (8) the consistency of the arsenic-related effect among cohorts which are geographically dispersed (Japan, Sweden, China, and several states of the U.S.), (9) the consistency of the arsenic-related effect from several sources of exposures: smelting, mining, and insecticide manufacturing, and (10) the failure of potential confounding from other workplace exposures to explain the observed association.

Notes

[1]SMR = [# observed deaths] ÷ [# expected deaths] • 100, where the number of expected deaths is based on age-, sex-, race- and calendar-year-specific rates in the general population.

[2]The reference population was white males from the state of Washington.

[3]These data are contained in Morris' 1978 testimony regarding a proposed federal standard for occupational exposures to inorganic arsenic (Lee-Feldstein 1986).

[4]The SMRs from Welch et al. (1982) shown in Table 9-10 were calculated based on general population rates (Weiss 1983, Higgins et al. 1983). If the arsenic-exposed smokers had been compared to general population smokers, their SMRs would have been lower. Conversely, if arsenic-exposed nonsmokers had been compared to general population nonsmokers, their SMRs would have been higher. Thus the relative risk of respiratory cancer death due to arsenic exposure is probably even higher among nonsmokers than it is among smokers in this cohort, even though it appears to be lower. This issue, however, does not affect the clear finding of a dose-related effect of arsenic regardless of smoking status.

[5]Risk ratio = [risk in exposed] ÷ [risk in unexposed].

TABLE 9-1

SUMMARY OF EPIDEMIOLOGIC STUDIES OF CANCER IN RELATION TO AIRBORNE ARSENIC EXPOSURE*

Study Population	Author(s)	Type of Study	Results	Highlights and Deficiencies
Smelter workers-Tacoma, Washington (Analysis of deaths for 1946-1960)	Pinto and Bennett (1963)	Proportionate mortality	No difference in lung cancer proportionate mortality between exposed and unexposed workers.	Workers leaving the plant before retirement were not included. In the classification of workers by exposure, the "non-exposed" group apparently were exposed since they also had high levels of arsenic in the urine.
Smelter workers-Tacoma, Washington (follow-up from 1950-1971)	Milham and Strong (1974)	Cohort	40 observed lung cancer deaths versus 18 expected (P <0.001).	Urinary arsenic levels of persons living around the smelter decreased with distance from the smelter.
Smelter workers-Tacoma, Washington (follow-up from 1949-1973)	Pinto et al. (1977)	Cohort	32 observed respiratory cancer deaths, versus 10.5 expected (P <0.05). Dose response seen by urinary arsenic levels and by duration and intensity of exposure.	Study consisted of only pensioners.
Smelter workers-Tacoma, Washington (Follow-up from 1941-1976)	Enterline and Marsh (1982)	Cohort	104 respiratory cancer deaths observed versus 52.5 expected (P <0.01). Dose response found by intensity and duration of exposure.	Short-term high-intensity arsenic exposures appeared to have a greater effect than did long-term low-intensity exposures; SO_2 exposure was found to have little or no effect.
Smelter workers-Anaconda, Montana (Follow-up from 1938 to 1963)	Lee and Fraumeni (1969)	Cohort	147 respiratory cancer deaths observed versus 44.7 expected (P <0.01). Dose response found by intensity and duration of exposure.	A dose response was found between exposure to sulfur dioxide and respiratory cancer mortality. Exposure to sulfur dioxide could not be separated from exposure to arsenic, however.
Smelter workers-Anaconda, Montana (Follow-up from 1964 to 1977)	Lubin et al. (1981)	Cohort	146 respiratory cancer deaths versus 88.7 expected (P <0.01).	Exposure to sulfur dioxide was not found to have an independent effect on cancer risk.
Sample of 1800 of the smelter workers-Anaconda, Montana (Follow-up from 1938-1977)	Welch et al (1982); Higgins et al. (1982)	Cohort	24 respiratory cancer deaths versus 4.6 expected (P <0.01) in the heavy exposure category. Dose response found by intensity (both time-weighted average and ceiling level categories) of exposure.	Analysis of lung cancer mortality by SO_2 exposure found that SO_2 did not play an important role in the respiratory cancer process.

* Source: Adapted from EPA 1984

9-1 (continued)

Study Population	Author(s)	Type of Study	Results	Highlights and Deficiencies
Smelter workers-Anaconda, Montana (follow-up from 1938 to 1977)	Lee-Feldstein (1983)	Cohort	302 respiratory cancer deaths observed versus 105.8 expected ($P < 0.01$). Dose response found by duration and exposure.	
Lung cancer from the parish where the Ronnskar smelter is located	Axelson et al. (1978)	Case-control	For smelter workers, the lung cancer mortality odds ratio was 4.6; there also was a significantly ($P < 0.02$) elevated risk of leukemia and myeloma among smelter workers.	Exposure to sulfur dioxide did not appear to be associated with lung cancer.
Lung cancer deaths in the city of Saganoseki-machi, Japan	Kuratsune et al. (1974)	Case-control	58% of lung cancer cases were found to be former smelter workers versus 15.8% in controls.	The cause of death listed on the death certificate was validated using detailed pathologic analysis.
Copper smelters in Sagnoseki-machi, Japan	Tokudome and Kuratsune (1976)	Cohort	29 trachea, lung, and bronchus cancer deaths versus 2.44 expected ($P < 0.01$); 3 observed colon cancer deaths versus 0.59 expected ($P < 0.05$). A lung cancer dose response was seen by length of employment and level of exposure.	The latent period ranged from 13 to 50 years, with an average of 37.6 years.
Smelter workers in Magna, Utah	Rencher et al. (1977)	Proportionate mortality and cohort	7 percent of the deaths were lung cancer deaths compared to 0 to 2.2 percent for other factory workers and 2.7 percent for the State; the lung cancer death rate was found to be 10.1 per 10,000 versus 2.1 and 3.3 per 10,000 for mine workers and the State, respectively.	
Residents living near a smelter in El Paso, Texas	Rom et al. (1982)	Case-control	No association was found between lung cancer and distance from the plant.	Effects of migration, smoking and occupation were not considered.

9-1 (continued)

Study Population	Author(s)	Type of Study	Results	Highlights and Deficiencies
Arsenical pesticide manufacturing workers	Ott et al. (1974)	Proportionate mortality and cohort	10.2% and 3.5% of deaths in the exposed group were from cancer of the respiratory system and from lymphatic and hematopoietic cancers, except leukemia, respectively, versus 5.7 and 1.4% in the controls; the cohort mortality study found 20 respiratory cancer deaths and 5 deaths of the lymphatic and hematopoietic tissues versus 5.8 and 1.3 expected, respectively (both significant at $P < 0.01$).	A respiratory cancer mortality dose response was not found below an average dosage of 3890 mg of arsenic, but above that dosage there was a good dose response. It should be noted, however, that all of the respiratory cancer at or below 3890 mg had less than one year of exposure. Thus, it is unlikely that those deaths were due to arsenic exposure.
Retirees of an arsenical pesticide plant in Baltimore, Maryland (follow-up from 1960 to 1972)	Baetjer et al. (1975)	Proportionate mortality and cohort	The proportionate mortality ratio (PMR) was 6.58 for respiratory cancer ($P < 0.05$); for cause-specific mortality the observed-to-expected ratios were 16.67 for respiratory cancer and 50 for lymphatic cancer (both with $P < 0.05$).	The cohort study was limited to pensioners only.
Retirees of an arsenical pesticide plant in Baltimore Maryland (follow-up 1946 to 1977)	Mabuchi et al. (1979)	Cohort	12 observed lung cancer deaths versus 3.6 expected ($P < 0.05$); a dose response by duration of employment was seen for those with exposure of high intensity.	
Wenatchee Valley orchard workers in the state of Washington	Nelson et al. (1973)	Cohort	No difference was found between the cohort and the state of Washington for overall cancer mortality or for lung cancer mortality.	
German vintners	Roth (1958)	Proportionate mortality	Of 47 autopsies among vintners with chronic arsenic intoxication, 64% of the deaths were due to cancer, 60% to lung cancer; 6 of the 47 and 13 of the 47 were reported to have liver and skin tumors, respectively.	No controls were used. There was no indication of how the autopsy cases were selected.

9-1 (continued)

Study Population	Author(s)	Type of Study	Results	Highlights and Deficiencies
Residents of Deer Lodge and Silver Bow Counties, Montana	Newman et al. (1976)	Ecological correlation	There was an increase found in the incidence of lung cancer among men. In one of the cities there was also an increase in lung cancer among women.	No adjustment was made for cancer cases which may be occupational.
All counties in the United States with smelters	Blot and Fraumeni (1975)	Ecological correlation	Average lung cancer mortality rates were significantly elevated for both males and females in 36 counties with smelters processing copper, lead, or zinc ores.	
Residents near a smelter in Utah	Lyon et al. (1977)	Case-control	No association between cancer and distance from the smelter was found.	Lymphoma cases which may have an association with arsenic exposure were used as controls. Effects of smoking, migration, and occupation were not considered.
Residents near Ronnskar-verken smelter in northern Sweden	Pershagen et al. (1977)	Ecological correlation	A significantly higher mortality rate for lung cancer was noted for men in the exposed area. The increase was no longer significant when occupational cases were excluded, however.	When excluding occupational cases of lung cancer from the study population, lung cancer cases for a comparable occupational group were not excluded from the comparison population.
Population surrounding an arsenical pesticide facility	Matanoski et al. (1976, 1981)	Ecological correlation	The lung cancer mortality for males in the census tract in which the plant was located was 3-4 times higher than the control tracts ($P < 0.05$).	The difference in the lung cancer mortality rate in the index tract could not be explained by occupation.
Arsenical sheep dip manufacturing workers	Hill and Faning (1948)	Proportionate mortality	29.3 percent of deaths were due to lung cancer versus 12.9 percent of deaths among workers in the same geographic area who were not exposed to arsenic ($P < 0.05$). The excess in cancer deaths was mainly due to an excess in lung cancer and skin cancer.	

TABLE 9-1 (CONTINUED)

SUMMARY OF EPIDEMIOLOGIC STUDIES OF CANCER IN RELATION TO AIRBORNE ARSENIC EXPOSURE

Study Population	Author(s)	Type of Study	Results	Highlights and Deficiencies
Smelter workers at Ronnskarsverken in northern Sweden	Wall S (1980)	Cohort	Using national rates, the SMR[1] for lung cancer was 288, for stomach cancer 174. Using local county rates, lung cancer incidence was elevated 5-fold. Life expectancy was inversely related to length of exposure in two departments with highest arsenic levels.	Detailed analysis was done for year and age at first employment, and for latency. Potential contribution to excess from exposures to other chemicals is not evaluated but other exposures included Pb, SO_2, Cd, Cu, and other chemicals.
Lung cancer cases and controls among Ronnskarverken copper smelter workers	Pershagen G, et al. (1981)	Case-control study nested within a cohort	Age-standardized rate ratios were 3.0 for arsenic (no smoking), 4.9 for smoking (no arsenic) and 14.6 for combination of both exposures.	Daily tobacco consumption among the smokers did not differ between exposure categories. Multiplicative effect found for combination of arsenic exposure and smoking.
Lung cancer cases and matched controls among residents near Ronnskarsverken smelter in northern Sweden	Pershagen G (1985)	Case-control	Mining work was associated with age-adjusted ORs of 10.4 among nonsmokers and 35.2 among smokers; smelter work was associated with age-adjusted ORs of 8.4 (nonsmokers) and 26.2 (smokers). Residence near smelter was associated with age- and occupation-adjusted ORs of 2.3 (nonsmokers) and 2.2 (smokers).	Confounding due to smoking or residence in a house with potential radon exposure could not explain increase in lung cancer risk among those residing in exposed areas, nor among smelter workers. Differs from 1981 report by Pershagen et al. in hat arsenic exposure per se is not examined.
Smelter workers-Anaconda, Montana (Follow-up from 1938 to 1977)	Lee-Feldstein (1986)	Cohort	Observed respiratory cancer deaths in 3 cohorts (defined by year of first employment) were 114, 110 and 38, compared to expected deaths 23.5, 45.7 and 16.9 respectively ($p<.01$ for each of these). Found a linear relationship between cumulative exposure based on arithmetic means of air samples in the plant and respiratory cancer mortality.	Estimates of exposures did not utilize time-exposures factors, i.e. it was assumed that each worker spent 100% of his time at the location where measurements were make. Found an elevated risk even for low cumulative exposures. Study included over 190,000 person-years of follow-up.

[1] SMR = standardized mortality ratio defined as ([observed number of deaths] % [expected number of deaths]) x 100 where the expected number of deaths is based on age-, sex-, and calendar year-specific rates in the general population.

TABLE 9-1 (CONTINUED)

Study Population	Author(s)	Type of Study	Results	Highlights and Deficiencies
Smelter workers, Anaconda, Montana (follow-up from 1938-1981)	Higgins et al. (1985)	Cohort (N=8044)	Dose-response trends using three different indices of exposure (ceiling, time-weighted average [TWA], and cumulative). Using cumulative exposure, SMRs rose from 142 for those with lowest exposure to 396 in the high exposure group.	Approx. 200,000 person-years of follow-up. Essentially replicates for the whole cohort the findings of Welch et al. (1982), who had analyzed a subset. Used quantified exposure data, but cumulative exposure was assigned incorrectly: final cumulative exposure was assigned to every person-year of a given worker.
Lung cancer deaths and matched controls among smelter workers, Anaconda, Montana (follow-up from 1938-1977)	Lee-Feldstein (1989)	Case-control, nested in cohort (280 cases, 1583 controls)	Compared 5 different indices of exposure (maximum category, TWA [arithmetic means], TWA [geometric means], cumulative [arithmetic means], and cumulative [geometric means]). Found that each of these was a significant predictor of lung cancer risk. Men who were younger at first employment had greater risk than those first employed later in life.	No smoking data were collected. Time-exposure factors were not used in quantifying exposure. Assumes an exponential relationship between exposure and lung cancer, although the actual relationship appears to be supralinear.
Smelter workers, Tacoma, Washington (follow-up from 1941-1976)	Enterline et al. (1987a)	Cohort (N=2802)	Found supralinear dose-response, using estimates of air exposures, with SMRs from approx. 140 to 480. Best fit was a power function. Determined urine-to-air relationship using data from departments with both types of measurement.	Used air measurements of arsenic to reanalyze an earlier study (Enterline and Marsh 1982) that had characterized exposures as urinary arsenic.
Smelter workers at eight U.S. plants, including Garfield Smelter (follow-up from 1949-1980)	Enterline et al. (1987b)	Cohort (N=6078), and nested case-control	In cohort analysis, lung cancer SMR significantly elevated only for the Garfield smelter. Case-control analysis found significant arsenic effect after simultaneously adjusting for smoking and sulfur dioxide. After controlling for arsenic and smoking, sulfur dioxide had no adverse effect.	Exposure levels were low at the Garfield smelter, and very low at all the other smelters, resulting in low power: range was 0.05 to 0.28 to detect increase predicted by dose-response from Tacoma smelter.
Smelter workers, Ronnskarsverken, northern Sweden (follow-up from 1958-1982)	Sandstrom et al. (1988)	Cohort study of incidence (N=611)	120 incident lung cancer cases observed versus 51.7, 35.8, or 45.2 expected using as referents males from all of Sweden, the county, or the municipality. Age-adjusted incidence rate appears to have begun declining in the 1970s.	No quantified exposure data were used. Decline in incidence over time could be due to declining exposures, earlier medical notification, or changing smoking habits.

TABLE 9-1 (CONTINUED)

Study Population	Author(s)	Type of Study	Results	Highlights and Deficiencies
Smelter workers, Ronnskarsverken, northern Sweden	Jarup et al. (1989)	Cohort (N=3916)	Overall SMR=372 (106 observed versus 28.5 expected, 95% C.I.=304-450). Strong positive dose-response, either supralinear or linear with elevated intercept. Dose-response unchanged when exposure was lagged or a latency period was assumed. Intensity of exposure showed more of an effect than duration of exposure. No dose-response was observed for sulfur dioxide exposure.	Extended the follow-up of Wall (1980). Includes over 125,000 person-years of follow-up. No smoking data were collected. Rates were standardized for residents of county.
Living lung cancer cases in 1985 and age matched living controls among tin miners in China	Taylor et al. (1989)	Case-control, nested in cohort (107 cases, 107 controls)	Comparing the 2nd, 3rd, and highest quartiles of exposure to the lowest quartile, odds ratios (ORs) were 6.8, 23.9, and 22.6, indicating a strong, supralinear, dose-response. These ORs were adjusted, using logistic regression, for age, radon exposure, year of starting employment, and duration of smoking.	Individual cumulative exposures were based on industrial hygiene measurements and occupational history. Arsenic effect was independent of smoking and of radon. Smoking appeared to have little or no effect, perhaps because there were almost no nonsmokers. It was therefore difficult to evaluate synergism between arsenic and smoking.
Pesticide manufacturing workers. (Extends follow-up of Ott et al. by 9 years)	Sobel et al. (1988)	Cohort (N=611)	In new follow-up period, observed 9 lung cancer deaths versus 7.8 expected based on U.S. population, SMR=116. Elevated SMRs did not decline with time since exposure ended.	More complete ascertainment than in original study. Did not use local, regional or statewide rates for comparison. Used industrial hygiene data to quantify individual exposures, but did not report analyses using these exposure estimates. No explanation was given for not using this information.
Lung cancer deaths between 1968 and 1980, and matched deceased controls among orchard workers in the state of Washington	Wicklund et al. (1988)	Case-control (155 cases, 155 controls)	Exposure to only lead arsenate was reported or presumed for 9 cases and 11 controls; the smoking-adjusted OR was 0.79. Exposure to both lead arsenate and DDT exposure was reported or presumed for 89 cases and 89 controls; the smoking-adjusted OR was 1.12. No dose-response was observed based on acres, years, or acre-years.	Interviews conducted with proxies only. Analyses were adjusted for smoking using Mantel-Haenszel method. Lead arsenate exposure was presumed if the proxy reported that the deceased had sprayed before 1945. Strong possibility of misclassification, which would probably have been nondifferential, given that deceased controls were used.

TABLE 9-2

SUMMARY OF OCCUPATIONAL STUDIES CONCERNED WITH RESPIRATORY CANCER MORTALITY AND ARSENIC EXPOSURE

Study	No. of persons in Study	Deaths				SMR[1] Respiratory Cancer
		Period of observation	Total No.	Cancer	Respiratory Cancer	
Lee and Fraumeni 1969, copper smelter	8,047	1938-63	1,877	305	147	329
Ott el al. 1974, insecticide manufacturers	603	1940-73	95	35	20	345
Tokudome and Kuratsune 1976, copper smelter	839	1949-71	157	55	29	912
Rencher et al. 1977, copper smelter	244	1959-69	244	41	17	306
Pinto et al. 1978, pensioners from copper smelter	527	1949-73	324	69	32	305
Mabuchi et al. 1979, pesticide manufacturer	1,050 males	1946-77	197	47	23	168
Wall 1980, copper smelter	3,958	Unspecified-1976	953	245	79	500, locally 288, nationally
Enterline and Marsh 1980, copper smelter	2,776	1941-76	1,061	232	104	190
Lubin et al. 1981, copper smelter	5,403	1964-77	1,628	304	146	165
[Lee-Feldstein 1983], copper smelter	8,045	1938-77	3,522	609	302	285

[1] SMR = standardized mortality ratio, defined as ([observed number of deaths] / [expected number of deaths]) x 100.

(From Lee-Feldstein 1983, Table 9)

TABLE 9-3

Respiratory Cancer Deaths and Standardized Mortality Ratios (SMRs)[1] by Cumulative Arsenic Exposure at Time of Retirement Among 582 Retired Workers Aged 65 Years and Over: Tacoma, Washington, Copper Smelter

Cumulative Exposure (μg As/l urine) (-years)	Observed Deaths	Expected† Deaths	SMR
<2000	1	0.70	142.3
2000-	3	1.65	181.8
3000-	6	4.39	136.8
6000-	5	1.64	305.3
9000-	6	1.74	345.5 *
12000-	6	1.53	393.2 **
15000+	7	2.30	304.9 *

* $p < 0.05$.

** $p < 0.01$

† Based on Washington state white males

[1]SMRs = standardized mortality ratios, defined as ([observed number of deaths] / [expected number of deaths]) x 100.

Source: Enterline and Marsh 1982, Table 10.

TABLE 9-4

RESPIRATORY CANCER MORTALITY FOR 2802 TACOMA SMELTER WORKERS[1]

Arsenic Exposure Cumulative (ug/m^3 -years)	Observed	Follow-Up Starting On Entry Into Study		Follow-Up Starting At Termination Of Employment	
		Expected[2]	SMR[3]	Expected[2]	SMR[3]
<750	9	6.6	136	6.3	144
750-	15	8.8	170	7.3	206[4]
2000-	19	10.3	184[4]	7.8	242[5]
4000-	21	10.3	205[5]	7.3	288[5]
8000-	23	10.4	221[5]	6.9	332[5]
20000-	13	4.9	264[5]	3.2	409[5]
45000+	4	1.2	339	.8	477[4]

[1]From Enterline et al. 1987, Table 2

[2]Based on rates for white males in the State of Washington

[3]SMR = standardized mortality ratio defined as ([observed number of deaths] ÷ [expected number of deaths]) x 100 where the expected number of deaths is based on age-, sex-, and calendar year-specific rates in the general population.

[4]$p<.05$

[5]$p<.01$

TABLE 9-5

RESPIRATORY CANCER MORTALITY FOR 4099
ANACONDA SMELTER WORKERS

Arsenic Exposure	Observed	Expected	SMR[1†]
Cumulative ($\mu g/m^3$ -years)			
<833	15	8.2	183[†]
833-	24	9.2	260[*]
2,083-	22	15.2	145
8,333-	40	15.8	253[†]
41,667-	16	6.4	251[†]
208,333-	7	0.9	798[†]
≥416,667	5	1.1	469[†]

[1] SMR = standardized mortality ratio, defined as ([observed number of deaths] / [expected number of deaths]) x 100 where the expected number of deaths is based on age-specific rates for white males in the general population of Idaho, Montana, and Wyoming.

[†] $p \leq .05$

[*] $p \leq .01$

(Adapted from Lee Feldstein 1986, Table 3; these data are from "Cohort II", the workers first employed between 1925 and 1947)

TABLE 9-6

RESPIRATORY CANCER MORTALITY FOR 1800
ANACONDA SMELTER WORKERS

Arsenic Exposure	Observed	Expected	SMR[1]
TWA ($\mu g/m^3$)			
<100	11	7.9	138
100-	22	7.3	303*
500-	29	7.7	375*
≥5,000	18	2.6	704*
30-Day Ceiling ($\mu g/m^3$)			
<100	8	6.2	129
100-	4	3.4	116
500-	41	11.8	348*
≥5,000	27	4.1	662*
Cumulative ($\mu g/m^3$-years)			
<500	4	5.8	69
500-	9	5.7	157
2,000-	27	6.8	400*
≥12,000	40	7.3	550*

[1]SMR = standardized mortality ratio, defined as ([observed number of deaths] / [expected number of deaths]) x 100.

*$p \leq .01$

(Adapted from Welch et al. 1982, Tables 7 and 9)

TABLE 9-7

RESPIRATORY CANCER MORTALITY FOR 8044
ANACONDA SMELTER WORKERS

Arsenic Exposure	Observed	Expected	SMR[1†]
TWA ($\mu g/m^3$)			
<100	76	50.3	151*
100-	125	50.4	248*
500-	115	39.3	293*
≥5,000	22	4.1	538*
30-Day Ceiling ($\mu g/m^3$)			
<100	45	30.0	150
100-	20	10.5	190
500-	220	90.4	243*
≥5,000	53	13.2	402*
Cumulative ($\mu g/m^3$ -years)			
<500	51	45.9	142
500-	67	37.5	179*
2,000-	122	46.0	265*
≥12,000	98	24.8	396*

[1] SMR = standardized mortality ratio, defined as ([observed number of deaths] / [expected number of deaths]) x 100.

† All entries were significant at $p \leq .05$

* $p \leq .01$

(Adapted from Higgins et al. 1985, Tables 21 and 22)

TABLE 9-8

RESPIRATORY CANCER MORTALITY
AMONG 1982 DECEDENTS PREVIOUSLY
EMPLOYED IN A CHEMICAL MANUFACTURING PLANT

CUMULATIVE[†] EXPOSURE (mg As)	OBSERVED	EXPECTED[¶]	OBSERVED + EXPECTED
<1	1	1.77	.6
1-	2	1.01	2.0
2-	4	1.38	2.9
4-	3	1.36	2.2
6-	3	1.70	1.8
12-	2	.97	2.1
24-	3	.77	3.9
60-	5	.79	6.3
≥ 96	5	.72	7.0

[†]Assumes inhalation of 4 m^3 air/8-hour day. This almost certainly underestimates exposure.

[¶]Expected deaths were calculated by fitting a multivariate regression line to the proportion of deaths due to respiratory cancer using age and date as predictor variables.

(Excerpted from Ott et al. 1974, Table 4)

TABLE 9-9

SMOKING HABITS BY LEVEL OF ARSENIC EXPOSURE
FOR 1800 ANACONDA SMELTER WORKERS

ARSENIC EXPOSURE	SMOKING HABITS		
($\mu g/m^3$, TWA)	% NONSMOKERS	% SMOKERS (CIGARETTES ONLY)	% UNKNOWN
<100	13.2	66.5 (60.9)	20.3
100-	13.1	68.3 (60.7)	18.6
500-	13.6	69.2 (59.8)	17.2
≥5,000	13.7	71.2 (62.3)	15.1

(Excerpted from Welch et al. 1982, Table 11)

TABLE 9-10

RESPIRATORY CANCER MORTALITY BY ARSENIC EXPOSURE
STRATIFIED BY SMOKING HABITS

ARSENIC EXPOSURE ($\mu g/m^3$, TWA)	SMR [1,2]	
	SMOKERS	NONSMOKERS
<100	120	95
100-	312	89
500-	359	286
≥5,000	803	620

[1]SMR = standardized mortality ratio, defined as ([observed number of deaths] / [expected number of deaths]) x 100.

[2]These values are misleading, since smokers and nonsmokers in the cohort were compared separately to a general population comprised of both smokers and nonsmokers. A better analysis would have compared smoking workers to smokers in the general population and nonsmoking workers to nonsmokers in the general population.

(Adapted from Welch et al. 1982, Table 12)

TABLE 9-11

SUMMARY OF THE EPIDEMIOLOGIC EVIDENCE
REGARDING THE INTERACTION OF SMOKING AND ARSENIC
ON RESPIRATORY CANCER

	MEASURE OF EFFECT	JOINT EFFECTS OF ARSENIC AND SMOKING		
		Additive	>Additive but <Multiplicative	Multiplicative
RENCHER et al. (1977)	% of deaths due to lung cancer		X	
WELCH et al. (1982)	SMR[1]		X	
ENTERLINE (1983)	Absolute death rate		X	
PERSHAGEN et al. (1981)	SRR[2]			X
PERSHAGEN (1985)	SRR[2]			
Occupational:			X[3]	
Environmental:				X[3]

[1]Standardized mortality ratio

[2]Standardized rate ratio

[3]The observation of a different degree of synergism for environmental as opposed to occupational exposures is discussed in Appendix E.

10.0 MECHANISMS OF TOXICITY AND CARCINOGENICITY

This chapter discusses mechanisms by which arsenic induces adverse health effects, and addresses the questions regarding a threshold for carcinogenic effects, the evidence for initiation of cancer, and the apparent contradiction between the results of animal and human studies investigating carcinogenicity.

10.1 General Mechanisms

Two mechanisms have been proposed as explanations for the toxic and carcinogenic effects of arsenic (see e.g., EPA 1984):

1. Trivalent arsenic attacks free sulfhydryl (-SH) groups on enzymes and other proteins (Schoolmeester and White 1980, Willhite and Ferm 1984, Knowles and Benson 1984). This mechanism affects a wide variety of enzymes, including transaminases, oxidases, dehydrogenases, kinases, lipase, acid phosphatase, liver arginase, cholinesterase, and adenyl cyclase (Willhite and Ferm 1984, Schoolmeester and White 1980). The clinical significance of most of these inhibitions is uncertain (Schoolmeester and White 1980). Pentavalent arsenic does not act as a sulfhydryl reagent (Johnstone 1963), though it undergoes reduction to As(III) *in vivo*.

A primary effect of As(III) is interference with energy metabolism. As(III) disrupts the pyruvate oxidase system by combining with the two sulfhydryl groups of lipoic acid to form a six-membered ring (Winship 1984, Schoolmeester and White 1980, NAS 1977).

2. The mechanism of action most often attributed to pentavalent arsenic is "arsenolysis" in which inorganic As(V) competes with inorganic phosphate to form unstable arsenate esters in the place of more stable phosphate esters (Schoolmeester and White 1980, Willhite and Ferm 1984). As DNA and RNA are held together by phosphate ester linkages, arsenic substitution for phosphorous may cause breaks in these nucleic acids (Schoolmeester and White 1980, EPA 1984). For acute and chronic toxicity, arsenolysis is considered a less important mechanism than sulfhydryl group inhibition by As(III) (Schoolmeester and White 1980); but for teratogenesis arsenolysis may be more important.

10.2 Teratogenic Effects

Pentavalent arsenic is more damaging than As(III) in certain aspects of teratogenesis possibly due to the proposed nucleic acid-weakening effect of As(V) (arsenolysis). Different genes are active during organogenesis and development than in later life.

Researchers investigating the action of copper and cadmium (Hanlon and Ferm 1974) have suggested that metal teratogens may act by interfering with the transfer of specific growth-controlling factors, possibly hormones, across the nuclear membrane by interacting with protein carriers. Since trivalent arsenic interacts with sulfhydryl groups of protein, As(III) may be teratogenic by this mechanism. Since As(V) compounds are reduced to the trivalent state, they may act similarly.

10.3 Genotoxic and Carcinogenic Effects

Both sulfhydryl group binding and arsenolysis have been proposed as mechanisms for genotoxic effects of arsenic (See Chapter 7, Section 10.1, and EPA 1984). Arsenic compounds are clastogenic and elevate rates of sister chromatid exhange (Oberly et al. 1982, Clive et al. 1979). They have not, however, been shown to cause base-pair substitutions or frame-shift mutations. Observations in the TK system (Oberly et al. 1982, Clive et al. 1979) indicate that both As(III) and As(V) compounds can cause heritable loss of function of a gene. In Chinese hamster ovary (CHO) cells, the highest clastogenicity of sodium arsenite was detected at the border between the G_1 and S stages of the cell cycle (Lee et al. 1986d). Data indicate that arsenite is co-clastogenic with ethyl methanesulfonate (EMS) in these cells only in the G_1 and early S stages of the cell cycle whereas caffeine acts only in the late S and/or G_2 stages (Jan et al. 1986). However, treatment during the G_2 phase potentiated chromatid exchanges and breaks induced by UV light or 4-nitroquinoline 1-oxide (Lee et al. 1986c).

Arsenic compounds inhibit the immune system and a may play a role in the transformation of mammalian cells by viruses. They have induced morphological transformation of Syrian hamster embryo cells without co-treatment (Lee et al 1985b). Recently, researchers found that sodium arsenite and sodium arsenate amplified the dihydrofolate reductase gene and conferred methotrexate resistance in mouse 3T6 cells; this effect may relate to arsenic's carcinogenicity since amplification of oncogenes is found in many tumors (Lee et al. 1988). One author has suggested that effects of

As(V) on semiconductor properties of DNA may affect carcinogenesis (Marczynski 1988).

10.4 Threshold Effects

10.4.1 Arsenic Epidemiology and Thresholds

Lamm and Lederer (1984) have argued that there is a threshold for arsenic-induced carcinogenesis. They cite the lack of an elevated risk in the low-exposure groups in several of the occupational studies. This argument is not convincing for several reasons:

a. Frequently the mortality rates of occupational cohorts are lower than those of the general population because occupational cohorts are healthier. This is known as the "healthy worker effect," and has been well characterized in the epidemiological literature (McMichael 1976, Fox and Collier 1976). This phenomenon could explain the lack of an elevated risk in low-exposure groups.

b. Low exposures are not expected to produce large increases in respiratory cancer deaths. Even so, Higgins et al. (1985) found statistically significant excesses in all the low-exposure categories, regardless of whether exposure was assessed using cumulative dose or a time-weighted average. Lee-Feldstein (1986) found significant excesses in the low-exposure categories for those hired before 1947.

c. The size of the low-dose group is frequently too small to have the statistical power to detect the small increase in risk which might be

predicted from low-level exposure. Where significant excesses were not observed in the low-exposure groups, the power to detect increased mortality given true SMRs (standardized mortality ratios) of 125, 150 and 200 ranged from 10% to 60% (Table 10-1). The risks predicted by the risk assessment contained in this document (Chapter 11) for those in the low-exposure categories of these studies were too small to be detectable with a probability of even 10%.

DHS staff conclude that the epidemiological evidence does not support a threshold-mediated mechanism for carcinogenicity by arsenic compounds.

10.4.2 Arsenic Toxicology and Thresholds

A threshold dose of a toxicant is one below which a specified outcome does not occur. While threshold models for carcinogenesis (based on, for example, saturation of detoxification enzymes, the existence of DNA repair mechanisms, or recurrent toxicity) have been proposed, none has been convincingly demonstrated.

In the case of arsenic, there is evidence of genotoxicity with little evidence of specific-locus mutagenicity (See Chapter 7). The mechanisms of genotoxicity mentioned above (Section 10.3) are not necessarily associated with a threshold. A single instance of sulfhydryl group binding to an enzyme might result in misrepair or breakage of DNA. Likewise, a single instance of arsenolysis might result in DNA damage. The staff of DHS agrees with the conclusion of the International Agency for Research on Cancer (IARC) that there is insufficient evidence to justify creating separate

classes of carcinogens (based on mechanism) for which different risk assessment methods would be used (IARC 1983). In the absence of compelling evidence to the contrary, DHS treats carcinogenesis as a nonthreshold phenomenon.

10.5 Discrepancy Between Animal and Human Data for Carcinogenicity

As summarized in Chapter 9, the evidence for human carcinogenicity of arsenic is strong. In contrast, the evidence for animal carcinogenicity is equivocal (Chapter 8). Because the animal studies are not uniformly negative[1] and because no animal carcinogenicity bioassay has been conducted according to a standardized protocol (such as that of the National Toxicology Program), these studies do not definitively establish or preclude the carcinogenicity of arsenic in animals. Intratracheal instillation of arsenic, which has produced pulmonary tumors in experimental animals, allows greater deposition and retention of toxicants than ordinary inhalation and may irritate pulmonary tissue (See Chapter 8).[2] For inhalation, the staff of DHS concludes that the animal studies are not adequate to evaluate the potential for arsenic's carcinogenicity in nonhuman species. In only one inhalation study were animal exposures adequately representative of human exposures associated with cancer. Other possible explanations for qualitatively different responses of humans and animals to arsenic include differences in pharmacokinetics, target tissues, and sensitivity to toxicity.

Human lung is structurally and histochemically different from that of laboratory animals. The Clara cell, the principal source of the secretory

lining material for the bronchioles and the site within the lung for the metabolism of xenobiotic substances by the cytochrome P-450 system, differs among species. Ultrastructurally, human Clara cells appear different from those of small animals; for example, the human cells have little agranular endoplasmic reticulum (AER), which is found in abundance in Clara cells of mice, rats, hamsters, guinea pigs, and rabbits. Although there appears to be a correlation between AER abundance and cytochrome P-450 activity, Plopper (1983) noted that P-450 activity has not been assessed in species whose Clara cells have little AER in the adult. It is possible that lab animal lung can detoxify arsenic (or other compounds involved in pulmonary carcinogesis) where human lung cannot. A variety of differences in pulmonary histochemistry among species, as well as among humans of different blood types, have been tabulated (Spicer et al. 1983).

Species differences in clearance of xenobiotic substances, bacteriocidal activity, and biological response to a variety of pulmonary toxins have been reported, and therefore toxic effects observed in laboratory species may not necessarily be generalized (Brain and Mensah 1983).

The skin is an organ in which arsenic-associated cancer has been found in humans but not in repeated experiments with laboratory animals. Epidermis, like lung tissue, is epithelial. Compared to most lab animals, humans have relatively hairless epidermis with a thicker squamous cell layer.

Arsenic may induce cancer through a mechanism which does not involve direct binding or damage to the DNA of somatic cells, such as inhibition of DNA repair, induction of dormant genes, or suppression of immune system

responses. Laboratory animals could be less susceptible than humans to induction of cancer by these indirect mechanisms. It may also be that other toxic effects from the doses of arsenic compounds used in animal studies inhibit tumor promotion (Milner 1969).

In summary, the animal data with respect to arsenic-induced carcinogenicity are generally inadequate and neither confirm nor contradict the human evidence. The reasons for the discrepancy between animal and human data have not been identified.

10.6 Initiation versus Promotion

Some investigators have proposed that arsenic may act as a promoter in carcinogenesis and not as an initiator (Enterline and Marsh 1982, Brown and Chu 1983a, 1983b). Evidence supporting this position includes: (1) an observed decline in the relative risk of lung cancer after termination of employment at a smelter (Enterline and Marsh 1982), (2) the absence of strong data demonstrating carcinogenicity in animals with short lifetimes (see Chapter 8), and (3) several standard mutagenicity assays in which arsenic tests negative (see Chapter 7).

Even if arsenic is not a carcinogen in animals, this would not preclude a role as an initiator of cancer in humans. For instance, if the carcinogenic agent is a metabolite, then a particular metabolic pathway, unique to humans, could explain arsenic's induction of cancer.

The fact that arsenic has not been shown to be directly mutagenic also does not preclude a role for arsenic in initiating a tumorigenic response. If most DNA repair mechanisms are rapid responses to common events, then arsenic's inhibition of such repair may be almost simultaneous with the insult that induces a somatic mutation. Most of the mechanisms of action proposed for arsenic (for example, competition with phosphate groups, clastogenesis, binding to sulfhydryl groups on enzymes, and inhibition of DNA repair) could either initiate tumors or act so early in the carcinogenic process as to be indistinguishable from the initiating event.

One possible mechanism of arsenic carcinogenesis involves mutation by a chromosomal mechanism (See Section 10.3, above). By chromosomal rearrangement or clastogenesis, arsenic might initiate or stimulate the inappropirate transcription of a gene involved with cell transformation. For example, a clastogenic event might inactivate a suppressor sequence in an operon. Such an event could occur at an early or late stage in a carcinogenic process.

If an agent acts solely as a promoter of cells that have already undergone irreversible changes, then the time period between exposure to the agent and diagnosable cancer could be relatively short. The epidemiologic evidence weighs more strongly towards longer latency periods between exposure to arsenic and respiratory cancer death, but age at first exposure could be a confounding factor. In one cohort of occupationally exposed workers, the pattern of risk with time since termination of exposure does not support arsenic acting solely as a promoter (see Appendix B).

The staff of DHS concludes that the evidence for arsenic acting only in the late stages of carcinogenesis is not convincing. Therefore, the risk assessment presented in Chapter 11 makes no assumption regarding the timing of arsenic's carcinogenic activity.

Notes

[1]Ingestion studies in both mice and rats of a wide variety of strains are uniformly negative. Skin painting studies in mice are also negative. Two routes produced mixed results: intratracheal instillation and subcutaneous injection. Intramuscular injection was negative in rats and rabbits while intravenous injection was positive in mice. Finally, only two cancer bioassays used inhalation as the route of exposure. For one of these studies, no final report was ever published (Berteau 1986). The other study (Glaser et al. 1986) used an inappropriate animal model, too few animals, and relatively low doses.

[2]The statistically insignificant malignant tumors seen in intratracheal instillation experiments (See Chapter 8) do not moot the questions raised by the discrepancies between animal and human findings with regard to arsenic carcinogenesis.

TABLE 10-1

POWER TO DETECT EXCESS MORTALITY
GIVEN PREDICTED AND SPECIFIED SMRs[1]
AMONG ARSENIC-EXPOSED WORKERS
IN LOW DOSE CATEGORIES[2]

SOURCE	Observed SMR	Predicted SMR[3]	Statistical Power to Detect Excess Mortality Given: Predicted SMR:[4]	SMR of: 125	150	200
Enterline et al. (1987) Lowest cumulative dose	143.8	109.3	.05	.10	.24	.60
Lee-Feldstein (1986) Cohort III (hired after 1947) Lowest cumulative dose	134	115.4	.07	.10	.20	.46

[1] SMRs = standardized mortality ratios defined as ([observed number of deaths] + [expected number of deaths] x 100 where the expected number of deaths is based on age-, sex-, and calendar year-specific rates in the general population.

[2] Only categories for which the SMR was not significantly elevated are shown.

[3] Based on the risk assessment of Chapter 11, and on the midpoint of the range of exposures.

[4] See note 3. These SMR values are found in the next column to the left.

11.0 CANCER RISK ASSESSMENT

The staff of DHS has used human data for its cancer risk assessment of arsenic because (1) these data showed a strong, consistent association with increased respiratory cancer in epidemiologic studies, (2) quantitative exposure measurements were made in several of these studies, and (3) clear dose-response relationships were observed. No risk assessment has been conducted using animal data because the cancer bioassays using relevant routes of exposure have been negative and because no adequate inhalation bioassay has been published. There may be an additional cancer risk resulting from deposition of airborne arsenic onto soil, crops, or sources of water. Risks due to ingestion of arsenic that makes its way into the food chain or water supply were not evaluated for this document. It is recommended that these secondary routes of exposure be taken into account for evaluating risks due to point sources.

A quantitative risk assessment was conducted for ambient exposures using data from two cohorts of smelter workers: one from Anaconda, Montana, and the other from Tacoma, Washington. Direct linear models were fitted to these dose-response data, and unit risks for low-level exposures were obtained by applying the fitted model to background respiratory cancer death rates in both California and the U.S., using separate lifetables for males and females. Finally, the excess risks to California residents from ambient arsenic exposure were derived by multiplying the unit risks times average concentrations measured in the state as reported in Part A.

Chapter 9 describes the occupational studies on which this quantitative cancer risk assessment was based. The quality of data from these occupational studies is discussed in detail below. The exposure assumptions used by Lee-Feldstein (1986) differ markedly from those used by Welch et al. (1982), Lubin et al. (1981) and Higgins et al. (1985), and are likely to result in underestimates of potency.[1] Nevertheless, risk estimates based on the dose-response data in the Lee-Feldstein (1986) paper are included in this document for comparison with other estimates.

A recent reanalysis of the Tacoma cohort incorporated newly available historical data on air concentrations in the plant, and reassessed the previously reported conversion of urinary concentrations of arsenic to air levels (Enterline et al. 1987). In this analysis the best-fitting model for relating cumulative airborne arsenic exposures to lung cancer mortality was curvilinear: the slope decreased as dose increased. Because this relationship yields an extremely steep slope at low doses, and because such an extreme departure from linearity resulted in implausibly high estimates of risk at low doses, the staff of DHS did not use the model fitted by Enterline et al. for quantitative risk assessment, but instead fitted linear models to subsets of the data and to adjusted data from their report.

The carcinogenic risk assessment for arsenic is discussed in six sections:

(1) the strengths of and uncertainties in the data;

(2) uncertainties due to dose-response assumptions;

(3) the model and its assumptions;

(4) the extrapolation to the California and U.S. populations to obtain unit risks;

(5) comparison with other risk assessments; and

(6) calculation of risk at ambient levels of arsenic in California.

The staff of DHS considers the predicted risks presented in this chapter to be the best estimates available at the present time. Estimates derived in any risk assessment are not exact predictions, but rather represent plausible estimates based on current scientific knowledge and methods. It is important to recognize that uncertainties are present both in the data and in the extrapolation process, and that these uncertainties necessitate the use of assumptions. In the presentation of this risk assessment, the staff has attempted to explain the assumptions made at each step, and the direction in which each assumption may affect the risk estimates.

11.1 Strengths and Limitations of the Data

11.1.1 Description and Strengths of the Data

The quantitative cancer risk assessment for arsenic considered data from the occupational mortality studies of smelter workers in Anaconda, Montana by Welch et al. (1982), Higgins et al. (1985) and Lee-Feldstein (1986), and in Tacoma, Washington by Enterline et al. (1987). The strengths of these studies are: (1) the use of detailed quantitative exposure estimates based on individual work histories in combination with industrial hygiene surveys going back to the 1940's (1938 for some departments in the Tacoma plant); (2) over 45,000 person-years (PY) of follow-up for 1800 workers (Welch et al. 1982), approximately 200,000 PY for 8000 workers (Higgins et al. 1985 and Lee-Feldstein 1986) and over 70,000 PY for 2802 workers (Enterline et al. 1987); (3) the demonstration of a clear dose-response relationship of

respiratory cancer mortality to cumulative arsenic exposure (in all of these reports) and to several other indices of exposure (Welch et al. 1982, Higgins et al. 1985, Lee-Feldstein 1989); (4) the similarity in smoking habits for workers with different levels of arsenic exposure (Welch et al. 1982); (5) the demonstration of an arsenic-related dose-response for nonsmokers and smokers separately (Welch et al. 1982); (6) the finding of no change in the standardized mortality ratios (SMRs) when workers in the Anaconda plant exposed to asbestos were removed from the analysis (Welch et al. 1982, Higgins et al. 1985); and (7) the finding of an arsenic effect independent of SO_2 exposure at the Tacoma plant (Enterline and Marsh 1982), and at the Anaconda plant (Lubin et al. 1981). (A similar finding was noted by Pershagen et al. (1981) and by Jarup et al. (1989) for workers at the Ronnskar plant).

Data from the study by Jarup et al. (1989) of smelter workers at Ronnskarsverken would also have been appropriate for a risk assessment. However, the analyses for this document were completed prior to publication of these data, and a careful comparison of the dose-response information revealed that these data would not yield a substantially different risk value from the analysis presented herein. Graphs of Hertz-Picciotto et al. (1989) show that the dose-response data from Ronnskar do not differ markedly from the Tacoma data. DHS staff have calculated 95% confidence intervals on the SMRs from the Ronnskar workers and each of these includes the value predicted by the Tacoma dose-response data. For these reasons, a risk assessment based on the data of Jarup et al. (1989) is not presented.

Lee-Feldstein (1989) fitted logistic regression models to several different indices of exposure: cumulative, peak and time-weighted average. The cumulative exposure data were not different from those reported by Lee-Feldstein in 1986 and evaluated for this risk assessment.

Industrial hygiene area samples provided the basis for the exposure estimates. For example, at the Anaconda plant, a total of 702 measurements were taken between 1943 and 1965 where arsenic was known or suspected to be present (Morris 1978) In the analysis of Lee-Feldstein et al. (1986), work areas were ranked on a relative scale from 1 to 10. These were grouped and mean measurements were assigned to each group of work sites. For each individual worker, time spent in each work area was based on his employee record. For each calendar-year of observation his cumulative exposure was estimated as the sum of three terms: [time spent in heavy (medium, light) exposure areas] X [mean heavy (medium, light) exposure]. Analyses were conducted using both arithmetic and geometric means.

For the analysis of Higgins et al. (1985), there were 826 measurements taken from the same time period. Samples collected at each work location were averaged, and then weighted by an exposure factor representing an estimate of the fraction of time spent at the location. This calculation produced an exposure index for each department. Departments for which no measurements were available were assigned to the light exposure grouping, since measurements were taken wherever substantial exposures were suspected. Each worker's exposure was calculated by multiplying the exposure index by the time spent in each department, based on work records, and summing over all

the departments. The workers were then divided into four levels based on their final cumulative exposure.

Exposure estimates for the Tacoma plant (Enterline et al. 1987) were based on both urinary arsenic and air concentration measurements. Exposures were estimated for each department and each year or group of years. First, departmental urinary arsenic values were reported as geometric means from individual workers (these data covered the periods 1948-52 and 1973-75). Using departments where both types of measurements were available, a urinary-to-air conversion was estimated. Next, this conversion was applied to departments lacking air monitoring data. Augmenting these data with air measurements from 1938 onwards (which were themselves weighted to reflect work-time spent at each sampling site), the exposures for each year in each of the fifteen departments with pre-1970's measurements were derived by linear regression. These regression lines had similar slopes and therefore the median percent decline was used to extrapolate back in time for those departments lacking data between 1938 and the 1960's. For all departments, pre-1938 exposures were assumed to equal 1938 estimates. Individual work histories were used to calculate exposures for each worker.

Unlike Welch et al. (1982) and Higgins et al. (1985), Lee-Feldstein (1986) and Enterline et al. (1987) correctly apportioned person-years of follow-up into exposure categories: when a worker begins employment, his person-years of follow-up should fall in the lowest exposure category, until he has accumulated a large enough dose to move to the next exposure category, and so on (Breslow and Day 1987). Because the analyses of Welch et al. (1982) and of Higgins et al. (1985) assigned every person-year of a given worker to

his final exposure level, exposures were grossly overestimated for a large proportion of person-years. In particular, this would inflate the person-years in the heavy exposure categories and deflate them in the lower exposure categories; however, the deaths would not be redistributed, since the highest exposure level has been achieved at the time of death. Schneiderman et al. (1979) suggested that the use of final exposure level underestimates potency. However, the degree to which the different exposure categories are affected, the distribution of person-years into the exposure categories, and the underlying shape of the true dose-response curve may influence the estimated slope in an unpredictable manner.

These studies showed clear increases in lung cancer mortality which were related to quantified arsenic exposures. Additionally, major confounding influences could be ruled out (See Chapter 9). Therefore, the data from these studies were suitable for conducting a risk assessment. Since the analysis of Welch et al. (1982) was essentially replicated by Higgins et al. (1985) using the full cohort and a slightly longer follow-up period, only the latter was considered for this risk assessment.

11.1.2. Limitations of the Data

Uncertainties in the quantitative interpretation of the data used for this risk assessment derive from four main sources: (a) the accuracy of the exposure assessment for workers in the cohort, (b) the accuracy of the measures of cancer mortality, (c) the potential effects of confounding factors, (d) demographic characteristics of the cohort, which differ from

those of the general population, and (e) characteristics of ambient environmental exposures, which may differ from smelter exposures.

11.1.2a Uncertainties in the exposure estimates

Uncertainty as to the validity of the exposure estimates in the Anaconda smelter stems from (i) applying exposure levels measured in 1943-1965 to both earlier and later years, (ii) applying department-based data to individual workers, (iii) using the average measurement to represent job sites with widely ranging exposure measurements, (iv) using time-exposure-factors (i.e., factors representing the proportion of a workday actually spent in a location with exposure to arsenic by persons employed there) determined during one period for earlier and later periods (Higgins et al. 1985), (v) assuming that workers spent their entire workday at a given worksite (Lee-Feldstein 1986), and (vi) assuming that unmeasured job sites involved light exposures only.

Assumptions (i), (ii), (iii) and (iv) were likely to involve inaccuracies that underestimated some exposures and overestimated others. It is unclear which biases would predominate and whether these errors are systematically related to the outcome, respiratory cancer death. Thus, one cannot determine whether the misclassification of exposure would be differential or nondifferential. Therefore, the net direction of such errors is unknown. Assumption (v) leads to substantial overestimation of exposure, which biases estimates of unit risk downward. Assumption (vi), if wrong, is likely to underestimate the exposure, and therefore to bias estimates of unit risk upward.

In the Tacoma study exposure assumptions were: (i) the use of urinary-to-air relationships from some departments to estimate air exposures in departments where only urinary arsenic data were available, (ii) the application of 1938 exposure estimates to the years 1926-1938, and (iii) the use of linear interpolation and extrapolation to estimate air concentrations for some departments for some years. Because the departments with urinary data were not random, it is unclear what type of biases would be incurred by assumptions (i) and (iii). Assumption (ii) would probably underestimate the very early exposures, leading to an overestimate of risk.

In both the 1986 report of Lee-Feldstein and the 1987 report of Enterline and colleagues, no adjustment was made to the exposures in consideration of a possible latency period: for those individuals who continued to work at their respective smelters, exposures continued to be accumulated up to (or close to) the end of observation. This would tend to underestimate potency.

11.1.2b Uncertainties in the outcome data

In the study of Higgins et al. (1985), losses to follow-up represented 4.5% of the cohort. In the 1986 study by Lee-Feldstein, follow-up loss was approximately 10%. In the study by Enterline et al. (1987), those with unknown status comprised 1.8%. If those lost to follow-up were more (or less) likely to die of lung cancer than those who were traced, then the estimates of risk could be too low (or too high). If loss to follow-up were independent of the cause of death (respiratory cancer vs. other), then no bias would result, since these persons only contributed years prior to being lost. Loss to follow-up is usually more common for living than deceased

subjects. The staff of DHS believes that any bias due to differential loss to follow-up in these studies would have a negligible effect on the unit risk estimation.

11.1.2c Uncertainty due to confounding from and interaction with other carcinogens

While the evidence overwhelmingly supports the conclusion that the observed excess in respiratory cancer is primarily due to arsenic exposure (see Section 9.2), partial confounding from smoking and other workplace exposures cannot be precluded, and this effect could introduce bias in the observed ratios. Considering that Welch et al. (1982) showed a similar distribution of smokers at all levels of arsenic exposure, and that three separate analyses of these cohorts (Welch et al. 1982, Lubin et al. 1981, and Enterline and Marsh 1982) which controlled for either SO_2 or asbestos exposures showed no significant incremental risk beyond that due to arsenic alone, the staff of DHS concludes that bias due to confounding is likely to be small. Error in the estimated mortality ratios resulting from interactions is discussed below (see Section 11.4 and Appendix E).

11.1.2d Characteristics of the cohort

The dose-response relationships used for estimating the unit risk were observed in adult white male workers. No reports of sex differences in arsenic's carcinogenicity are available. Risks for younger age groups resulting from environmental arsenic exposure could be underestimated for several reasons: (1) children are more likely to play in dirt contaminated

by arsenic emissions and receive higher exposures than adults; (2) tracheobronchial particle deposition is generally more efficient in smaller (younger) individuals than in larger (older) people (Phalen et al. 1985); and (3) rapidly proliferating lung tissues in growing children and adolescents may be more susceptible to carcinogenic agents. A study of cigarette smoking among U.S. veterans revealed higher overall mortality ratios among men who began smoking before the age of 20 as compared to those who began later, after controlling for duration (Kahn, 1966). DHS staff conducted a sensitivity analysis which indicated that under a multiplicative model the error due to larger effective doses at younger ages is not likely to be large, i.e., is probably less than two-fold.

11.1.2e Differences between environmental and occupational exposures

The use of occupational data to extrapolate risks at ambient environmental levels involves several assumptions: (i) that the potency of As(III) does not differ from that of As(V), and (ii) that the percent of arsenic deposited or absorbed in the lung is similar for the two types of exposure. Since ambient environmental exposures involve a smaller proportion of As(III), the effect of a potency difference would be to cause overestimation of risks from ambient exposures, however the magnitude of such overestimation would depend on both the difference in As(III):As(V) ratio and the difference in potency. The effect of dissimilarity in the deposition or absorption rate is unknown.

11.1.3 Uncertainties in the Epidemiological Data Used for this Risk Assessment

Table 11-1 lists the uncertainties due to data-related assumptions and other assumptions discussed below. Also included in the table are the direction and estimated magnitude of error due to these assumptions. The staff of DHS knows of no way to quantify the effects of these assumptions.

11.2 Dose-Response Assumptions

In order to use occupational dose-response data for estimating risks from continuous low-level ambient exposures, it is assumed that the cumulative lifetime dose is a reasonable summary measurement for estimating the carcinogenic potency of arsenic. Thus, for the purpose of this risk assessment, short-term high exposures are considered equivalent to long-term low exposures provided the cumulative dose is the same. Kodell et al. (1987) showed the effect of this assumption on extrapolations from bioassays with lifetime exposures to estimate risks from short-term intermittent exposures. They concluded that, depending on the stage of carcinogenesis affected, excess risk could be overestimated by several orders of magnitude, or underestimated by less than an order of magnitude.

In our risk analysis for arsenic, the extrapolation goes in the opposite direction: from shorter occupational exposures to lifetime environmental exposures. If arsenic acts only at middle or late stages, the use of cumulative lifetime dose in the occupational setting may overestimate risks for continuous lifetime exposure. Otherwise (if arsenic acts on early

stages), the use of cumulative dose may underestimate risks from environmental exposures. Environmental exposures typically begin in childhood. Since the smelter workers' exposure was accrued only during adult life, if arsenic functions strongly in the early stages of carcinogenesis, the occupational studies did not observe the full potential carcinogenic impact of arsenic because competing causes of death intervened. On the other hand, short occupational exposures may be more potent than the same cumulative dose spread out over a lifetime. This could simply be due to the intensity of occupational exposures or, if arsenic functions most strongly in the later stages of carcinogenesis, this could be because workers are older and have more initiated cells than do children. Counter-arguments could be offered, however, (e.g., children have greater cell turnover and may therefore be more vulnerable) and none of these hypotheses can be substantiated for arsenic at this time.

While some empirical data have shown a dose-rate influence on carcinogenicity for specific compounds (e.g. Littlefield and Gaylor 1985), there are no data available for arsenic's carcinogenicity which distinguishes an effect of dose-rate different from that of cumulative exposure. The report by Higgins et al. (1985) reported dose-related effects using 3 different exposure indices: 30-day ceiling, time-weighted average (TWA), and cumulative. The data could not distinguish between the effect of the 30-day ceiling and the TWA. Furthermore, the relationship between TWA exposure and lung cancer SMR did not differ from the relationship between cumulative exposure and lung cancer SMR. Lee-Feldstein (1989) conducted a similar analysis on a nested case-control study and had similar findings. Reports by both Higgins et al. (1985) and Lee-Feldstein (1986, 1989)

indicate that cumulative arsenic exposure is a sensitive predictor of lung cancer mortality: significantly elevated SMRs were observed even among those receiving low cumulative occupational exposures.

Another major assumption is that a dose-response relationship at a high range of exposures can be used to predict risks at a low range. For each cumulative exposure group designated by Higgins et al. (1985), Lee-Feldstein (1986) or Enterline et al. (1987), the mean (if published) or the midpoint was used in estimating the slope parameter, β, of the models discussed in Section 11.3. Separate values for $\hat{\beta}$ were estimated from each report. The cumulative exposure levels and equivalent ambient exposures are shown in Table 11-2. These exposures are approximately two to four orders of magnitude higher than exposures California residents are expected to receive (75 yrs at 1.9 ng/m^3 = 143 ng/m^3 -years = 0.14 μg/m^3 -years). The uncertainty due to applying dose-response data observed at such high levels to ambient exposures is large in comparison to the uncertainty from many of the other assumptions. However, the staff of DHS know of no way to quantify this uncertainty. It is frequently expected that the direction of error due to the use of a linear extrapolation will be towards overestimation of the true risk. This expectation appears to be based on observations in lifetime animal experiments with data of fewer dimensions and greater homogeneity than epidemiologic data.

Using linear extrapolation and cumulative lifetime dose is likely to entail the greatest uncertainties of any of the assumptions used in this risk assessment.

11.3 Mathematical Model Used for Extrapolation of Cancer Risk

11.3.1 Selection of Models

Data from the Anaconda and Tacoma smelters show nonlinear relationships between cumulative dose and the relative risk (or SMR) for death from lung cancer. As shown in Figure 11-1, these dose-response curves are concave downward (their slopes remain positive but decrease as exposure increases). Notwithstanding this observation, the staff of DHS has used linear models for this risk assessment for reasons discussed below.

There are several possible explanations for the observed nonlinearities in the dose-response curves. These include: (1) a healthy survivor effect; (2) competing causes of death among those with heavy exposures; (3) differential confounding at different dose levels; (4) a dose-dependent interaction with smoking; (5) misclassification of exposures; and (6) true nonlinearity in the carcinogenic potency.

(1) The healthy survivor effect is a form of the healthy worker effect. In any working population, one finds heterogeneous susceptibility to disease. If, for any reason, susceptible individuals are more likely to leave the jobs involving hazardous exposures, they will terminate at lower cumulative exposure levels than the more resistant workers who continue on those jobs. The measure of response would then rise less rapidly at higher cumulative exposure levels, resulting in the observed curvature. Robins (1986) has shown that a model based on differential "survivorship" (or conversely, job leaving) may explain

the unusual relationship between duration of exposure and lung cancer mortality in the Anaconda cohort.

(2) If competing causes of death were not independent of arsenic dose, then the effect of high arsenic exposure on lung cancer might appear to be smaller than would be predicted from lower exposure groups. Breslow and Day (1987) conducted analyses of the Anaconda cohort in which exposure was measured as duration of employment at low, medium, and heavy arsenic jobs. The coefficient for years of heavy arsenic exposure was lower using a proportionate mortality analysis as compared to an analysis using an external comparison. This pattern suggests increased mortality from competing causes in this group as compared to those in lower exposure categories (Breslow and Day 1987, pp. 215-216). In the same cohort, Welch et al. (1982) found that SMRs for all causes of death, all malignancies, all diseases of the heart and ischemic heart disease among the men who had received heavy exposure to arsenic were greater than corresponding SMRs among the other men. The data, therefore, appear to support a role for competing risks in explaining the observed nonlinearity.

(3) The dose-response relationship shown in Figure 11-1 could occur if smoking habits differed by exposure level. This would require the low exposure person-years to include more smokers or heavier smokers than the high exposure person-years. In other words, nonsmokers would be more likely to reach the higher exposure levels. However, Welch et al. (1982) showed the percent of cigarette smokers to be very similar for four levels of exposure at the Anaconda, Montana, smelter. A

similar lack of association can reasonably be assumed for the Tacoma, Washington, smelter. Similar dose-response relationships were observed at both plants. If confounding from smoking were responsible for the curvature of the dose-response relationship at the Tacoma plant, it could not explain the curvature for the Anaconda workers.

(4) As noted in Chapter 9, interaction between arsenic and smoking was observed in several occupational cohorts. The SMRs in the occupational studies represent a mixture of heterogeneous effects, since the magnitude of the effect of arsenic differs for smokers compared to nonsmokers. In particular, the combined effect of smoking and arsenic was greater than additive, but less than multiplicative. The case-control study of Pershagen (1985) was the only report which contained numbers that allowed calculation of a test of homogeneity. An exact test does not exist, but an approximate test for homogeneity (Gart 1971) shows a p-value of 0.14. This test is known to be of low power (Fleiss 1981), particularly when the number in any stratum is small; thus the test indicates lack of homogeneity. This test, combined with the clear pattern from three studies each showing risk ratios in smokers to be about half the risk ratios in nonsmokers (Table 11-4), strongly suggests that the carcinogenic potency of arsenic differs between smokers and nonsmokers. On the other hand, among those exposed to arsenic at low environmental levels, smokers and nonsmokers showed very similar relative risks (Pershagen 1985). Thus, the data support a multiplicative relationship at low doses, but a less-than-multiplicative relationship at higher doses. Given such dose-dependent interaction, the observed SMRs for lung cancer would

not increase linearly with cumulative exposure to arsenic, but would be concave downward. This pattern is exactly what was observed.

(5) Uncertainty in the exposure estimates has already been discussed (Section 11.1.2a). Since exposures were assigned without reference to the vital status and cause of death, errors of exposure measurement would be nondifferential with respect to outcome. On the other hand, they might not be random with respect to the true exposure. Systematic misclassification may have artificially depressed the exposure estimates at low doses, or artificially inflated them at high doses. Either of these effects, or a combination of them both, could have been responsible for the nonlinear dose-response relationship. Under such circumstances, the dose-response curve would appear more concave downward than the true relationship (Breslow and Day 1987, p. 265).

(6) Finally, it is possible that the carcinogenic potency of airborne arsenic diminishes at higher exposure levels.

Enterline et al. (1987) fitted a power function to the data on the Tacoma smelter workers. This model provided an excellent fit to the observed data. If one assumes that the same power relationship applies at low doses, then the predicted risks at levels of arsenic found in California ambient air are implausibly high: 15% of the population would be predicted to die of lung cancer induced by ambient arsenic levels. Vital statistics do not show that 15% of mortality in California is due to lung cancer. On empirical grounds,

therefore, the power model that fit the Tacoma data can be rejected, at least for the purpose of low-dose extrapolation.

Because the model which best fit the observed data in the high-dose range appeared to be inappropriate for low-dose extrapolation, the arguments for linearity at low doses were reviewed. While supralinearity (i.e., decreasing positive slope with increasing dose) was observed for both cohorts of arsenic smelter workers, use of a linear model is usually considered to be health-protective. Nonlinearities in dose-response relationships, both observed and predicted, are generally sublinear (i.e. the curves have increasing slope with increasing dose) at low doses (Crump et al. 1976). This includes nonlinearities observed at the molecular level (Hoel et al. 1983) and at the population level in epidemiologic investigation (Doll & Peto, 1978), those predicted by the multistage theory of carcinogenesis (Armitage and Doll 1954) and those predicted for a genetically heterogeneous population in which the prevalence of susceptibles increases monotonically with dose (Cornfield 1977, Peto 1978, Schneiderman et al. 1979). Under rare conditions supralinearity might be predicted at chronic low-level exposures (with, for example, certain pharmacokinetics, a bimodal distribution of susceptibility, or synergistic effects of multiple exposures (Berenbaum 1985)). Nevertheless, many authors consider low-dose linearity to be a health-protective assumption (Peto 1978, Crump et al. 1976, Guess et al. 1977, Armitage 1982). With regard to asbestos (Peto 1979) and radiation (NRC 1980), it has been argued that the assumption of linearity for extrapolation to low-level exposures is appropriate even though sublinear or quadratic relationships have also been suggested by some research, on the grounds that linearity is biologically plausible,

mathematically tractable and robust to uncertainties in the exposure measurements. Biological plausibility stems from (1) the observation that some cellular events involving interactions with DNA occur at a rate that is linear in dose (Zeise et al. 1987, Evans et al. 1979) and (2) the recognition that unless the mechanism of carcinogenic activity for a given substance is unique, then linearity would be expected (Crump et al. 1976, Guess et al. 1977). For these reasons, the staff of DHS generally uses linear dose-response models for extrapolating from epidemiologic studies of workers exposed at high doses to lower level environmental exposures.

The least plausible explanations for the observed nonlinearity in the range of occupational exposures are differential confounding by cigarette smoking and decreasing arsenic potency with increasing dose. Each of the other four explanations offered above is consistent with low-dose linearity. The impact of a healthy survivor effect, competing risks or measurement error would be negligible at environmental levels, and if the relationship with smoking were multiplicative at low levels of arsenic, there would be no distortion of a true linear relationship. Because these perturbing effects would be smaller at the lower exposure levels in the occupational studies, a reasonable approach, considering the arguments cited above supporting low-dose linearity, is to fit a linear model to data from the lower exposure groups in the occupational cohorts.

Each of the risk estimates presented below was derived under the assumption of low-dose linearity. In all of these models, the dose of arsenic was measured as cumulative $\mu g/m^3$ -years; the response was measured as the relative increase in risk over the background (risk ratio). In addition,

the models assume that the mechanism of carcinogenesis is a nonthreshold process (see Section 10.5).

An alternative model was considered in which the response would be measured as the absolute added risk over the background (risk difference). Such an approach would be inappropriate for extrapolating from occupationally exposed adult males to the general population, i.e., to both sexes at all ages. Lacking age-specific data, an additive dose-response model would treat the added cancer risk as being independent of age. In other words, a five-year-old who received a total arsenic exposure equal to that of a fifty-year-old would be expected to have the same additional lung cancer hazard. Biologically, such an assumption is implausible: the increase in cancer risk with age is a function of many factors including cellular and hormonal changes associated with aging. If increasing cumulative exposure to a carcinogen such as arsenic were the only factor, then the age-dependence of cancer incidence would be approximately linear. In fact, it is a power function of age, the power ranging anywhere from 2 to 10, depending on the site (Armitage & Doll 1954, Doll 1971, Doll & Peto 1978). Thus, the additive risk model is not appropriate for this risk assessment because we lack age-specific data on arsenic's carcinogenicity and because the assumption that risk is independent of age for a given cumulative dose is unlikely.

The risk estimates derived by DHS represent plausible upper bounds, not worst-case scenarios. If the linear model had been fitted to estimates of exposure based on assumptions that were extreme (e.g., using only the lowest measurements of exposure in the occupational studies, thereby inflating the

potency estimate), if the lung cancer deaths in the occupational studies had been replaced by upper confidence limits, and if the determination of population risk had been based solely on maximum concentrations in the ambient air, then the resulting risk estimates would represent a worst-case scenario. These approaches were not adopted. The risk estimates presented here are plausible: they use the best available exposure estimates, the observed mortality data, and mean concentrations of arsenic in ambient air.

11.3.2 Regression Model Not Adjusted for Interaction with Smoking

The observed deaths at each exposure level are assumed to be Poisson random variables. Because the expected numbers of deaths are based on large populations, the variances are negligible and hence the expected deaths are treated as dose-specific constants. The regression model used to achieve a linear extrapolation is described by the equation:

$$E[obs_i] = [\alpha + \beta(d_i)] \cdot Exp_i$$

where $E[\cdot]$ represents the expectation of a random variable, d_i represents the average cumulative dose of arsenic (in $\mu g/m^3$ -years) for exposure group i, obs_i represents the observed number of deaths in exposure group i, Exp_i represents the expected number of deaths in group i based on the standard population, α represents the risk ratio predicted for a cumulative dose (d) of zero, and β is the slope parameter (in $[\mu g/m^3 \text{ -years}]^{-1}$). The value of $\hat{\beta}$ was estimated using maximum likelihood methods, by means of an iterative reweighting algorithm.

The data to which this regression model was fit are from Enterline et al. (1987), Higgins et al. (1985), and Lee-Feldstein (1986) (see Tables 9-6 and

11-2). For Enterline et al. (1987), data from both the analysis in which follow-up began with termination of employment and the analysis in which follow-up began at start of employment were used. For Lee-Feldstein (1986), data from cohort II (workers whose employment began between 1925 and 1947) were used. For Higgins et al. (1985), data from the analyses with and without exposure factors were used. The Enterline et al. (1987) data included seven dose groups; analyses included (1) all the dose groups and (2) a subset consisting of only the lowest 4 dose groups. Similar analyses were performed using the seven-level Lee-Feldstein (1986) data, although since no mean was provided for the highest cumulative exposure level, data from this level were not used, leaving only six points for the most encompassing analysis. The Higgins (1985) data also provided no mean for the highest exposure level, leaving only three points for analysis.

The values of $\hat{\beta}$ from fitting this regression model to each of these datasets and subsets are shown in Table 11-3A. They range from 5.47×10^{-6} to 1.65×10^{-4}. The slope based on the Lee-Feldstein (1986) data is far lower than those based on the other data. This was predicted based on an evaluation of the exposure assessment used in that paper, wherein it was assumed that 100% of each employee's workday was spent at the highest-exposure worksite implied by his job category (see Sections 11.1.1 and 11.1.2a); this systematically overestimated exposure levels.

Because of the method of analysis used in Higgins et al (1985), this study suffered from a great deal of exposure misclassification. This misclassification was less systematic than that of Lee-Feldstein (1986), however. The firmest findings are those of Enterline et al. (1987), in

terms of the quality of exposure data and method of analysis. To calculate unit risk, the staff of DHS has selected the MLE (maximum likelihood estimate) slope and upper 95% confidence bound based on use of the four lowest exposure groups from the Enterline et al. (1987) analysis, with follow-up beginning at termination of employment. For information, the staff has also calculated a unit risk using the Lee-Feldstein (1986) cohort II data and using the data of Higgins et al. (1985). However, as discussed above, the exposure assumptions in Lee-Feldstein study were predicted to result in marked underestimation of carcinogenic potency, and the analytic method in the study of Higgins et al. was also expected to bias the potency estimates.

11.3.3 Regression Model Adjusted for the Smoking-Arsenic Interaction

A risk assessment was also conducted using an adjustment for the strong interaction between arsenic and smoking observed in several occupational cohorts. Since the combined effect of smoking and arsenic was greater than additive, but less than multiplicative, the SMRs in the occupational studies are not an accurate reflection of arsenic's effect. The staff of DHS has determined further that the crude SMRs, in which smokers were not distinguished from nonsmokers, are not simple weighted averages of the effect in smokers and the effect in nonsmokers. A method to estimate arsenic's effects in nonsmokers and in smokers is presented in Appendix E. The method requires knowledge of the prevalence of smokers in the cohort, the independence of smoking and exposure, and auxiliary data consisting of a risk ratio for smoking alone and an estimate of the ratio of interaction

(defined as the risk ratio for arsenic exposure in smokers divided by the risk ratio for arsenic exposure in nonsmokers).

The prevalence of smoking was independent of the level of arsenic exposure in the Anaconda cohort (Welch et al. 1982), but may have been higher than in the general population. Thus, a purely internal comparison between the different dose levels was considered the most valid means of estimating arsenic's effect. Also, there appeared to be no reason for smokers to be distributed differently among the exposure levels in the Tacoma cohort, hence smoking was assumed to be independent of arsenic exposure in this cohort as well.

Each dose-specific crude SMR was adjusted taking the low-dose SMR in each study as the baseline. Next, using the methods shown in Appendix E, a nonsmokers' SMR and a smokers' SMR were derived. From the nonsmokers' SMR, observed and expected deaths among nonsmokers were inferred (see Appendix E). Finally, a regression model was fitted to the inferred nonsmokers' data to find the slope of the line relating cumulative arsenic dose to excess relative risk. This procedure was applied to the data of Enterline et al. (1987) under the assumption that the interaction between smoking and arsenic varies as a function of dose, and that the joint effects at low doses are multiplicative. This assumption is both biologically plausible and supported by the data of Pershagen (1985), Enterline (1983), and Rencher et al. (1977).

The inferred observed deaths for nonsmokers at each dose are treated as Poisson random variables. The regression model used for extrapolation is analogous to the model described in Section 11.3.2 above:

$$E[Obs^{*}_{i,\bar{s}}] = [1 + \beta(d_i - d_1)] \cdot Exp^{*}_{i,\bar{s}}$$

where $E[\cdot]$ represents the expectation of a random variable, d_i represents the average cumulative dose of arsenic (in $\mu g/m^3$ -years) for exposure group i (d_1 being the lowest dose), $Obs^{*}_{i,\bar{s}}$ represents the inferred observed number of deaths among nonsmokers in exposure group i, $Exp^{*}_{i,\bar{s}}$ represents the inferred expected number of deaths among nonsmokers in exposure group i, and β is the slope parameter to be estimated (in $[\mu g/m^3 \text{ -years}]^{-1}$). At the lowest dose level ($d = d_1$), the expectation of the observed deaths is equal to the expected number of deaths. Because the interaction of smoking and arsenic has been assumed to be multiplicative at low doses, the slopes (relative to background rates) for smokers and nonsmokers are equal at low doses, even though the background risks are different.

The maximum likelihood estimate for β was 2.30×10^{-4} using the data on nonsmokers inferred (by the methods of Appendix E) from the study by Enterline et al. (1987) (See Table 11-3B). Goodness of fit was assessed by means of a χ^2-goodness-of-fit test statistic for the null hypothesis that the model does fit the data. A low value of the test statistic, associated with a high p-value, indicates that the model is consistent with the data, i.e., one cannot reject the null hypothesis. An excellent fit was obtained: $\chi^2_{(5)}=1.04$, $p=0.96$ (See Table 11-3B). The slope is in units of cumulative $(\mu g/m^3 \text{ -work years})^{-1}$. An upper 95% confidence limit was estimated and used in evaluating unit risks, but it should be noted that the model was fitted to inferred rather than "true" data, and that the inferred data are

not known to share the properties of true data with respect to statistical inference, so the actual confidence level is not known.

11.4 Extrapolation to the General Population

The estimated carcinogenic potencies of arsenic were applied to lifetable data for males and females of the California and U.S. populations to obtain unit risks for four categories with respect to smoking: nonsmokers, former smokers, light smokers (<1 pack/day) and heavy smokers (≥1 pack/day). A unit risk represents the predicted excess risk of lung cancer death due to continuous lifelong exposure to arsenic at a concentration of 1 $\mu g/m^3$. This level of exposure is about 500 times the average environmental level measured in California ambient air. It is close to the average exposure of the low-dose group in each of the two cohorts used for this risk assessment.

An upper bound for each unit risk was also derived. Both the maximum likelihood estimate and the upper bound were then multiplied by (average ambient exposure)/(1 $\mu g/m^3$) to estimate the risks to the California population.

11.4.1 Calculation of Unit Risk

The unit risk is a function of age-specific survival, the background rate of lung cancer mortality, the cumulative dose, and the potency. Calculation of the unit risk involved four steps.

(i) Age-specific survival and lung cancer death rates differ by smoking status. Thus, the observed all-cause and lung cancer death rates in each age interval were partitioned into rates for never, former, light and heavy smokers by the methods described in Appendix F. These calculations used the background death rates (all smoking categories combined) based on 1980 census data for California (Bureau of the Census 1982), age-specific death rates for California from 1979-80 vital statistics data (California Department of Health Services 1982) and on 1982 vital statistics data for the U.S. (U.S. Department of Health and Human Services 1986).

(ii) Background lifetime lung cancer risks were derived using these rates. Separate lifetables were constructed for males and females in each smoking category, using five-year age intervals. The lifetable allows one to adjust for competing causes of mortality in evaluating the risks due to a particular cause. The current lifetable assumes that the death rates observed at each age level will apply in the future, for individuals alive today or yet to be born. The lifetables were constructed using standard statistical methods (Chiang 1984), as described in Appendix C. The last age interval was taken as 70-74, since reliable smoking-habit-specific RRs for lung cancer and for all-cause mortality were not available past age 74. For each of the eight gender and smoking habit categories, the lifetime probability of a lung cancer death was found by summing over all age intervals the unconditional probability of lung cancer death in each age interval. This was done for both California and U.S. population data for each gender and smoking category yielding a background lifetime probability of dying from lung cancer.

(iii) Lifetables were then constructed assuming continuous lifelong exposure to arsenic for each gender and smoking habit category. The estimate for $\hat{\beta}$ was applied to each age interval in the lifetable to obtain the predicted age-specific lung cancer death rate in a population exposed continuously to 1 $\mu g/m^3$ arsenic. Since the model was fitted to work-year doses, the environmental doses were multiplied by 4.38, which is the ratio of a full year to a work-year: (365 days/250 days) • (24 hours/8 hours). Applying the fitted model, new lung cancer rates were calculated to reflect the arsenic effect:

$$\text{lungrate}_{A,j} = \text{lungrate}_{\bar{A},j} \cdot (1 + \hat{\beta} \cdot d_j)$$

where A indicates arsenic exposure, $\bar{A}$ indicates nonexposure, d_j represents the accumulated dose of arsenic from birth to the midpoint of age interval j. The effects of smoking and arsenic are assumed to be multiplicative at low doses. This assumption is supported by the only available low-dose data which were stratified by smoking (Pershagen 1985). Hence the same $\hat{\beta}$ is applied to all four categories of smoking. However, since the background rates are different, the excess risk due to arsenic exposure differs for the four smoking categories.

(iv) The background lifetime probabilities of lung cancer death (step ii) were subtracted from the probabilities obtained for an exposed population (step iii) to produce the unit risk estimates. Unit risks for males and females in each of the four smoking categories for both the California and U.S. populations are shown in Table 11-3. Using the upper bounds for the slope, upper bounds on the unit risks were also derived.

11.4.2 Recommendation for Unit Risk Estimate

As discussed above, there is considerable uncertainty surrounding this or any estimate of risk due to low-level exposures to environmental carcinogens. A summary of assumptions in this risk assessment is provided in Table 11-1.

11.4.2a Assumptions tending to bias unit risk estimates downward

Assumptions tending to cause underestimation of environmental risks included: (i) the misclassification of exposure levels due to limitations in the collection and analysis of data on the smelter workers, (ii) the use of exposures without consideration of the lag time between a carcinogenic exposure and death from cancer, and (iii) the use of lung cancer as the only carcinogenic endpoint.

As described above (Section 11.1), the assumptions regarding exposure data in the occupational studies are not directly testable, and the magnitude of error is difficult to quantify. The fact that exposures were not lagged to allow for latency implies underestimation of risk, but analyses by Enterline and Marsh (1982) and by Jarup et al. (1989a) might suggest that the underestimation is small. Carcinogenic effects at other sites have been reported, e.g., liver (Tokudome & Kuratsune 1976) and large intestine (Enterline & Marsh 1982, Tokudome & Kuratsune 1976). By using only lung cancer effects, this risk assessment slightly underestimates the effect of ambient arsenic exposure.

11.4.2b Assumptions with unknown effect on unit risk estimates

The direction and magnitude of error due to several sources of uncertainty are unknown, including (i) the assumption that age-specific death rates observed in 1980 or 1982 will apply in the future, (ii) the use of current smoking rates at each age to predict future risks when smoking patterns are in flux, (iii) variability in ambient exposure levels, (iv) the assumption that the risk ratios for lung cancer due to arsenic are the same among all age groups and both sexes, (v) the use of cumulative dose rather than dose rate in characterizing short-term occupational exposure, and (vi) the use of linear models.

The death rate assumption probably entails only small biases (e.g., less than two-fold). A major reduction in smoking prevalence could reduce risks from ambient arsenic exposure by several-fold, but the current trends seem to be a shift from male to female smokers. The variability in ambient arsenic levels is also unlikely to introduce substantial bias, unless new sources are introduced close to population centers.

The assumption of a constant risk ratio at all ages (iv) may be in error, particularly if the carcinogenic activity of arsenic is limited to certain stages of a multistage process. The staff of DHS conducted a sensitivity analysis assuming a higher arsenic effect at younger ages. (An age-dependent effect would be plausible in light of the report of Phalen et al. (1986) showing greater lung deposition of particulates in children.) The sensitivity analysis indicated that, because of the low background level of

lung cancer at young ages, the lifetime risk estimates are probably not substantially biased.

Recent work by Kodell et al. (1987) suggests that if arsenic acts at an early stage of carcinogenesis, then the use of cumulative exposures in the occupational setting may entail substantial underestimation of risks from low-level environmental exposures. If arsenic acts primarily at late stages, then this assumption may not introduce much bias at all.

The assumption of linearity (vi) could entail considerable bias, but it is not possible to determine the magnitude or direction of bias.

11.4.2c Assumptions tending to bias unit risk estimates upward

Few assumptions would be expected to upwardly bias the risk estimates. The main one is that As(III) and As(V) in inhaled air have similar carcinogenic potency. Environmental risks would be overestimated if As(III) were a more potent carcinogen than As(V) because As(III) constitutes a smaller proportion of the arsenic in ambient air than of the arsenic in smelter workplaces. Nevertheless, no difference in carcinogenic potency between the two species of arsenic has been demonstrated, although As(III) is more active in some assays of genotoxicity (see Chapter 7). As(V) is metabolized to As(III) in vivo, however (see Chapter 2).

11.4.2d Recommendation

The staff of DHS recommends the use of the upper-bound risk estimates shown in Table 11-5C. Many of the assumptions used here are known or suspected to result in some underestimation of risk. Also, the data of Jarup et al. (1989), while consistent with those of Enterline et al. (1987a), showed slightly higher risks throughout the range of occupational exposures. In addition, there is statistical uncertainty surrounding the potency estimates. These estimates are based on the $\hat{\beta}$ value calculated from the data of Enterline (1987) where follow-up starts at termination of exposure, using the model that adjusts for the interaction between arsenic and smoking (see Section 11.3.3).

11.5 Previous Risk Assessments by the U.S. Environmental Protection Agency

A comparison of the unit risks derived in this document by the staff of DHS and those reported by EPA (1984) is shown in Table 11-7. The EPA used four published reports to derive five estimates of unit risk. (See EPA 1984, pp. 7-134.) The four reports were: Enterline and Marsh (1982), Lee-Feldstein (1983), Welch et al. (1982),[3] and Brown and Chu (1983a, 1983b). These risk estimates all fell within one order of magnitude of each other. Because Enterline and Lee-Feldstein have revised their exposure data, the staff of DHS does not recommend the risk assessments based on these earlier reports. The risk assessment based on the analyses by Brown and Chu (i) uses only the low exposure group and (ii) assumes a model in which arsenic acts only in the late stages of carcinogenesis. The staff of DHS has concluded (Section 10.7) that early-stage effects cannot be excluded. Additionally, the use of

low-dose data alone may not be justified since low-dose person-years tend to be dominated by workers who left employment after a short time.

The remaining risk estimate derived by the EPA was based on the report by Welch et al. (1982), which examined a subset of 1800 workers from a cohort of 8044 male workers at the Anaconda smelter. The DHS staff utilized the data of the whole cohort (Higgins et al. 1985) with four more years of follow-up and obtained a risk estimate about 20% lower. For the Tacoma cohort, the staff of DHS conducted a quantitative cancer risk assessment with more recently published data from the reanalysis by Enterline et al. (1987).

The DHS staff risk assessment further differs from that of the EPA (1984) in that the arsenic-smoking interaction has been incorporated to derive separate unit risks for four categories of smoking. Also, the U.S. age-specific all-cause and lung cancer mortality rates for 1982 were used to construct lifetables, while EPA used 1976 rates. Additionally, this document uses rates for California.

11.6 Estimated Risks at Ambient Airborne Concentrations of Arsenic

The staff of the Air Resources Board has estimated the population-weighted mean ambient concentration of arsenic in California to be 1.9 ng/m^3. With this information, the staff of DHS has estimated the risks due to inhalation of airborne arsenic among residents of these areas of California to be in the range of 0.8 to 25 excess lifetime cancer deaths per million persons (see Table 11-5C). For this estimation, it was assumed that the

concentrations of arsenic in indoor air are identical to ambient (outdoor) concentrations. If indoor concentrations differ from outdoor concentrations, time spent indoors would affect cancer risks due to arsenic. The range in the risk estimates reported here mainly reflects variability due to different excess risks among smokers compared to former and never-smokers. Excess risks are over ten times higher for heavy smokers as compared to never-smokers. The range of risks presented here also reflects (a) statistical uncertainty and (b) male-female differences.

At industrial sites the risk may be higher. During a one-month period in May-June 1986, at a distance of one kilometer from a secondary lead smelter in California, an average concentration of 61 ng As/m^3 was measured. While the emissions from this site were subsequently reduced (Shimp 1986), they are indicative of potential exposures near point sources of arsenic. Therefore, exposure measurements for the site were used in risk estimations which are shown in Appendix D. These estimations indicate that if arsenic emissions from that facility had continued unabated for a lifetime (75 years), 6 to 9 excess cancer deaths might have occurred among 725,000 residents of the surrounding area.

Notes

[1] As noted in Chapter 9, Lee-Feldstein (1986) explicitly discarded time exposure factors which indicated the proportion of a work day spent in areas with exposure to arsenic; this led to exposure estimates which were five to ten times higher than those used in previous reports.

[2] The problem of using the final exposure level was addressed by Enterline (1976), who suggested that exposure period and follow-up period should not overlap.

[3] The EPA refers to this report as Higgins et al., though Higgins is not the first author.

TABLE 11-1

SUMMARY OF POTENTIAL BIASES IN CANCER RISK ASSESSMENT FOR ARSENIC DUE TO USE OF ASSUMPTIONS

	Potential Bias In Risk Estimate Due To Use of Assumption	
	Direction	Magnitude
I. DATA ASSUMPTIONS*		
Exposure Assessment		
Misclassification due to:		
- Departmental measurements applied to individuals	?	?
- Averaging of measurements within a department	↓	?
- Time exposure factors** determined for one period applied to earlier and later periods (Anaconda, Higgins et al. 1985)	?	?
Measurement from one time period applied to earlier periods	↑	?
later periods	↓	?
Use of urinary-air relationship to estimate air doses where data were lacking (Tacoma)	↓	?
Unmeasured departments assumed to have low exposures only (Anaconda)	↑	?
No adjustment to consider latency period (Anaconda, Lee-Feldstein 1986; Tacoma, Enterline et al. 1987)	↓	?
Application of highest cumulative exposure attained to person-years before this level was reached (Anaconda, Higgins et al. 1985)	?	?
Net effect of above:	?	small to moderate
Time exposure factors** not used (Anaconda, Lee-Feldstein 1986)	↓	moderate
Response Assessment		
Loss to followup assumed to be nondifferential	?	negligible
II. EXTRAPOLATION OF DOSE-RESPONSE RELATIONSHIP		
Choice of dose measure (cumulative dose vs. dose rate)	↓	if early stage affected
Linear model for high-to-low-dose extrapolation.	?	could be large

TABLE 11-1 (continued)

III. EXTRAPOLATION TO GENERAL POPULATION		
From adults to children	↓	small
From males to females	?	small
IV. LIFETABLE ASSUMPTIONS		
Use of current mortality rates	?	small
Use of current smoking patterns	?	small to moderate
IV. AMBIENT AIR MEASUREMENTS	?	?

? = effect on risk estimate can not be ascertained.

↓ = potential downward bias in estimated risk.

↑ = potential upward bias in estimated risk.

*Except where indicated, each entry here applies to all three of the studies for which risk assessments were performed: the studies of the Anaconda smelter by Higgins et al. (1985) and Lee-Feldstein (1986), and the study of the Tacoma smelter by Enterline et al. (1987).

**These factors represent the proportion of a workday actually spent in a location with exposure to arsenic by persons employed there.

TABLE 11-2

ARSENIC EXPOSURE LEVELS OF
WORKERS IN THREE STUDIES

	Range in Occupational Setting	Midpoint or Mean	Equivalent Ambient Exposure*
	CUMULATIVE EXPOSURE IN $\mu g/m^3$ -YEARS		
I. Anaconda Smelter (Higgins et al. 1985)			
Low	<500	250	57.1†
Middle	500-1999	1250	285.4
High	2000-11999	7000	1598.2
Very High	12000+	N.R.	---
II. Anaconda Smelter (Lee-Feldstein 1986)			
1	<833	416.7	95.1
2	833-2083	1458.3	333.0
3	2083-8333	5208.3	1189.1
4	8333-41667	25000.0	5707.8
5	41667-208333	125000.0	28538.8
6	208333-416667	312500.0	71347.0
7	416667+	N.R.	---
III. Tacoma Smelter (Enterline et al. 1987)††			
1	<750	401.0	91.6
2	750-1999	1316.9	300.7
3	2000-3999	2944.3	672.2
4	4000-7999	5731.9	1308.7
5	8000-19999	12554.9	2866.4
6	20000-44999	28614.0	6532.9
7	45000+	59166.7	13508.4

* Adjusted from occupational exposure (250 workdays/year, 8 hours/day) to environmental exposure (365 days/year, 24 hours/day). Adjustment factor = 4.38

† Ambient exposures away from industrial sources average 2.2 ng/m^3 in California, which for a 75-year lifespan accumulates to about 165 ng/m^3-years or 0.2 $\mu g/m^3$-years. The extrapolation therefore covers 2 to 3 orders of magnitude. The range of extrapolation is smaller for those exposed close to industrial sources.

†† With follow-up starting at termination of employment.

N.R. = Not reported.

TABLE 11-3A

RESULTS OF FITTING DOSE-RESPONSE MODEL
TO OBSERVED ARSENIC-LUNG CANCER DATA

	Slope		95% Confidence Interval	Goodness of fit	
	$\hat{\beta}$	(SE)[1]	(of $\hat{\beta}$)	χ^2	p
Data:					
I. Anaconda Smelter (Higgins et al. 1985)					
No exposure factors[2]:	9.06×10^{-5}	(1.79)[3]	(-13.7, 31.8)[3]	.16(1)[4]	.68
With exposure factors:	1.08×10^{-4}	(0.27)	(-2.2, 4.6)	.44(1)	.51
II. Anaconda Smelter, Cohort II[5] (Lee-Feldstein 1986)					
All dose groups:	5.47×10^{-6}	(3.91)	(-5.4, 16.3)	7.4(4)	.12
Lowest 4 dose groups:	1.11×10^{-5}	(1.85)	(-6.8, 9.1)	4.7(2)	.09
III. Tacoma Smelter (Enterline et al. 1987)					
Follow-up starting at entry into study:					
All dose groups:	2.13×10^{-5}	(0.55)	(0.71, 3.55)	.72(5)	.98
Lowest 4 dose groups:	7.70×10^{-5}	(2.66)	(-3.74, 19.1)	.16(2)	.92
Follow-up starting at termination of employment:					
All dose groups:	3.76×10^{-5}	(1.33)	(0.33, 7.19)	2.47(5)	.78
Lowest 4 dose groups:	1.65×10^{-4}	(1.55)	(-0.85, 4.15)	.39(2)	.82

[1] Standard error.

[2] Exposure factors reported by the investigators indicate the proportion of each workday during which the workers were exposed. The analysis did or did not incorporate these factors, as indicated.

[3] The standard errors and confidence intervals given in parentheses are of the same order of magnitude as their corresponding slopes. For example, the (1.79) in the first row equals 1.79×10^{-5}.

[4] Degrees of freedom for the χ^2 values are given in parentheses.

[5] Those hired between 1925 and 1947.

TABLE 11-3B

RESULTS OF FITTING DOSE-RESPONSE MODEL
TO OBSERVED ARSENIC-LUNG CANCER DATA
ADJUSTED FOR THE INTERACTION WITH SMOKING

	Slope		95% Confidence Interval	Goodness of fit	
	$\hat{\beta}$	(SE)[1]	(of $\hat{\beta}$)	χ^2	p
Data:					
Tacoma Smelter, All Dose Groups (Enterline et al. 1987)					
Follow-up starting at entry into study:					
Adjusted ρ_i - Set I[2]	1.28×10^{-4}	(0.30)[3]	(0.50, 2.05)[3]	.75(5)[4]	.98
Adjusted ρ_i - Set II	1.17×10^{-4}	(0.15)	(0.77, 1.57)	.21(5)	.999
Follow-up starting at termination of employment:					
Adjusted ρ_i - Set I	2.30×10^{-4}	(0.53)	(0.95, 3.65)	1.04(5)	.96
Adjusted ρ_i - Set II	1.97×10^{-4}	(0.30)	(1.19, 2.75)	.39(2)	.996

[1] Standard error.

[2] Set I: ρ_i = {.9, .8, .7, .6, .6, .5, .4};
Set II: ρ_i = {.95, .9, .85, .75, .65, .5, .3}.

[3] The standard errors and confidence intervals given in parentheses are of the same order of magnitude as their corresponding slopes. For example, the (0.30) in the first row equals 0.30×10^{-4}.

[4] Degrees of freedom for the χ^2 values are given in parentheses.

TABLE 11-4

RATIOS OF INTERACTION FOR ARSENIC
COMPARING SMOKERS TO NONSMOKERS

Data	Ratio[1]
Occupationally Exposed:	
Rencher et al. 1977	0.591
Enterline 1983	0.564
Pershagen 1985	0.376
Environmentally Exposed:	
Pershagen 1985	0.917

[1] The ratio of the relative risk for smokers to the relative risk for nonsmokers.

TABLE 11-5A

UPPER BOUND (AND MAXIMUM LIKELIHOOD ESTIMATES)
OF EXCESS LUNG CANCER RISKS
DUE TO AMBIENT ARSENIC EXPOSURE
IN CALIFORNIA

BASED ON DATA FROM ENTERLINE ET AL. (1987)
(FOUR LOWEST CUMULATIVE EXPOSURE GROUPS, TACOMA SMELTER EMPLOYEES)
ANALYZED WITH FOLLOW-UP STARTING AT TERMINATION OF EMPLOYMENT

	MALES			FEMALES		
Smoking Category	% By Smoking Category	Unit Risk ($1\ \mu g/m^3$) Deaths per Million:	Risk at Average Ambient Level ($1.9\ ng/m^3$) Deaths per Million:	% By Smoking Category	Unit Risk ($1\ \mu g/m^3$) Deaths per Million:	Risk at Average Ambient Level ($1.9\ ng/m^3$) Deaths per Million:
Never	42	1400* (560)**	3 (1)	59	720 (280)	1 (0.5)
Former	32	6000 (2400)	11 (5)	15	3300 (1300)	6 (2)
Light (<1 pack/day)	19	8500 (3400)	16 (6)	21	4700 (1900)	9 (4)
Heavy (>1 pack/day)	7	15000 (6000)	29 (11)	5	9300 (3700)	18 (7)
	100			100		
Population-weighted average:		5200 (2100)	10 (4)		2400 (940)	4 (2)

Overall unit risk (for males and females combined): 3800 (1500)

Overall risk at ambient levels: 7 (3)

* Upper bound estimate, 95% confidence.

** Numbers in parentheses are maximum likelihood estimates.

TABLE 11-5B

UPPER BOUND (AND MAXIMUM LIKELIHOOD ESTIMATES)
OF EXCESS LUNG CANCER RISKS
DUE TO AMBIENT ARSENIC EXPOSURE
IN CALIFORNIA

BASED ON DATA FROM ENTERLINE ET AL. (1987)
(ALL CUMULATIVE EXPOSURE GROUPS, TACOMA SMELTER EMPLOYEES)
ANALYZED WITH FOLLOW-UP STARTING AT TERMINATION OF EMPLOYMENT

	MALES			FEMALES		
Smoking Category	% By Smoking Category	Unit Risk ($1\ \mu g/m^3$) Deaths per Million:	Risk at Average Ambient Level ($1.9\ ng/m^3$) Deaths per Million:	% By Smoking Category	Unit Risk ($1\ \mu g/m^3$) Deaths per Million:	Risk at Average Ambient Level ($1.9\ ng/m^3$) Deaths per Million:
Never	42	240* (130)**	0.5 (0.2)	59	120 (65)	0.2 (0.1)
Former	32	1000 (550)	2 (1)	15	560 (290)	1 (0.6)
Light (<1 pack/day)	19	1500 (770)	3 (1)	21	810 (430)	2 (0.8)
Heavy (>1 pack/day)	7	2600 (1400)	5 (3)	5	1600 (850)	3 (2)
	100			100		
Population-weighted average:		900 (470)	2 (0.9)		410 (210)	0.8 (0.4)

Overall unit risk (for males and females combined): 650 (340)

Overall risk at ambient levels: 1 (0.6)

* Upper bound estimate, 95% confidence.

** Numbers in parentheses are maximum likelihood estimates.

TABLE 11-5C

UPPER BOUND (AND MAXIMUM LIKELIHOOD ESTIMATES)
OF EXCESS LUNG CANCER RISKS
DUE TO AMBIENT ARSENIC EXPOSURE
IN CALIFORNIA

BASED ON DATA FROM ENTERLINE ET AL. (1987)
(ALL CUMULATIVE EXPOSURE GROUPS, TACOMA SMELTER EMPLOYEES)
ANALYZED WITH FOLLOW-UP STARTING AT TERMINATION OF EMPLOYMENT
AND
ADJUSTED FOR THE INTERACTION WITH SMOKING

	MALES			FEMALES		
Smoking Category	% By Smoking Category	Unit Risk ($1\ \mu g/m^3$) Deaths per Million:	Risk at Average Ambient Level ($1.9\ ng/m^3$) Deaths per Million:	% By Smoking Category	Unit Risk ($1\ \mu g/m^3$) Deaths per Million:	Risk at Average Ambient Level ($1.9\ ng/m^3$) Deaths per Million:
Never	42	1200* (780)**	2 (1)	59	630 (400)	1 (0.8)
Former	32	5300 (3400)	10 (6)	15	2900 (1800)	5 (3)
Light (<1 pack/day)	19	7400 (4700)	14 (9)	21	4100 (2600)	8 (5)
Heavy (>1 pack/day)	7	13000 (8400)	25 (16)	5	8200 (5200)	16 (10)
	100			100		
Population-weighted average:		4600 (2900)	9 (5)		2100 (1300)	4 (2)

Overall unit risk (for males and females combined): 3300 (2100)

Overall risk at ambient levels: 6 (4)

* Upper bound estimate, 95% confidence.

** Numbers in parentheses are maximum likelihood estimates.

TABLE 11-6

UNIT RISKS:
NUMBER OF EXCESS LUNG CANCER DEATHS
DUE TO LIFETIME EXPOSURE TO 1 $\mu g/m^3$ ARSENIC

(Deaths per million)

CALIFORNIA

SMOKING STATUS	MALES		FEMALES	
	Best Estimate	Upper[1] Bound	Best Estimate	Upper[1] Bound
Never	780	1200	400	630
Former	3400	5300	1800	2900
Light	4700	7400	2600	4100
Heavy	8400	13000	5200	8200

U. S.

Never	660	1000	420	670
Former	2900	4500	1900	3000
Light	4000	6300	2800	4400
Heavy	7200	11000	5500	8700

[1] 95% confidence limit. Estimates are derived by fitting the model described in Section 11.3.3 to the data of Enterline et al. (1987).

TABLE 11-7

COMPARISON OF UNIT RISKS DERIVED BY EPA[1] AND BY DHS[2]

AGENCY	AUTHORS	SMELTER COHORT	UNIT RISK[3]
EPA	1. Brown and Chu (1983)	Anaconda	1300
	2. Lee-Feldstein (1983)	Anaconda	2800
	3. Welch et al. (1982)	Anaconda	5000
	4. Enterline and Marsh (1982)	Tacoma	6800
DHS	5. Lee-Feldstein (1986)	Anaconda cohort II[4]	140
		Low exposure subset[5]	760
	6. Higgins et al. (1985)	Anaconda[6]	3900
	7. Enterline et al. (1987)	Tacoma[7]	600
		Low exposure subset[5]	3500
		Tacoma[7], full cohort, adjusted for interaction with smoking.	3100

[1] EPA risk estimates are from risk difference model ("absolute risk"). For each dataset the Agency examined, the risk ratio model gave either a poor fit or an estimate similar to that of the risk difference model.

[2] DHS risk estimates are based on risk ratio model. For datasets (6.) and (7.) good or excellent fits were obtained using the risk ratio model. The risk difference model was not used for reasons described in the text. Slopes are based on internal comparisons for each cohort. Separate risk estimates were made by smoking category and the value in the table represents a population weighted average, using U.S. data for the distribution of smoking habits.

[3] Upper bound, cancer deaths attributable to airborne arsenic exposure per million persons exposed to 1 μg As/m^3 over a lifetime.

[4] Those hired between 1925 and 1947.

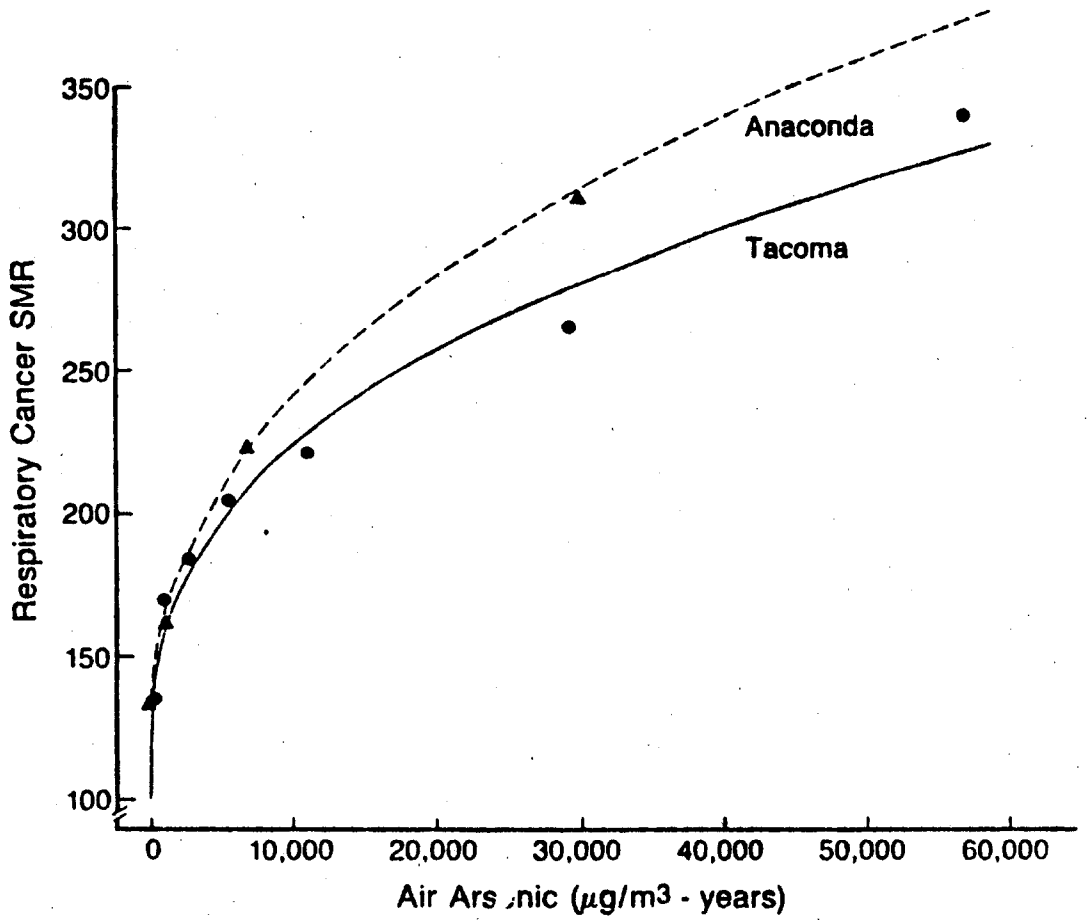
[5] The workers in the four lowest cumulative exposure groups (see Table 11-2).

[6] Using exposure factors reported by the investigators (see Table 11-3A)

[7] With follow-up starting at termination of employment.

FIGURE 11-1

LUNG CANCER VS. ARSENIC EXPOSURE AT TWO SMELTERS:
ANACONDA, MT AND TACOMA, WA



Source: Enterline et al. (1987).

APPENDIX A

INTERACTION BETWEEN SMOKING AND ARSENIC

This appendix describes the five studies that examined the interaction between smoking and arsenic. The results of these five studies are summarized in Chapter 9, Table 9-11.

Rencher et al. (1977) compared smelter workers to those working at the mine and concentrator (where arsenic exposure was considerably lower) of the same copper corporation in Utah. The measure of effect was the proportion of mortality due to lung cancer. The results are shown in Table A-1. The authors used a multiplicative scale for judging interaction: "The increase from .7 to 3.3 for the mine is greater proportionally than the increase from 3.3 to 9.2 for the smelter, i.e., the ratio is 4.7 for the mine and 2.8 for the smelter" (Rencher et al. 1977 at 756).

If an additive scale is used, however, the situation is reversed. At the smelter, the proportion of deaths due to lung cancer was 5.9 percentage points higher in smokers than in nonsmokers (9.2% vs. 3.3%), while in the mine and concentrator the corresponding differences were only 2.6 and 2.5 percentage points, indicating that smoking carries a greater risk among smelter workers than among those employed at other sites; equivalently, the risk difference due to arsenic is greater for smokers than for nonsmokers. Thus, the effect of arsenic and smoking is greater than the sum of their separate effects: they interact synergistically. Rencher et al. further reported negative results when testing for interaction between smoking and

worksite; however, the authors did not describe which tests were used. The results of this study suggest that the combined effects of smoking and arsenic are greater than additive but less than multiplicative.

The second study shedding light on the smoking-arsenic interaction was that of Welch et al. (1982) (see Table A-2). These investigators used the SMR as the measure of effect, and as pointed out earlier (see Section 9.2.2, Smoking and Confounding), the SMRs for smokers and nonsmokers were both calculated using the general population to derive expected deaths. If more comparable controls had been used (i.e., if nonsmokers at the smelter had been compared to nonsmokers in the general population and smokers at the smelter had been compared to smokers in the general population), the SMRs for nonsmokers would have been far higher than those for smokers, as argued by Weiss (1983), who suggested that "negative interaction" may be operating. Clearly, this observation refers to the risk ratio or multiplicative scale. These data are also consistent with risks which are greater than additive for the effects of arsenic and smoking combined.

A third treatment of the arsenic and smoking relationship was by Enterline (1983), who used death rates as the measure of effect and examined both the additive and multiplicative scales (in his terminology, "absolute" and "relative" scales). His data have been adapted and reorganized in Table A-3. Again, the risks due to combined exposure to arsenic and smoking were greater than additive, but less than multiplicative. Thus the risk difference is larger for smokers, though the risk ratio is larger for nonsmokers.

The fourth paper on this subject was by Pershagen et al. (1981), who conducted a matched case-control study within a cohort of workers at the Ronnskarsverken copper smelter in Sweden. Using rate ratios standardized for age as the measure of effect, their results indicated a multiplicative relationship. These findings are shown in Table A-4 (adapted from Pershagen et al. 1981, Table 1) where it can be seen that the risk ratio due to arsenic exposure was about 3 for either smokers or nonsmokers. This corresponds to a synergistic effect, i.e., since the effects of arsenic and smoking are exactly multiplicative, they are greater than the sum of the separate effects.

The fifth paper was a case-control study (Pershagen 1985) that was not limited to smelter workers. It compared lung cancer cases to controls among smelter workers, residents near the smelter, and residents of a reference area. The resulting age-adjusted relative risks are shown in Table A-5. It appears that smoking and <u>environmental</u> arsenic exposure have a multiplicative effect, while the effect of smoking and <u>occupational</u> arsenic exposure is less than multiplicative. This may indicate that the degree of interaction is dose-dependent.

TABLE A-1

PERCENTAGE OF DEATHS DUE TO LUNG CANCER AT EACH LOCATION FOR SMOKERS AND NONSMOKERS

	LOCATION		
	Mine (Low As)	Concentrator (Low As)	Smelter (High As)
Nonsmokers	0.7	0.8	3.3
Smokers	3.3	3.3	9.2

(Adapted from Rencher et al. 1977, Table 6)

TABLE A-2

RESPIRATORY CANCER SMR BY ARSENIC EXPOSURE
STRATIFIED BY SMOKING HABITS

	ARSENIC EXPOSURE ($\mu g/m^3$, TWA)			
	<100	100-500	500-5000	>5000
Nonsmokers	95	89	286	620
Smokers	120	312	359	803

(Adapted from Welch et al. 1982, Table 12)

TABLE A-3

RELATIVE RISKS FOR LUNG CANCER
DUE TO SMOKING AND ARSENIC EXPOSURE

	Washington State Males	Retired Smelter Workers
Nonsmokers	1.0	5.1
Smokers	7.2	20.7

(Adapted from Enterline 1983)

TABLE A-4

AGE-ADJUSTED RATE RATIOS FOR LUNG CANCER
DUE TO ARSENIC EXPOSURE AND SMOKING

	No As	As
Nonsmokers	1.0	3.0
Smokers	4.9	14.6

(Extracted from Pershagen et al. 1981, Table 1)

TABLE A-5

AGE-ADJUSTED RATE RATIOS FOR LUNG CANCER
DUE TO ARSENIC EXPOSURE AND SMOKING

	Reference area	Exposed area	Smelter workers
Nonsmokers	1.0	2.3	8.4
Smokers	8.3	17.5	26.2

(Extracted from Pershagen 1985, Table 5)

APPENDIX B

INITIATION vs. PROMOTION:
REVIEW OF THE EVIDENCE FROM PUBLISHED REPORTS ON
LATENCY and FOLLOW-UP TIME

Latency represents the time elapsed between initial exposure to a disease-causing or carcinogenic agent and the expression of a disease such as cancer. If arsenic acts only as a late-stage carcinogen or promoter, then one would expect short latencies for arsenic-induced cancers. Additionally, one would expect a decline in excess cancer rates with increasing time since termination of exposure. The evidence on latency and follow-up time is presented below.

Latency

Enterline and Marsh (1982) reported that their study of 2802 smelter workers in Tacoma, Washington, provided evidence of a short latency for arsenic carcinogenesis. For workers with less than 10 years of exposure, they found significantly elevated SMRs 10-19 and 20-29 years after start of exposure, but not 30+ years after start of exposure. For longer durations of employment, however, longer latencies were observed. Thus, the latencies observed in this study ranged from 10 to over 30 years.

Three other studies indicated long latencies for arsenic-induced respiratory cancer deaths. Tokudome and Kuratsune (1976) observed 29 respiratory cancer deaths in a population of 2,675 refinery workers. They reported a mean latency (defined as the interval from first employment at the copper smelter

to date of death) of 37.6 years, with a range of 13-50 years. Only three of these 29 deaths occured less than 30 years after initiation of exposure. When the latency periods were examined separately for those with heavy, medium, or light exposures, no group had a particularly short latency.

Another epidemiologic study reporting latency periods (Ott et al. 1974) examined respiratory cancer deaths among workers exposed to arsenic-containing insecticides. The SMR was not elevated in the interval 0-15 years after first exposure. The SMR was significantly elevated 15-34 years after initial exposure for those receiving low- or high-level exposures. Among those with high-level exposures, the SMR continued to be elevated 35 or more years after initial exposure.

A third examination of latency was conducted using mortality data for Swedish smelter workers (Wall 1980). Only three out of 76 lung cancer deaths occurred less than 15 years after start of employment. These three cases "were among the oldest men at first employment," which could indicate other causative exposures either at previous jobs or from lifestyle risk factors or possibly an age-interaction effect. The mean latency appeared to be about 30 years.

With regard to the length of latency for arsenic-related respiratory cancer, the epidemiologic evidence varies but weighs towards long latencies (15-45 years). The relationship of latency to the stage of carcinogenesis at which an agent acts is complex. A full analysis of latency must take into account the age at first exposure, the length of exposure, and the time since exposure terminated. Such an analysis would shed light on whether arsenic

acts primarily in the initiation, promotion, or proliferation stage of carcinogenesis.

Models for Carcinogenesis

An in-depth analysis of the epidemiologic issues relevant to arsenic's activity as an initiator or a promoter was provided by Brown and Chu (1983a, 1983b). These authors applied the multistage theory of carcinogenesis to the Anaconda, Montana, cohort to determine whether arsenic acts at an early or late stage in the carcinogenic process. The mathematics of the multistage model indicates that the excess risk[1] of cancer is dependent on the following: (1) the concentration of the carcinogenic agent, (2) the duration of exposure, (3) the age at which exposure began, and (4) for individuals whose exposure has terminated, the length of follow-up after exposure ceased.

If a carcinogen acts only at an early stage of carcinogenesis, the excess risk will be independent of age at first exposure (for fixed duration and concentration) both for those still being exposed and for those whose exposure has terminated. Also, if the agent acts solely at an early stage, then among those whose exposure has terminated, excess risk will increase with longer follow-up as more "initiated cells" have the opportunity to pass through later stages. If a carcinogen acts only on the penultimate stage, then the later the age at first exposure, the higher the probability of some cells having passed through the earlier stages, and therefore, the higher the excess risk (for fixed duration and concentration). However, a longer follow-up will not increase the excess risk for those whose exposure has

terminated, because not much time needs to past for such late effects to result in clinically detectable tumors. This assumes that the carcinogen is not stored in the body for long periods. Excess risk increases with age at first exposure because some cells of older individuals have had longer to reach the stage(s) at which the agent acts.

Brown and Chu used two approaches to study the effects on excess lung cancer risk of the four exposure variables: concentration, duration, age at first exposure, and length of follow-up after termination of exposure. The first approach was to stratify on these variables and indirectly standardize the rates. The second approach was to model the data assuming a Poisson distribution of lung cancer deaths.

The stratified analysis indicated that the excess lung cancer rate among those continuously exposed to arsenic was a steeply increasing function of age at first exposure, after simultaneously adjusting for duration and level of exposure. This is consistent with arsenic's acting solely as a late-stage carcinogen or promoting agent. The excess lung cancer rate for those whose exposure had ceased was an increasing function of age at initial exposure, and of time since exposure stopped (after simultaneously controlling for the other of these two factors and also for duration and level of exposure). The dependence on age at first exposure is consistent with late-stage carcinogenicity, while the dependence on time since exposure ended could indicate an effect of arsenic on an early stage. Other explanations for these findings are discussed Brown and Chu (1983b).

The results of the modeling analysis are similar. While the use of a mixed effects model (both early and late stage effects) gives a better fit, the purely penultimate-stage model is also a good fit. The authors conclude that the data

> "are apparently too limited to clearly discriminate between the mixed effect and pure effect hypotheses. Therefore, under this multistage model of carcinogenesis, we conclude: (1) arsenic does not act solely at the first stage of the process; and (2) arsenic does act at a late stage, but may act at an earlier stage as well."

In a different cohort of smelter workers, Enterline and Marsh (1982) reported that SMR's were highest in the decade immediately following termination of employment, that this held true even for those employed less than 10 years and that SMR's for each level of exposure duration and exposure intensity were much higher in the first five years after termination than in subsequent years.

At first sight these findings might appear to contradict those of Brown and Chu, who observed excess risk to increase with time since exposure ended. However, Enterline and Marsh used a multiplicative model (i.e., the SMR was the measure of association) while Brown and Chu used an additive model (i.e., excess risk was the measure of association). Since background rates will increase with age, and since age will increase as the interval since exposure ended grows longer, it is possible for excess risk to rise while the SMR could fall, remain constant, or rise. In an extended analysis, Brown and Chu (1983b) report a ten-fold rise in the excess mortality rate with increasing time since employment terminated, while the SMR falls 40%. (SMR's were not shown but can be calculated from the data in Table 1 of that

report.) If excess risk remains constant while the background rate increases, then the SMR will decline. Thus, the findings of Brown and Chu are compatible with those of Enterline and Marsh. Also, it should be noted that the deaths in the first five years following termination included men whose termination was due to their fatal illness, that is, the illness was the cause of the termination.

Except for the analysis of Brown and Chu, all of the epidemiologic studies of arsenic-exposed cohorts reviewed by DHS staff used the SMR rather than the excess risk (risk difference) as a measure of outcome. Neither the experimental nor the epidemiologic data provide a clear basis for choosing between a multiplicative or an additive model for arsenic's carcinogenicity even though the multistage theory would support an additive model when comparing the cancer risk in an exposed population to an unexposed population with a substantial background risk of cancer at that site. Neither the analysis of Brown and Chu or that of Enterline and Marsh contradicts the hypothesis of arsenic's acting as an initiator. In light of the above evidence regarding the relationship between latency and follow-up time on the one hand and respiratory cancer risk on the other, the staff of DHS concludes that arsenic should be considered to have a role in both early- and late-stage carcinogenesis.

Notes

[1]Excess risk here refers to absolute excess risk, [observed - expected]/[person-years-at-risk], not the excess relative risk.

APPENDIX C

CONSTRUCTION OF LIFETABLES

TO DETERMINE UNIT RISK

The construction of life tables is described in detail by Chiang (1984). The abridged life table uses age intervals larger than one year (in this case, five-year age intervals). The data collected from vital statistics are:

m_i = annual death rate for age interval i (observed and predicted)

ℓ_i = annual lung cancer death rate for age interval i

The life table is constructed by calculating the following (refer to tables on the accompanying pages):

(1) The probability of dying in the i^{th} age interval, given survival to the beginning of that interval:

$$q_i = 1-\exp(-5 \cdot m_i)$$

(2) The probability of surviving the i^{th} age interval, given survival to the beginning of that interval:

$$p_i = 1-q_i$$

(3) The cumulative probability of surviving to the beginning of the i^{th} age interval:

$$c_i = p_1 \cdot p_2 \cdots p_{i-1} = \prod_{j=1}^{i-1} p_j$$

(4) The probability of dying of lung cancer in the i^{th} interval, given survival to the beginning of that interval:

$$p\ell_i = q_i \cdot (1 - \exp(-5 \cdot \ell_i))$$

(5) The unconditional probability of dying of lung cancer in the i^{th} interval, (i.e. not conditioned on surviving to the beginning of the interval):

$$p\ell_i \cdot c_i$$

(6) The cumulative probability of dying of lung cancer through the end of the i^{th} interval:

$$c\ell_i = p\ell_1 c_1 + p\ell_2 c_2 + \cdots + p\ell_i c_i = \sum_{j=1}^{i} p\ell_j c_j$$

The life table for an exposed population is constructed in an identical manner such that only the data for the age-specific lung cancer death rates are modified. (This also changes the age-specific overall death rates.) Lung cancer death rates (ℓ_i) for an exposed population are derived by adding the observed rates in an unexposed population to the excess rates predicted by the respective model for the i^{th} interval. These excess rates depend on the cumulative dose and the background lung cancer rate. The overall death rates (m_i) are obtained by adding the observed death rates from all other causes to the predicted lung cancer death rates. From these values, new survival probabilities are derived using equations (1) and (2) above. Thus, a new life table is constructed.

The cumulative probability of a lung cancer death for the last age interval in an exposed population is then compared to the same probability in an unexposed population. The difference between the two is the lifetime probability of lung cancer death due to exposure.

APPENDIX D

HYPOTHETICAL ESTIMATES OF LUNG CANCER MORTALITY FROM RESIDENTIAL EXPOSURE TO ARSENIC EMITTED FROM A SECONDARY LEAD SMELTER:[1]

Subgroup of the Exposed Population	No. of People	Estimated Contribution To Mortality[2] Best Est	95% UCL	Average Individual Risk[3] Best Est	95% UCL
Male Never-Smokers	152,340	0.438	0.673	2.9E-06	4.4E-06
Male Former Smokers	116,068	1.454	2.266	1.3E-05	2.0E-05
Male Light Smokers	68,916	1.193	1.878	1.7E-05	2.7E-05
Male Heavy Smokers	25,390	0.786	1.216	3.1E-05	4.8E-05
Female Never-Smokers	214,001	0.315	0.497	1.5E-06	2.3E-06
Female Former Smokers	54,407	0.361	0.581	6.6E-06	1.1E-05
Female Light Smokers	76,170	0.729	1.150	9.6E-06	1.5E-05
Female Heavy Smokers	18,136	0.347	0.548	1.9E-05	3.0E-05
Total Population:[4]	725,428	5.585	8.871	7.7E-06	1.2E-05

[1] The exposure data used in these estimations are emissions modeling estimates generated in 1986 by the Air Resources Board regarding a smelter in City of Industry, CA. This smelter has subsequently modified its operations so as to emit less arsenic (Shimp 1987).

[2] Estimate of the expected excess number of deaths from lung cancer among the people in the specified subgroup of the exposed population. Best Est = Best estimate based on unit risk estimates from the linear model discussed in chapter 11. 95% UCL = Upper 95% confidence limit of this estimate.

[3] Average lifetime excess risk of death from lung cancer corresponding to the mortality estimate for the specified subgroup of the exposed population (see note 2).

[4] Values in this row may not represent exact totals, due to rounding error.

HYPOTHETICAL ESTIMATES OF LUNG CANCER MORTALITY FROM RESIDENTIAL EXPOSURE TO ARSENIC EMITTED FROM A SECONDARY LEAD SMELTER:

Arsenic Concentration[2] Range	Avg[3]	No. of People Exposed	q[4] Best Est	q[4] 95% UCL	Mortality[5] Best Est	Mortality[5] 95% UCL	Individual Risk[6] Best Est	Individual Risk[6] 95% UCL
< 1	0.3	266,567	2.09	3.32	0.167	0.266	6.3E-07	1.0E-06
1-2	1.5	174,969	2.09	3.32	0.549	0.871	3.1E-06	5.0E-06
2-3	2.5	92,221	2.09	3.32	0.482	0.765	5.2E-06	8.3E-06
3-4	3.5	51,589	2.09	3.32	0.377	0.599	7.3E-06	1.2E-05
4-5	4.5	33,011	2.09	3.32	0.310	0.493	9.4E-06	1.5E-05
5-6	5.5	19,676	2.09	3.32	0.226	0.359	1.1E-05	1.8E-05
6-7	6.5	14,095	2.09	3.32	0.191	0.304	1.4E-05	2.2E-05
7-8	7.5	12,403	2.09	3.32	0.194	0.309	1.6E-05	2.5E-05
8-9	8.5	7,916	2.09	3.32	0.141	0.223	1.8E-05	2.8E-05
9-10	9.5	7,838	2.09	3.32	0.156	0.247	2.0E-05	3.2E-05
10-20	15	30,657	2.09	3.32	0.961	1.527	3.1E-05	5.0E-05
20-40	30	8,951	2.09	3.32	0.561	0.892	6.3E-05	1.0E-04
40-60	50	1,813	2.09	3.32	0.189	0.301	1.0E-04	1.7E-04
60-80	70	1,003	2.09	3.32	0.147	0.233	1.5E-04	2.3E-04
80-100	90	495	2.09	3.32	0.093	0.148	1.9E-04	3.0E-04
100-120	110	503	2.09	3.32	0.116	0.184	2.3E-04	3.7E-04
120-140	130	210	2.09	3.32	0.057	0.091	2.7E-04	4.3E-04
140-160	150	171	2.09	3.32	0.054	0.085	3.1E-04	5.0E-04
160-180	170	0	2.09	3.32	0	0	N/A	N/A
180-200	190	227	2.09	3.32	0.090	0.143	4.0E-04	6.3E-04
> 200	225	1,112	2.09	3.32	0.523	0.831	4.7E-04	7.5E-04
Totals:		725,427			5.585	8.871	7.7E-06	1.2E-05

[1] The exposure data presented here are emissions modeling estimates generated in 1986 by the Air Resources Board regarding a smelter in City of Industry, CA. This smelter has subsequently modified its operations so as to emit less arsenic (Shimp 1987).

[2] ng/m^3.

[3] Midpoint of the range, or, for the high and low ranges, an estimated average.

[4] Lifetime unit risk factor $\times 10^6$, $(ng/m^3)^{-1}$. Best Est = Best estimate from the linear model discussed in chapter 11. 95% UCL = Upper 95% confidence limit of this estimate.

[5] Estimate of the expected excess number of deaths among the people exposed to lifetime average arsenic concentrations in the specified range. Based on unit risk estimate (see note 4).

[6] Estimate of the lifetime excess risk of death from lung cancer among the people exposed to average arsenic concentrations in the specified range. Based on unit risk estimate (see note 4).

APPENDIX E

DERIVATION OF THE ARSENIC EFFECT IN SMOKERS AND NONSMOKERS

It is desired to have an estimate of the risk ratio (RR) in smokers, and the risk ratio in nonsmokers. From Appendix A, it can be seen that these will be different, i.e., since the joint effect of smoking and arsenic are nonmultiplicative, smokers and nonsmokers have different RRs due to arsenic.

When the proportion of smokers is equally distributed among exposed and unexposed, these risk ratios, under certain assumptions, can be estimated from 4 pieces of information: (1) the magnitude of interaction, or specifically the ratio of the arsenic-related RR in smokers as compared to the RR in nonsmokers, (2) the proportion of smokers in the study, (3) the RR due to smoking (in the absence of arsenic exposure), and (4) the observed, crude RR in which smokers and nonsmokers have been pooled. These data were taken from published reports as follows:

The magnitude of interaction was estimated from the studies reviewed in Appendix A. In the range of occupational exposures, this ratio of interaction (denoted ρ) averages approximately 0.4 to 0.6. Based on data of Pershagen (1985), Enterline (1983) and Rencher et al. (1977), the ratio of interaction is likely to be dose dependent, with values close to 1 at lower, environmental levels, ranging to about 0.4 at the higher occupational exposures. Therefore, values for ρ_i were interpolated for the different dose levels.

Arsenic exposure appeared to be independent of smoking (Welch et al. 1982). The proportion of cigarette smokers (P_s) in the Anaconda cohort (Higgins et al. 1985, Welch et al. 1982) was reported as 60 - 62% at all levels of arsenic exposure. A similar proportion of smokers was assumed for the study by Enterline et al. (1987). Because the general population males of the same ages may have had a different prevalence of smoking, only internal comparisons were made. That is, the low-dose exposure group served as controls.

The risk ratio for lung cancer among current smokers due to smoking (denoted σ) was based on data from the large longitudinal study of U.S. veterans which gave an overall mortality ratio of 10.9 for current smokers of cigarettes aged 35-84 (Kahn, 1966). In the absence of age-specific data in the arsenic-exposed cohorts, this value was assumed to hold at all ages of the men during their follow-up period. In addition, it is assumed that this RR is constant over time.

The observed SMR for each dose level was assumed to equal the crude RR. The SMR is a close approximation to the RR, particularly when the age intervals are less than 10 years (5 year age intervals had been used in the studies by Higgins et al. 1985 and Enterline et al. 1987) and the outcome is relatively rare, as it is for single sites of cancer (Doll and Peto 1978, Symons and Taulbee 1981).

Thus for each observed dose-specific SMR_i (adjusted in relation to the low-dose group), $SMR^*_{i,\tilde{s}}$, the effect in nonsmokers was derived using the relationship (see mathematical derivation at end of this appendix):

$$SMR^*_{i,\tilde{s}} = \frac{\sigma P_s + P_{\tilde{s}}}{\sigma \rho_i P_s + P_{\tilde{s}}} SMR_i$$

where $P_s = 0.6$, $P_{\tilde{s}} = 0.4$, $\sigma = 10.9$ and ρ_i varied according to the dose level from 1.0 to 0.4. The smokers SMR at dose i is then $SMR^*_{i,s} = SMR^*_{i,\tilde{s}} \cdot \rho_i$. The values of SMR_i, $SMR^*_{i,\tilde{s}}$, the interpolated value of ρ_i, and $SMR^*_{i,s}$ for the two cohorts are shown in Table E-1.

Using these smoking habit specific SMRs, P(s) and ρ_i, the observed deaths at each dose level were partitioned among smokers and nonsmokers using the relations:

$$Obs_i = (P_s \cdot \sigma \rho_i + P_{\tilde{s}}) \, x$$

$$Obs^*_{i,\tilde{s}} = x \cdot P(\tilde{s})$$

$$Exp^*_{i,\tilde{s}} = \left(\frac{Obs^*_{i,\tilde{s}}}{SMR^*_{i,\tilde{s}}} \right)$$

(See Table E-2.) Note that because these are not "true" data, their statistical properties are not known. However, for the purpose of this risk assessment, DHS staff has treated these inferred observed and expected deaths for nonsmokers as if they were characterized by the known statistical properties of similarly structured data.

Mathematical Details
****

Let P_s = proportion of smokers

$P_{\sim s}$ = proportion of nonsmokers

x = risk in nonsmokers not exposed to arsenic

αx = risk in nonsmokers exposed to arsenic

σx = risk in smokers not exposed to arsenic

$\rho\sigma\alpha x$ = risk in smokers exposed to arsenic

Thus σ is the relative risk due to smoking in the absence of arsenic, α is the relative risk due to arsenic in the absence of smoking, and ρ is the ratio of interaction. Further,

Let RR_c = crude (observed) risk ratio due to smoking

RR_{wa} = weighted average of risk ratios at each level of smoking, with weights equal to the proportion in each stratum.

Then:

$$RR_c - RR_{wa} =$$

$$= \frac{[\rho\sigma\alpha\ P_s + \alpha P_{\sim s}]x}{[\sigma P_s + P_{\sim s}]x} - \left[\frac{\rho\sigma\alpha x P_s}{\sigma x} + \frac{\alpha x P_{\sim s}}{x}\right]$$

$$= \frac{\rho\sigma\alpha\ P_s + \alpha P_{\sim s} - (\rho\alpha P_s + \alpha P_{\sim s})\ (\sigma P_s + P_{\sim s})}{\sigma P_s + P_{\sim s}}$$

$$= \frac{\rho\sigma\alpha\ P_s + \alpha P_{\sim s} - \rho\alpha P_s P_{\sim s} - \rho\sigma\alpha\ P_s P_s - \alpha P_{\sim s} P_{\sim s} - \sigma\alpha P_{\sim s} P_s}{\sigma P_s + P_{\sim s}}$$

$$= \frac{\rho\sigma\alpha P_s - \rho\sigma\alpha P_s(1-P_{\tilde{s}}) + \alpha P_{\tilde{s}} - \alpha P_{\tilde{s}}(1-P_s) - \rho\alpha P_s P_{\tilde{s}} - \sigma\alpha P_{\tilde{s}} P_s}{\sigma P_s + P_{\tilde{s}}}$$

$$= \frac{\rho\sigma\alpha\ P_s P_{\tilde{s}} + \alpha P_s P_{\tilde{s}} - \rho\alpha P_s P_{\tilde{s}} - \sigma\alpha\ P_s P_{\tilde{s}}}{\sigma P_s + P_{\tilde{s}}}$$

$$= \frac{P_s P_{\tilde{s}}\ (\sigma - 1)\ (\rho - 1)\alpha}{\sigma P_s + P_{\tilde{s}}}$$

Solving for α in terms of RR_c, σ, and ρ:

$$RR_c - \left[\frac{\rho\sigma\alpha x P_s}{\sigma x} + \frac{\alpha x P_{\tilde{s}}}{x}\right] = \frac{P_s P_{\tilde{s}}\ (\sigma - 1)\ (\rho - 1)\alpha}{\sigma P_s + P_{\tilde{s}}}$$

$$RR_c = \left[\rho P_s + P_{\tilde{s}} + \frac{P_s P_{\tilde{s}}\ (\sigma - 1)\ (\rho - 1)}{\sigma P_s + P_{\tilde{s}}}\right] \cdot \alpha$$

Therefore,

$$\alpha = RR_c \cdot \left[\rho P_s + P_{\tilde{s}} + \left(\frac{P_s P_{\tilde{s}}\ (\sigma - 1)\ (\rho - 1)}{\sigma P_s + P_{\tilde{s}}}\right)\right]^{-1}$$

$$= \left[\frac{\sigma P_s + P_{\tilde{s}}}{\sigma\rho P_s(1-P_{\tilde{s}}) + \rho P_s P_{\tilde{s}} + \sigma P_s P_{\tilde{s}} + P_{\tilde{s}}(1-P_s) + P_s P_{\tilde{s}}(\sigma\rho - \sigma - \rho + 1)}\right] \cdot RR_c$$

$$= \frac{\sigma P_s + P_{\tilde{s}}}{\sigma\rho P_s + P_{\tilde{s}}} \cdot RR_c$$

TABLE E-1

CRUDE AND INFERRED SMRs[1]

FROM TWO SMELTER STUDIES

	SMR_c (crude SMR)	SMR_s^* (inferred nonsmoker SMR)	ρ (ratio of interaction)	SMR_s^* (inferred smoker SMR)
Higgins et al. (1985)	1.42	1.0	1.0	1.0
	1.79	1.55	0.8	1.24
	2.65	3.00	0.6	1.80
	3.95	5.26	0.5	2.63
Enterline et al. (1987)	1.36	1.0	1.0	1.0
	1.70	1.54	0.8	1.23
	1.84	1.88	0.7	1.32
	2.05	2.43	0.6	1.46
	2.21	2.62	0.6	1.57
	2.64	3.67	0.5	1.84
	3.39	5.72	0.4	2.29

SMRs = standardized mortality ratios defined as ([observed number of deaths] ÷ [expected number of deaths]) x 100 where the expected number of deaths is based on age-, sex-, and calendar year-specific rates in the general population.

TABLE E-2

OBSERVED LUNG CANCER DEATHS,

INFERRED DATA FOR NONSMOKERS,

and PREDICTED DEATHS FOR NONSMOKERS BASED ON REGRESSION MODEL[1]

		Inferred Data		
	OBS^*	OBS^*_s	EXP^*_s	$PRED^*_s$
Higgins et al. (1985)	51	2.94	2.94	(served as controls)
	67	4.76	3.06	3.92
	122	11.29	3.76	10.92
	98	10.68	2.03	11.05
Enterline et al. (1987)	9	0.52	0.52	(served as controls)
	15	1.07	0.69	0.77
	19	1.53	0.81	1.07
	21	1.94	0.80	1.34
	23	2.13	0.81	1.93
	13	1.42	0.39	1.82
	4	0.53	0.09	0.73

[1]The regression model is described in Chapter 11. This model was fitted to the inferred data for nonsmokers, yielding the predicted values shown here.

APPENDIX F

DERIVATION OF SMOKING-CATEGORY-SPECIFIC DEATH RATES

Let:

$R_{all,j}$ = all-cause death rate in age interval j, and

$R_{lung,j}$ = lung cancer death rate in age interval j,

where all smoking categories have been combined. These data are from 1982 vital statistics (U.S. Department of Health and Human Services 1986).

Let:

$RR_{all,X,j}$ = the relative risk for all-cause mortality among those in smoking status X and age interval j,

where:

X = N, F, L or H for never, former, light or heavy smokers, respectively.

Also let:

$P_j(X)$ = Probability of being in smoking status X for those in age interval j.

These age-specific smoking probabilities are taken from data produced by the National Center for Health Statistics (U.S. Department of Health and Human Services 1985), or by the California Behavioral Risk Factor Surveillance Program (California DHS 1987).

Similarly, let:

$RR_{lung,X,j}$ = the relative risk for lung cancer mortality among those in smoking status X and age interval j.

These relative risks are taken from the longitudinal study of smoking-related mortality among U.S. veterans (Kahn, 1966). These data were considered preferable to the data of Doll and Peto (1978) because the latter only considered lifelong continuing smokers (i.e. those who had never quit), while the veterans data classified individuals according to current smoking status in a manner similar to prevalence data available from the U.S. Department of Health and Human Services, and the California DHS.

In the age categories in which no lung cancer deaths were reported for the never smokers, the data were supplemented using the report of Doll and Peto (1978). (From these latter data, a ratio was calculated comparing the RR in each age group for which no deaths were reported in the veterans study, to the RR in the lowest age group for which deaths were reported. In the study of U.S. veterans, this ratio was applied to each of the three smoker categories i.e., former, light, and heavy).

The age- and smoking-category-specific rates were calculated according to the following formulae:

Let:

$$Z_{lung} = R_{lung,j} \div \left[P_j(N) + P_j(F)RR_{lung,F,j} + P_j(L)RR_{lung,L,j} + P_j(H)RR_{lung,H,j}\right]$$

$$Z_{all} = R_{all,j} \div \left[P_j(N) + P_j(F)RR_{all,F,j} + P_j(L)RR_{all,L,j} + P_j(H)RR_{all,H,j}\right]$$

Then:

$$R_{lung,N,j} = P_j(N) \cdot Z_{lung} \qquad R_{all,N,j} = P_j(N) \cdot Z_{all}$$

$$R_{lung,F,j} = P_j(F) \cdot RR_{lung,F} \cdot Z_{lung} \qquad R_{all,F,j} = P_j(F) \cdot RR_{all,F} \cdot Z_{all}$$

$$R_{lung,L,j} = P_j(L) \cdot RR_{lung,L} \cdot Z_{lung} \qquad R_{all,L,j} = P_j(L) \cdot RR_{all,L} \cdot Z_{all}$$

$$R_{lung,H,j} = P_j(H) \cdot RR_{lung,H} \cdot Z_{lung} \qquad R_{all,H,j} = P_j(H) \cdot RR_{all,H} \cdot Z_{all}$$

APPENDIX G

SELECTED REPRODUCTIVE TOXICOLOGY STUDIES
OF
ARSENIC COMPOUNDS

Species	Reference	Dose Schedule[1]	Effects Reported	Remarks
Rat (female)	Kamkin 1982	Arsenic trioxide 3, 1, and 0.3 (2.3, .76, and 0.23)[1] $\mu g/m^3$, for 5 months, inhalation exposure.	Accumulation of arsenic in placenta at all doses. Rise in preimplantation mortality at 1 and 3 $\mu g/m^3$. Disrupted ossification at 1 and 3 $\mu g/m^3$.	Experiment report entitled 'For a revision of the maximum permissibee concentration of arsenic trioxide in the ambient air of inhabited areas.' [Translated.] Report lacks critical details of methods and data (See Chapter 6).
	Beaudoin 1974	Sodium arsenate 20 (7), 30 (7), and 40 (14) mg/kg, on one of days 7-12 of gestation, i.p.	Malformations (including eye defects, exencephaly, gonadal agenesis, renal agenesis, and skeletal defects) at all doses on days 9 and 10. NOEL at 20 (7) mg/kg on days 7,8,11, and 12, and 30 (11) mg/kg on days 7,11, and 12. All other doses were teratogenic or embryolethal.	Data from NOEL treatments not reported in detail.
		50 (18) mg/kg on one of days 7-12, i.p.	Embryolethal on all days of treatment.	
	Burk and Beaudoin 1977	Sodium arsenate 30 (11), 40 (14), and 50 (18) mg/kg on day 9, 10, 11, i.p.	Malformations at all doses on days 9 and 10 and at high dose on day 11. Decreased fetal weight in all groups except low dose/day 11. Fetal death at high dose on all days and at middle dose on days 9 and 10.	Study paid special attention to the details of renal agenesis.

Rat (male)	Kamil'dzhanov 1982	Arsenic trioxide 42.8 (32.4) mg/m^3 for 48 hours, 10.5 (7.95) mg/m^3 for 120 hours, 1.92 (1.45) mg/m^3 for 252 hours, and 0.47 (0.36) mg/m^3 for 800 hours Continuous inhalation exposure.	Decreased period of motility of spermatozoa. [Central nervous system, blood enzyme, behavioral, and body weight effects were also seen.] Dose-duration-response analysis (linear extrapolation) indicated a threshold, at 4 months exposure to 0.024 (0.18) mg/m^3, for this effect. Using a coefficient of safety, a no-activity concentration of 0.001 (0.00076) mg/m^3 was calculated and recommended as an average daily MPC (maximum permissible concentration.)	The decrease in sperm motility was the most sensitive effect among many observed.
Hamster	Ferm and Hanlon 1985	Sodium arsenate (As(V)) 68-126 μmol/kg (5.1-9.44 mg As/kg), on day 8 (dose delivery started on days 4-7 and ended on day 13), by subcutaneous implants (osmotic minipumps).	Teratogenesis, reduced weight, at all dose levels, in a dose-dependent manner.	
	Ferm and Kilham 1977	Sodium arsenate 10 (3.6) mg/kg, with and without induced hyperthermia, on day 8, i.p.	Synergism between As and and hyperthermia in fetal death and teratogenesis.	Hyperthermia was used to model fever, and was induced by placement in an incubator at 40° C.
	Ferm and Saxon 1971	Sodium arsenate 20 (7.2) mg/kg, on day 8, i.v.	Increase in amniotic fluid volume, in cases of anencephaly and exencephaly. No such increase seen in exposed groups with renal agenesis, other malformations, or no malformations.	Experiment designed to address the question of the source of amniotic fluid.

	Hood and Harrison 1982	Sodium arsenite (As(III)) 25 (14.4) mg/kg on day 8, 11, or 12, 20 (11.5) mg/kg on day 9 or 10, by gavage; 5 (2.88) mg/kg on day 8, 11, or 12 2.5 (1.44) mg/kg on day 9 or 10 i.p.	Gavage: No malformations, although increased prenatal mortality or decreased fetal weight in most groups. I.p.: Malformations in low dose groups.	Not all effects were statistically significant.
	Hood, Harrison, and Vedel 1982	Sodium cacodylate 900-1000 (421-468) mg/kg, disodium methanearsonate 500 (128) mg/kg, on days 8-12 i.p.	Toxicity, teratogenesis, at all doses.	Sodium cacodylate dosing much more potent than disodium methanearsonate dosing.
	Willhite 1981	Sodium arsenate 20 (7.2) mg/kg sodium arsenite 2,5,10 (1.2,2.9,5.8) mg/kg disodium methylarsonic acid 20,50,100 (5.1,13, 26) mg/kg dimethlylarsinic acid, disodium salt 20,50,100 (7.0,18,35) mg/kg, on day 8, i.v.	Sodium arsenate, sodium arsenite: resorptions, deaths, teratogenesis at all doses. Disodium methylarsonic acid: No observed effects at 20 and 100 mg/kg. Dimethylarsinic acid: no "no observed effect level" (NOEL).	Methylarsonic acid may be an iniermediate in an arsenic methylation sequence which converts inorganic arsenic into dimethylarsinic acid.
Mouse	Nagymajtenyi et al. 1985	Arsenic trioxide 0.26 (.20), 2.9 (2.2), and 28.5 (21.6) mg/m^3 days 9-12, 4 hr/day. Inhalation exposure.	Fetal liver cell chromosome damage, teratogenesis, reduced birth weight. The authors reported that the effects other than reduced birth weight "...did not reach the level of significance" at the two lowest dose levels. Nevertheless, intergroup differences in the expected direction (increasing response with increasing dose) are found throughout the data.	Experiment designed to evaluate the 0.3 mg/m^3 maximum allowable concentration (MAC) in Hungary (and the USSR). No NOEL was established by this study.

	Baxley et al. 1981	Sodium arsenite 20 (11.5), 40 (23), 45 (26) mg/kg, on one of days 8-15, by gavage.	Fetal toxicity, malformations at 40, 45 mg/kg, and NOEL ("no discernible teratogenic or maternal toxic effects") at 20.	Data for 20 mg/kg were not presented in detail. N = 8 to 15 pregnant mice per treatment day.
	Morrissey and Mottet 1983	Sodium arsenate 30 (11) and 45 (16) mg/kg, on day 8 (other dosing on days 7, 8 1/2, and 9), i.p.	An increase in dense staining inclusions within neuroepithelium at 45 mg/kg. Exencephaly seen at both doses. Reduced fetal weight seen at 45 mg/kg.	45 mg/kg was the only dose examined histologically.
	Schroeder and Mitchener 1971	Arsenite (5.0 mg As/l) in deionized drinking water.	Increased male-to-female ratio in litters (from 0.93 in the first generation to 1.30 in the second and 1.71 in the third.) Decreased litter size.	
Chick (embryo)	Puzanova 1980	From 0 to 1.13 ng of (metallic?) arsenic, on days 3 and 4, intraamnionally.	Reduction in length of caudal half of the body, at doses above 0.067 ng. A variety of "organ specific" teratogenic effects were seen.	
(embryo cells in culture)	Lindgren et al. 1984	Limb bud cells, prior to cartilage formation, were cultured and exposed to concentrations of arsenite up to 25 μM (in 5μM increments) and/or of arsenate up to 200μM (in 50 μM increments).	Inhibition of cartilage formation at all concentrations of arsenite except perhaps 5 μM. (The authors reported ED_{50} between 5 and 10 μM.) Arsenate, by itself, had no effect at any concentration, but potentiated the effect of arsenite.	
Sea Urchin	Pagano et al. 1982 (a)Paracentrotus lividus (b)Sphaerechinus granularis	Sodium arsenite (As(III)), or sodium arsenate (As(V)), as follows: Embryos: 1E-5 M As(III) or 5E-6 M As(V) for 48 hr, or up to 1E-5 M for first 5 hours.	(a)40%, (b)80%, block at gastrula. (a)skeletal inhibition. As(V) stimulated mitotic mitotic activity at all doses, with increasing effect at higher doses. As(III) stimulated mitotic activity at 1E-7 M, less so at 1E-6 M, and inhibited mitotic activity	The authors suggested that since As(V) exhibited less spermiotoxic action than As(III) -- as expected -- but was more potent in inducing mitotic abnormalities, these data "might suggest an as yet overlooked hazard of As(V)."

			at 1E-5 M.	
		125-cell embryos: administered 1E-7 M As(III) or As (V).	Dramatic increase in mitotic abnormalities, As(V) being more potent than As(III).	
	Pagano et al. 1982 (continued)	Sperm pretreatment: 5E-5 M As(III) or As(V) for 2 min, or 1E-5 M As(III) or 1E-4 M As(V) for 5 min.	Damage to gut, skeleton; affected motility and adhesiveness. As(III) decreased fertility. As(V) quickened fertility.	
		Egg pretreatment: 1E-5 M As(III) or As(V), for 10 min.	Pathologic blastulae; block at gastrula (a).	
Fish (Freshwater, Colisa Fasciatus (Bl. and Sch.))	Shukla and Pandey 1984a,b	Arsenic trioxide 2.0 (1.5) mg/l or 14.0 (10.6) mg/l for 15 or 30 days in demineralized tap water.	Ovary (1984a): No appreciable histological change after 15 days at 14 mg/l, but 30 days resulted in marked degenerative changes. No marked change (NOEL) at 2.0 mg/l. Testis (1984b): No marked alterations in architecture at 2.0 mg/l for 15 or 30 days, or at 14 mg/l for 15 days, but noticeable structural and cellular changes after 30 days at 14 mg/l.	The authors suggested that impaired nucleic acid metabolism was mechanism responsible for effects seen. This was inferred in part because nucleoli in these cells were found to be of reduced diameter.

[1] The amount of each dose that is composed of arsenic atoms is given in parentheses. This is often referred to as the amount "as arsenic."

REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists) (1986) Documentation of the Threshold Limit Values and Biological Exposure Indexes, 5th ed. Cincinnati, OH: ACGIH.

Amacher DE and Paillet SC (1980) Induction of trifluorothymidine-resistant mutants by metal ions in L5178Y/TK$^{+/-}$ cells. Mutation Res 78:279-288.

Andersson A and Persson J (1982) Uptake by agricultural crops of trace elements from fly ash. Abstract from Toxline (SI - CA/100/018900M, Report, ISS KHM-TR-25, order no. DE83750583, 40 pp., Address - Statens Vattenfallsverk, Vaellingby (Sweden)).

Angele R, Schneider B and Jung EG (1983) PUVA therapy does not modify arsenic carcinogenesis in psoriatics. Dermatologica 166:141-145.

Axelson O (1980) Arsenic compounds and cancer. J Toxicol Environ Health 6:1229.

Araki S, Aono H and Murata K (1986) Adjustment of urinary concentration to urinary volume in relation to erythrocyte and plasma concentrations: An evaluation of urinary heavy metals and organic substances. Arch Environ Health 41:171-177.

Aranyi C, Bradof JN, O'Shea WJ, Graham JA and Miller FJ (1985) Effects of arsenic trioxide inhalation exposure on pulmonary antibacterial defenses in mice. J Toxicol Environ Health 15:163-172.

Arena JM (1974) Poisoning: Toxicology--Symptoms--Treatments. Springfield, IL: Charles C. Thomas.

Armitage P (1982) The assessment of low-dose carcinogenicity. Biometrics Suppl, March, pp. 119-129.

Armitage P and Doll R (1954) The age distribution of cancer and a multi-stage theory of carcinogenesis. Br J Cancer 8:1-12.

Axelson O (1980) Arsenic compounds and cancer. J Toxicol Environ Health 6:1229-1235.

Axelson O, Dahlgren E, Jansson C-D and Rehnlund SO (1978) Arsenic exposure and mortality: A case referent study from a Swedish copper smelter. Br J Ind Med 35:8-15, 1978., as reviewed in EPA 1984.

Baetjer AM, Lillienfeld AM and Levin ML (1975) Cancer and occupational exposure to inorganic arsenic. In: Abstracts: 18th International Congress on Occupational Health, Brighton, England, September 14-19, 1975. Organizing Comittee, Brighton, England, p. 393, as reviewed in EPA 1984.

Baetjer AM, Levin ML and Lillienfeld AM (1975b) Analysis of mortality experience of Allied Chemical Plant. Fed Regist 40:3392-3403, as cited in Mabuchi et al. 1979.

Baroni C, Van Esch GJ and Saffiotti U (1963) Carcinogenesis tests of two inorganic arsenicals. Arch Environ Health 7:54.

Baxley MN, Hood RD, Vedel GC, Harrison WP and Szczech GM (1981) Prenatal toxicity of orally administered sodium arsenite in mice. Bull Environ Contam Toxicol 26:749-756.

Beaudoin AR (1974) Teratogenicity of sodium arsenate in rats. Teratology 10:153-158.

Beckett WS, Moore JL, Keogh JP and Bleecker ML (1985) Acute encephalopathy due to occupational exposure to arsenic. Brit J Ind Med 43:66-67.

Beckman L (1978) The Ronnskar smelter--occupational and environmental effects in and around a polluting industry in northern Sweden. Ambio 7:226-231.

Bencko V (1973) Health questions regarding atmospheric pollution by arsenic. Gig Sanit 38:85-87.

Bencko V and Symon K (1969) Suitability of hairless mice for experimental work and their sensitivity to arsenic. J Hyg Epidemiol Microbiol Immunol 13:1.

Bencko V and Symon K (1970) The cumulation dynamics in some tissue of hairless mice inhaling arsenic. Atmospheric Environment 4:157-161.

Berenbaum MC (1985) Consequences of synergy between environmental carcinogens. Environ Res 38:310-318.

Berteau PE, Flom JO, Dimmick RL and Boyd AR (1977) Studies on potential neoplastic effects of arsenic aerosols. Naval Biosciences Laboratory (School of Public Health, University of California, Berkeley) Technical Progress Report 52(part 4):72-83. Office of Naval Research, Arlington VA 22217.

Berteau PE, Flom JO, Dimmick RL and Boyd AR (1978) Long term study of potential carcinogenicity of inorganic arsenic aerosols to mice. Toxicol Appl Pharmacol 45:323.

Berteau PE (1986) Personal communication. California Department of Health Services.

Blakley BR, Sisodia CS and Mukkur TK (1980) The effect of methylmercury, tetraethyl lead, and sodium arsenite on the humoral immune response in mice. Toxicol Appl Pharmacol 52:245-254.

Blejer HP and Wagner W (1976) Case study 4: Inorganic arsenic--ambient level approach to the control of occupational carcinogenic exposures. Ann NY Acad Sci 271:179-187.

Blom S, Lagerkvist B and Linderholm H (1985) Arsenic exposure to smelter workers: clinical and neurophysiological studies. Scand J Work Environ Health 11:265-269.

Blot WJ and Fraumeni JF (1975) Arsenical air pollution and lung cancer. Lancet 11:142-144.

Boutwell, RK (1963) A carcinogenicity evaluation of potassium arsenite and arsanilic acid. J Agricul Food Chem 11:381.

Bovin JF and Wacholder S (1985) Conditions for confounding of the risk ratio and of the odds ratio. Am J Epidemiol 121:152-158.

Bowden DH (1983) Cell turnover in the lung. Am Rev Respir Dis 128:S46-S48.

Brain JD and Mensah GA (1983) Comparative toxicology of the respiratory tract. Am Rev Respir Dis 128:S87-S90.

Breslow NE and Day NE (1980) Statistical Methods in Cancer Research. Lyon, France: International Agency for Research on Cancer.

Breslow NE and Day NE (1987) Statistical Methods in Cancer Research, Vol II: The Design and Analysis of Cohort Studies. Lyon, France: International Agency for Research on Cancer.

Briggs GM (1986) Personal communication. University of California, Berkeley.

Brown CC and Chu KC (1983a) A new method for the analysis of cohort studies: Implications of the multistage theory of carcinogenesis applied to occupational arsenic exposure. Environ Health Perspect 50:293-308.

Brown CC and Chu KC (1983b) Implications of the multistage theory of carcinogenesis applied to occupational arsenic exposure. J Natl Cancer Inst 70:455-463.

Brown MM, Rhyne BC, Goyer RA and Fowler BA (1976) Intracellular effects of chronic arsenic administration on renal proximal tubule cells. J Toxicol Environ Health 1:505-514.

Buchet JP and Lauwerys R (1985) Study of inorganic arsenic methylation by rat liver in vitro: Relevance for the interpretation of observations in man. Arch Toxicol 57:125-129.

Buchet JP, Lauwerys R, Mahieu P and Geubel A (1982) Inorganic arsenic metabolism in man. Arch Toxicol Suppl 5:326-327.

Buchet JP, Geubel A, Pauwels S, Mahieu P and Lauwerys R (1984) The influence of liver disease on the methylation of arsenite in humans. Arch Toxicol 55:151-154.

Bureau of the Census (1982) 1980 Census of Population, Vol. 1, General Population Characteristics, Part 6, California. U.S. Department of Commerce, Washington, DC.

Burk D and Beaudion AR (1977) Arsenate-induced renal agenesis in rats. Teratology 16: 247-260.

Byron WR, Bierbower GW, Brouwer JB and Hansen WH (1967) Pathologic changes in rats and dogs from two-year feeding of sodium arsenite or sodium arsenate. Toxicol Appl Pharmacol 10:132-147.

California Department of Health Services (1982) Vital Statistics of California 1979-1980. Center for Health Statistics, Sacramento, CA.

California Department of Health Services (1987) Behavioral Risk Factor Surveillance System, California 1986 Annual Report. Sacramento, CA.

Campbell, KI (1976) Inhalation toxicology. Clin Toxicol 9:849-921.

Caren LD (1981) Environmental pollutants: Effects on the immune system and resistance to infectious disease. BioScience 31:582-586.

Carmignani M, Boscolo P and Innaccone A (1983) Effects of chronic exposure to arsenate on the cardiovascular function of rats. Brit J Indust Med 40:280-284.

Carmignani M, Boscolo P and Castellino N (1985) Metabolic fate and cardiovascular effects of arsenic in rats and rabbits chronically exposed to trivalent and pentavalent arsenic. Arch Toxicol Suppl 8:452-455.

Casto BC, Meyers J and DiPaolo JA (1979) Enhancement of viral transformation for evaluation of the carcinogenic or mutagenic potential of inorganic metal salts. Cancer Res 39:193-198.

Charbonneau SM, Tam GKH and Bryce F (1978) Pharmacokinetics and metabolism of inorganic arsenic in the dog. In: Trace Substances in Environmental Health--XII, Hemphill DD ed. Columbia, MO: University of Missouri, pp. 276-283.

Chen CJ, Chuang YC, Lin TM and Wu, HY (1985) Malignant neoplasms among residents of a blackfoot disease-endemic area in Taiwan: High-arsenic artesian well water and cancers. Cancer Research 45:5895-5899.

Chiang CL (1984) The Life Table and Its Applications. Malabar, Florida: Robert E. Krieger Publishing Co.

Chung HC and Liu CT (1982) Induction of lung cancer in rats by intratracheal instillation of arsenic-containing ore dust. Zhonghua Zhongliu Zazhi 4:14-16, as reviewed in EPA 1984.

Cikrt M and Bencko V (1974) Fate of arsenic after parenteral administration to rats, with particular reference to excretion via bile. J Hyg Epidemiol Microbiol Immunol 18:129-136.

Cikrt M, Bencko V, Tichy M and Benes B (1980) Biliary excretion of ^{74}As and its distribution in the golden hamster after administration of $^{74}As(III)$ and $^{74}As(V)$. J Hyg Epidemiol Microbiol Immunol 24:384-388.

Clive D, Johnson KO, Spector JFS, Batson AG and Brown MMM (1979) Validation and characterization of the L5178Y/TK$^{+/-}$ mouse lymphoma mutagen assay system. Mutation Res 59:61-108.

Cohn BA, Wingard DL, Cirillo PM, Cohen RD and Kaplan GA (1987) Is cigarette smoking a stronger risk factor for lung cancer mortality for women than for men? Evidence from a cohort study with follow-up into the 1980's. Presented at the annual meeting of the Society for Epidemiologic Research, June 16-19, Amherst, MA.

Cornfield J (1977) Carcinogenic risk assessment. Science 198:693-699.

Cornfield J, Haenszel W, Hammond EC et al. (1959) Smoking and lung cancer: Recent evidence and a discussion of some questions. J Natl Cancer Inst 22:173-203.

Council on Scientific Affairs, American Medical Association (1985) Effects of toxic chemicals on the reproductive system. JAMA 253:3431.

Crecelius, EA (1977) Changes in the chemical speciation of arsenic following ingestion by man. Environ Health Perspect 19:147-150.

Crump KS, Hoel DG, Langley CH and Peto R (1976) Fundamental carcinogenic processes and their implications for low dose risk assessment. Cancer Res 36:2973-2979.

Danielsson BRG, Dencker L, Lindgren A et al. (1984) Accumulation of toxic metals in male reproduction organs. Arch Toxicol Suppl 7:177-180.

Davies JM (1980) Letter to the editor. Arch Environ Health 35:123.

De Flora S, Zanacchi P, Camoirano A, Bennicelli C and Baldolati GS (1984a) Genotoxic activity and potency of 135 compounds in the Ames reversion testt and in a bacterial DNA-repair test. Mutation Res 133:161-198.

De Flora S, Camoirano A, Zanacchi P and Bennicelli C (1984b) Mutagenicity testing with TA97 and TA102 of 30 DNA-damagining compounds, negative with other Salmonella strains. Mutation Res 134:159-165

Deknudt Gh, Leonard A, Arany J, Jenar-Du Buisson G and Delavignette E (1986) In vivo studies in male mice on the mutagenic effects of inorganic arsenic. Mutagenesis 1:33-34.

Dinman BD (1960) Arsenic: Chronic human intoxication. J Occup Med 2:137-141.

DiPaolo JA and Casto BC (1979) Quantitative studies of <u>in vitro</u> morphological transformation of syrian hamster cells by inorganic metal salts. Cancer Res 39:1008-1013.

Doll R (1971) The age distribution of cancer: Implications for models of carcinogenesis. J Royal Stat Soc, Series A 134:133-166

Doll R (1978) An epidemiologic perspective of the biology of cancer. Cancer Res 38:3573-3583.

Doll R and Peto R (1978) Cigarette smoking and bronchial carcinoma: Dose and time relationships among regular smokers and lifelong non-smokers. J Epidemiol Commun Health 32:303-313.

Elwood JM and Elwood JH (1980) Epidemiology of Anencephalus and Spina Bifida. New York: Oxford University Press.

Emmelot P and Scherer E (1980) The first relevant cell stage in rat liver carcinogenesis: A quantitative approach. Biochim et Biophys Acta 605:247-304.

Enterline PE (1976) Pitfalls in epidemiological research. J Occup Med 18:150-156.

Enterline PE (1983) Sorting out multiple causal factors in individual cases. In: Methods and Issues in Occupational and Environmental Epidemiology, Chiazze L, Lundin FE and Watkins D eds. Ann Arbor, MI: Ann Arbor Science pp. 177-182.

Enterline PE (1983b) Population selection criteria: do they introduce bias? In: Methods and Issues in Occupational and Environmental Epidemiology, Chiazze L, Lundin FE and Watkins D eds. Ann Arbor, MI: Ann Arbor Science pp. 143-146.

Enterline PE (1986) Personal communication (letter). University of Pittsburgh Graduate School of Public Health, Pittsburgh PA.

Enterline PE and Marsh GM (1980) Mortality studies of smelter workers. Am J Indust Med 1:251-259.

Enterline PE and Marsh GM (1982) Cancer mortality among workers exposed to arsenic and other substances in a copper smelter. Am J Epidemiol 116:895-911.

Enterline PE, Henderson VL and Marsh GM (1987, 1987a) Exposure to arsenic and respiratory cancer: A reanalysis. Am J Epidemiol 125:929-938.

Enterline PE, Marsh GM, Esmen NA, Henderson VL, Callahan CM, Paik M (1987b) Some effects of cigarette smoking, arsenic and SO_2 on mortality among US copper smelter workers. J Occup Med 29:831-838.

EPA (U.S. Environmental Protection Agency) (1984) Health assessment document for inorganic arsenic: Final report. Office of Research and Development, Research Triangle Park, NC 27711 (EPA-600/8-83-021F).

EPA (1985) Arsenic: Health advisory (draft). Office of Drinking Water, Sept. 30.

EPA (1986) National emission standards for hazardous air pollutants; standards for inorganic arsenic. Federal Register 51:27956-28042.

Evans HJ, Buckton KE, Hamilton GE and Carothers A (1979) Radiation-induced chromosome aberrations in nuclear-dockyard workers. Nature 277:531-534.

Farmer JG and Lowell (1985) Arsenic speciation in urine from humans intoxicated by inorganic arsenic compounds. Human Toxicol 4:203-214.

Ferm VH (1976) Teratogenic effects and placental permeability of heavy metals. Current Topics in Pathology 62:145.

Ferm VH and Carpenter SJ (1968) Malformations induced by sodium arsenate. J Reprod Fert 17:199-201.

Ferm VH and Hanlon DP (1985) Constant rate exposure of pregnant hamsters to arsenate during early gestation. Environ Res 37:425-432.

Ferm VH and Kilham L (1977) Synergistic teratogenic effects of arsenic and hyperthermia in hamsters. Environ Res 14:483-486.

Ferm VH and Saxon A (1971) Amniotic fluid volume in experimentally induced renal agenesis and anencephaly. Experientia 27:1066.

Fishbein L (1981) Sources, transport and alterations of metal compounds: An Overview. I. Arsenic, beryllium, cadmium, chromium, and nickel. Environ Health Perspect 40:43-64.

Fisher AB, Buchet JP and Lauwerys RR (1985) Arsenic uptake, cytotoxicity and detoxification studied in mammalian cells in culture. Arch Toxicol 57:168-172.

Fleiss JL (1981) Statistical Methods for Rates and Proportions, 2nd ed. New York: John Wiley and Sons.

Foa V, Colombi A, Maroni M, Buratti M and Calzaferri G (1984) The speciation of the chemical forms of arsenic in the biological monitoring of exposure to inorganic arsenic. Sci Total Environ 34:241-259.

Fong K, Lee F and Bockrath R (1980) Effects of sodium arsenite on single-strand break formation and post-replication repair in E. coli following UV irradiation. Mutation Res 70:151-156.

Fox AJ and Collier PF (1976) Low mortality rates in industrial cohort studies due to selection for work and survival in the industry. Br J Prev Soc Med 30:225-230.

Freeman JL, Yousef MK, Naegle SR and Barth DS (1983) Biokinetics of ^{74}As, ^{109}Cd and ^{203}Pb: Wild and laboratory rodents. In: Trace Substances in Environmental Health--XVII, Hemphill DD ed. Columbia, MO: University of Missouri, pp. 51-57.

Friberg L and Kjellström T (1981) Toxic metals--pitfalls and prospects in risk estimation. In: Heavy Metals in the Environment, international conference, Amsterdam, Sep. 1981. Commission of the European Communities, and World Health Organization, co-sponsors.

Frost DV (1975) Is selenium depletion the answer to the "arsenic cancer" mystery? Feedstuffs, April 7, pp. 20-23.

Frost DV (1983) What do losses in selenium and arsenic bioavailability signify for health? Sci Total Environ 28:455-466.

Furst A (1983) A new look at arsenic carcinogenesis. In: Arsenic: Industrial, Biomedical, Environmental Perspectives, Lederer WH and Fensterheim RJ eds. New York: Van Nostrand Reinhold Company, p. 151 ff.

Gainer JH (1972) Effects of arsenicals on interferon formation and action. Am J Vet Res 33:2579.

Gainer JH and Pry TW (1972) Effects of arsenicals on viral infections in mice. Am J Vet Res 33:2299.

Gart JJ (1971). Review International Statistics Inst 39(2):Section 13, p. 159.

Gartrell MJ, Craun JC, Podrebarac DS and Gunderson EL (1986a) Pesticides, selected elements, and other chemicals in infant and toddler total diet samples, October 1980-March 1982. J Assoc Off Anal Chem 69:123-145.

Gartrell MJ, Craun JC, Podrebarac DS and Gunderson EL (1986b) Pesticides, selected elements, and other chemicals in adult total diet samples, October 1980-March 1982. J Assoc Off Anal Chem 69:146-161.

Gerber GB, Maes J and Eykens B (1982) Transfer of antimony and arsenic to the developing organism. Arch Toxicol 159-168.

Ghafghazi T, Ridlington JW and Fowler BA (1980) The effects of acute and subacute sodium arsenite administration on carbohydrate metabolism. Toxicol Appl Pharmacol 55:126-130.

Ginsburg JM (1965) Renal mechanism for excretion and transformation of arsenic in the dog. Am J Physiol 208(5):832-840.

Ginevan ME (1981) A Poisson trials approach to interpopulation comparisons of cause of death data. Environ Res 25:147-159.

Glaser U, Hochrainer D, Oldiges H and Takenaka S (1986) Long-term inhalation studies with NiO and As_2O_3 aerosols in Wistar rats. In: Health Hazards and Biological Effects of Welding Fumes and Gases: Proceedings of the International Conference on Health Hazards and Biological Effects of Welding Fumes and Gases, Copenhagen, February 18-21, 1985, Stern RM, Berlin A, Fletcher AC and Jarvisalo J, eds. New York: Excerpta Medica (Elsevier Science Publishing Company Inc.), pp. 325-328.

Goldsmith JF, Deane M, Thom J and Gentry G (1972) Evaluation of health implications of elevated arsenic in well water. Water Res 6:1133-1136.

Green MHL, Muriel WJ and Bridges BA (1976) Use of a simplified fluctuation test to detect low levels of mutagens. Mutation Res 38:33-42.

Green MHL, Gridges BA, Rogers AM et al. (1977) Mutagen screening by a simplified bacterial fluctuation test: use of microsomal preparations and whole liver cells for metabolic activation. Mutation Res 48:287-294.

Guess H, Crump K and Peto R (1977) Uncertainty estimates for low-dose-rate extrapolations of animal carcinogenicity data. Cancer Res 37:3475-3483.

Hamilton A and Hardy HL (1974) Industrial Toxicology, 3rd ed. Acton, MA: Publishing Sciences Group, Inc.

Hanlon DP and Ferm VH (1986a) Concentration and chemical status of arsenic in the blood of pregnant hamsters during critical embryogenesis: 1. Subchronic exposure to arsenate utilizing constant rate administration. Environ Res 40:372-379

Hanlon DP and Ferm VH (1986b) Concentration and chemical status of arsenic in the blood of pregnant hamsters during critical embryogenesis: 2. Acute exposure. Environ Res 40:380-390.

Hanlon DP and Ferm VH (1974) Possible mechanisms of metal ion induced teratogenesis. Teratology 9:A-18 - A-19.

Hansen TB and Andersen B (1986) Ozone and other air pollutants from photocopying machines. Am Ind Hyg Assoc J 47:659-665.

Harrington JT (1980) Alcohol, arsenic, and (rapidly) old kidneys. Arch Intern Med 140:167-168.

Harrison JWE, Packman EW and Abbott DD (1958) Acute oral toxicity and chemical and physical properties of arsenic trioxides. Arch of Indust Health 17:118.

Harvey SC (1975) Heavy Metals. In: The Pharmacological Basis of Therapeutics, 5th ed., Goodman LS and Gilman A eds. New York: Macmillan Publishing Co., p. 924.

Hays D (1981) Teratogenesis: A review of the basic principles with a discussion of selected agents: Part I. Drug Intelligence and Clinical Pharmacy 15:444-458.

Hemmerly J and Demerec M (1955) Test of chemicals for mutagenicity. Cancer Research suppl. 3:69-75.

Henry MC, Port CD and Kaufman DG (1975) Importance of physical properties of Benzo(a)pyrene-ferric oxide mixtures in lung tumor induction. Cancer Res 35:207-217.

Hertz-Picciotto I, Holtzman D (1989) Issues in conducting quantitative cancer risk assessments using epidemiologic data: arsenic as a case study. Exper Path 37:219-223.

Hertz-Picciotto I, Holtzman D. Dose-response relationship between arsenic inhalation exposure and risk of lung cancer. Proceedings of the Annual Meeting of the Society for Risk Analysis (in press).

Higgins I, Welch K, Oh M et al. (1981) Influence of arsenic exposure and smoking on lung cancer among smelter workers: A pilot study. Am J Indust Med 2:33-41.

Higgins I, Welch K, Oh M and Burchfiel C (1983) Response to letter to the editor. Arch Environ Health 38:190-191.

Higgins I, Welch KB, Oh MS et al. (1985) Arsenic exposure and respiratory cancer in a cohort of 8044 Anaconda smelter workers: A 43-year follow-up study. Unpublished report submitted to Chemical Manufacturers' Association and Smelters Environmental Research Association.

Hill AB and Fanning EL (1948) Studies in the incidence of cancer in a factory handling inorganic arsenic compounds of arsenic: I. Mortality experience in the factory. Brit J Indust Med 5:1.

Hindmarsh JT and McCurdy RF (1986) Clinical and environmental aspects of arsenic toxicity. CRC Crit Rev Clin Lab Sci 23:315-347.

Hine CH, Pinto SS and Nelson KW (1977) Medical problems associated with arsenic exposure. J Occup Med 19:391-396.

Hoel DG, Kaplan NL and Anderson MW (1983) Implication of nonlinear kinetics on risk estimation in carcinogenesis. Science 219:1032-1037.

Holland RH, McCall MS and Lanz HC (1959) A study of inhaled arsenic-74 in man. Cancer Res 19:1154.

Hollstein M, McCann J, Angelosanto FA et al. (1979) Short-term tests for carcinogens and mutagens. Mutation Res 65:133-226.

Hood RD (1983) Toxicology of prenatal exposure to arsenic. In: Arsenic: Industrial, Biomedical, Environmental Perspectives, Lederer WH and Fensterheim RJ eds. New York: Van Nostrand Reinhold Company, pp. 134-150.

Hood RD and Harrison WP (1982) Effects of prenatal arsenite exposure in the hamster. Bull Environ Contam Toxicol 29:671-678.

Hood RD, Harrison WP and Vedel GC (1982) Evaluation of arsenic metabolites for prenatal effects in the hamster. Bull Environ Contam Toxicol 19:679-687.

Hood RD and Vedel-Macrander G (1984) Evaluation of the effects of BAL (2,3-dimercaptopropanol) on arsenite-induced teratogenesis in mice. Toxicol Appl Pharmacol 73:1-7.

Huang RY, Jan KY and Lee TC (1987) Posttreatment with sodium arsenite is coclastogenic in log phase but not in stationary phase. Hum Genet 75:159-162.

Hueper WC (1954) Experimental studies in metal carcinogensis: VI. Tissue reactions in rats and rabbits after parenteral introduction of suspensions of arsenic, beryllium, or asbestos in lanolin. J Nat Cancer Inst 15:113, as reviewed in EPA 1984.

Hueper WC and Payne WW (1962) Experimental studies in metal carcinogenesis. Arch Environ Health 5:445-462.

Hughes JP, Polissar L, Van Belle G (1988) Evaluation and synthesis of health effects studies of communities surrounding arsenic producing industries. Int J Epidemiol 17:407-413.

IARC (International Agency for Research on Cancer) (1980) IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Vol. 23: Some metals and metallic compounds. United Nations: World Health Organization.

IARC (International Agency for Research on Cancer) (1987) IARC Monographs on the Evaluation of the Carcinogenic Risks to Humans, Suppl. 6, Genetic and related effects: an updating of selected IARC monographs from volumes 1 to 42. United Nations: World Health Organization.

IARC (1983) Approaches to classifying chemical carcinogens according to mechanism of activity. Joint IARC/IPCS/CEC Working Group Report, IARC Internal Technical Reports 83/001. Lyon, France.

Inamasu T, Hisanaga A and Ishinishi N (1982) Comparison of arsenic trioxide and calcium arsenate retention in the rat lung after intratracheal instillation. Toxicol Letters 12:1-5.

Institute of Labour Protection of Tin Mine Corporation, Yunnan (China) (1982) Induction of lung cancer in rats by intratracheal instillation of arsenic containing ore dust. Zhonghua Zhongliu Zazhi 4:14-16.

Irgolic KJ, Woolson EA, Stockton RA et al. Characterization of arsenic compounds formed by Daphnia magna and Tetraselmis chuii from inorganic arsenate. Environ Health Perspect 19:61-66.

Ishinishi N, Kodama Y, Nobutomo K and Hisanaga A (1977) Preliminary study on carcinogenicity of arsenic trioxide in rat lung. Environ Health Perspect 19:191-196.

Ishinishi N, Tomita M and Hisanaga A (1980) Study on chronic toxicity of arsenic trioxide in rats with special reference to the liver damages. Fukuoka Acta Med 71:27-40.

Ishinishi N and Yamamoto A (1983) Discrepancy between epidemiological evidence and animal experimental result. J UOEH 5(Suppl):109-116.

Ishinishi N, Yamamoto A, Hisanaga A and Inamasu T (1983) Tumorigenicity of arsenic trioxide to the lung in Syrian golden hamsters by intermittent instillations. Cancer Letters 21:141-147.

Ivankovic S, Eisenbrand G and Preussmann (1979) Lung carcinoma induction in BD rats after a single intratracheal instillation of an arsenic-containing pesticide mixture formerly used in vineyards. Int J Cancer 24:786-788, as reviewed in EPA 1984.

Jackson R and Grainge JW (1975) Arsenic and cancer. CMA Journal 113:396-401.

Jacobson-Kram D and Montalbano D (1985) The Reproductive Effects Assessment Group's report on the mutagenicity of inorganic arsenic. Environ Mutagenesis 7:787-804.

Jan KY, Huang RY and Lee TC (1986) Different modes of action of sodium arsenite, 3-aminobenzamide, and caffeine on the enhancement of ethyl methanesulfonate clastogenicity. Cytogenet Cell Genet 41:202-208.

Jarup L, Pershagen G, Wall S (1989, 1989a) Cumulative arsenic exposure and lung cancer in smelter workers: a dose-response study. Am J Indust Med 15:31-41.

Jarup L, Pershagen G (1989b) Cumulative arsenic exposure, smoking and lung cancer in smelter workers - a case-referent study. Presented at the Seventh International Symposium on Epidemiology in Occupational Health, Tokyo, Japan, October 11-13.

Jauge P and Del-Razo LM (1985) Uric acid levels in plasma and urine in rats chronically exposed to inorganic As(III) and As(V). Toxicology Letters 26:31-35.

Jelinek CF and Corneliussen PE (1977) Levels of arsenic in the United States food supply. Environ Health Perspect 19:83-87.

Johnstone RM (1963) Sulfhydryl agents: Arsenicals. In: Metabolic Inhibitors: A Comprehensive Treatise, Vol. 2, Hochster RM and Quastel JH eds. New York: Academic Press, p. 99.

Kadowaki K (1960) Studies on the arsenic contents in organ-tissues of the normal Japanese. Osaka City Med J 9:2083.

Kahn HA (1966) The Dorn study of smoking and mortality among U.S. veterans: Report on eight and one-half years of observation. In: Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases, Haenszel W ed. National Cancer Institute Monograph 19. Bethesda, MD: U.S. Department of Health Education and Welfare.

Kamil'dzhanov AX (1982) Hygenic basis for the maximum permissible concentration of arsenic trioxide in the ambient air. Gig Sanit (2):74-75.

Kamkin AB (1982) For a revision of the maximum permissible concentration of arsenic trioxide in the ambient air of inhabited areas. Gig Sanit (1):6-9.

Kanematsu N, Hara M and Kada T (1980) Rec assay and mutagenicity studies on metal compounds. Mutation Res 77:109-116.

Kanisawa M and Schroeder HA (1967) Life term studies on the effects of arsenic, germanium, tin, and vanadium on spontaneous tumors in mice. Cancer Res 27:1192-1195.

Kanisawa M and Schroeder HA (1969) Life term studies on the effect of trace elements on spontaneous tumors in mice and rats. Cancer Res 29:892-895.

Kerkvliet NI, Steppan LB, Koller LD and Exon JH (1980) Immunotoxicology studies of sodium arsenate--effects of exposure on tumor growth and cell-mediated tumor immunity. J Environ Path Toxicol 4:65-79.

Klaassen CD (1974) Biliary excretion of arsenic in rats, rabbits, and dogs. Toxicol Appl Pharmacol 29:447-457.

Klaassen CD (1985) Heavy Metals and Heavy Metal Antagonists. In: Goodman and Gilman's The Pharmacological Basis of Therapeutics, 7th ed., Gilman AG, Goodman LS, Rall TW and Murad F eds. New York: Macmillan Publishing Co., p. 1605.

Kleinbaum DG, Kupper LL and Morgenstern H (1982) Epidemiologic Research. New York: Van Nostrand Reinhold Company.

Knoth W (1966) Arsenbehandlung. Arch Klin Exp Derm 227:228-234, as reviewed in EPA 1984.

Knowles FC and Benson AA (1984) The enzyme inhibitory form of inorganic arsenic. Z ges Hyg 30:625.

Kodell RL, Gaylor DW, Chen JT (1987) Using average lifetime dose rate for intermittent exposure to carcinogens. Risk Anal 7:339-345.

Kowalczyk GS (1985) Air emission risk assessment model: Benzo(a)pyrene and arsenic emissions from the Mt. Tom Power Plant. In: Proceedings of the 78th Annual Meeting of the Air Pollution Control Association. 3:85-34.4.

Kroes R, Van Logten MJ, Berkvens JM, De Vries T and Van Esch GJ (1974) Study on the carcinogenicity of lead arsenate and sodium arsenate and on the possible synergistic effect of diethylnitrosoamine. Food Cosmet Toxicol 12:671-679, as reviewed in EPA 1984.

Kuratsune M, Tokudome S, Shirakusa T et al. (1974) Occupational lung cancer among copper smelters. Int J Cancer 13:552-558, as reviewed in EPA 1984.

Lagerkvist B, Linderholm H and Nordberg GF (1986) Vasospastic tendency and Raynaud's phenomenon in smelter workers exposed to arsenic. Environ Res 39:465-474.

Lamm SH and Lederer WH (1984) A possible carcinogenic threshold for arsenic exposure. Scand J Work Environ Health 10:128.

Lanz H Jr, Wallace PC and Hamilton JG (1950) The metabolism of arsenic in laboratory animals using As^{74} as a tracer. University of California Publications in Pharmacology 2:263-282.

Larramendy ML, Popescu NC and DiPaolo JA (1981) Induction by inorganic metal salts of sister chromatid exchanges and chromosome aberrations in human and Syrian hamster cell strains. Environ Mutagenesis 3:597-606.

Lauwerys R and Buchet JP (1985) Arsenic speciation in urine from humans intoxicated by inorganic arsenic compounds. Human Toxicol 4:529-530.

Lauwerys R and Buchet JP (1985) Arsenic speciation in urine from humans intoxicated by inorganic arsenic compounds. Human Toxicol 4:531-532.

Lee AM and Fraumeni JF (1969) Arsenic and respiratory cancer in man: An occupational study. J Natl Cancer Inst 42:1045-1052.

Lee TC, Huang RY and Jan KY (1985a) Sodium arsenite enhances the cytotoxicity, clastogenicity, and 6-thioguanine-resistant mutagenicity of ultraviolet light in Chinese hamsters. Mutation Res 148:83-89.

Lee TC, Oshimura M and Barrett JC (1985b) Comparison of arsenic-induced cell transformation, cytotoxicity, mutation and cytogenetic effects in Syrian hamster embryo cells in culture. Carcinogenesis 6(10):1421-1426.

Lee TC, Lee KC, Tzeng YJ, Huang RY and Jan KY (1986a) Sodium arsenite potentiates the clastogenicity and mutagenicity of DNA crosslinking agents. Environ Mutagenesis 8:119-128.

Lee TC, Wang-Wuu S, Huang RY, Lee KCC and Jan KY (1986b) Differential effects of pre- and posttreatment of sodium arsenite on the genotoxicity of methyl methanesulfonate in chinese hamster ovary cells. Cancer Res 46:1854-1857.

Lee TC, Tzeng SF, Chang WJ, Lin YC and Jan KY (1986c) Post-treatments with sodium arsenite during G2 enhance the frequency of chromosomal aberrations induced by S-dependent clastogens. Mutat Res 163:263-269.

Lee TC, Lee KCC, Chang C and Woon-Long Jwo (1986d) Cell-cycle dependence of the cytotoxicity and clastogenicity of sodium aresnite in Chinese hamster ovary cells. Bull Inst Zool, Academia Sinica 25:91-97.

Lee TC, Tanaka N, Lamb PW, Gilmer TM, Barret JC (1988) Induction of gene amplification by arsenic. Science 241:79-81.

Lee-Feldstein A (1983) Arsenic and respiratory cancer in humans: Follow-up of copper smelter employees in Montana. J Natl Cancer Inst 70:601-609.

Lee-Feldstein A (1986) Cumulative exposure to arsenic and its relationship to respiratory cancer among copper smelter employees. J Occup Med 28:296-302.

Lee-Feldstein (1989) A comparison of several measures of exposure to arsenic. Am J Epidemiol 129:112-124.

Leitch A and Kennaway EL (1922) Experimental production of cancer by arsenic. Brit Med J. 2:1107-1108, as cited in EPA 1984.

Léonard A and Lauwerys RR (1980) Carcinogenicity, teratogenicity and mutagenicity of arsenic. Mutation Res 75:49-62.

Le Quesne PM and McLeod JG (1977) Peripheral neuropathy following a single exposure to arsenic. J Neurol Sci 32:437-451.

Liebscher K and Smith H (1968) Essential and nonessential trace elements: A method of determining whether an element is essential or nonessential in human tissue. Arch Environ Health 17:881-890.

Lindgren A, Danielsson BRG, Dencker L and Vahter M (1984) Embryotoxicity of arsenite and arsenate: distribution in pregnant mice and monkeys and effects on embroynic cells in vitro. Acta Pharmacol Toxicol 54:311-320.

Littlefield NA, and Gaylor DW (1985) Influence of total dose and dose rate in carcinogenicity studies. J Toxicol Environ Health 15:545-550.

Lofroth G and Ames BN (1978) Mutagenicity of inorganic compounds in Salmonella typhimurium: arsenic, chromium, and selenium. Mutat Res 54:65-66 (abstract), as reviewed in EPA 1984.

Lubin JH, Pottern LM, Blot WJ, Tokudome S, Stone BJ and Fraumeni JF (1981) Respiratory cancer mortality among copper smelter workers: recent mortality statistics. J Occup Med 23:779-784.

Lugo G, Cassady G and Palmisano P (1969) Acute maternal arsenic intoxication with neonatal death. Am J Dis Child 117:328-330.

Lundgren KD (1954) Diseases of the respiratory organs of workers at a smelting work. Nordisk Hygienisk Tidskrift, pp. 66-82.

Luria SE and Delbrück M (1943) Mutations of bacteria from virus sensitivity to virus resistance. Genetics 28:491.

Lyon JL, et al. (1977) Arsenical air pollution and lung cancer. Lancet 2:869, as reviewed in EPA 1984.

Mabuchi K and Lilienfeld A (1980) Reply to letter to the editor. Arch Environ Health 35:123-125.

Mabuchi K, Lilienfeld AM and Snell LM (1979) Lung cancer among pesticide workers exposed to inorganic arsenicals. Arch Environ Health 17:312-320.

Mahaffey KR and Fowler BA (1977) Effects of concurrent administration of lead, cadmium, and arsenic in the rat. Environ Health Perspect 19:165-171.

Maiorino RM and Aposhian HV (1985) Dimercaptan metal-binding agents influence the biotransformation of arsenite in the rabbit. Toxicol Appl Pharmacol 77:240-250.

Marafante E and Vahter M (1984) The effect of methyltransferase inhibition on the metabolism of 74-As arsenite in mice and rabbits. Chem-Biol Interactions 50:49-57.

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

Marafante E, Vahter M and Envall J (1985) The role of the methylation in the detoxication of arsenate in the rabbit. Chem-Biol Interactions 56:225-238.

Marczynski B (1988) Carcinogenesis as the result of the deficiency of some essential trace elements. Medical Hypotheses 26:239-249.

Martell, AE (1981) Chemistry of carcinogenic metals. Environ Health Perspect 40:207-226.

Martell, AE, Berlin M, Brubaker G et al. (1981) Chemistry and metatolism of metals relevant to their carcinogenicity. Environ Health Perspect 40:27-34.

Massman VW and Opitz H (1954) Experimentelle untersuchungen über ekg-veränderungen bei chronischer arsenvergiftung. Zeitschrift für Kreislaufforschung 43:704-713, as cited in EPA 1984.

Matanoski G, Landau E and Elliott E (1976) Epidemiology studies: Task I--Phase I. Pilot study of cancer mortality near an arsenical pesticide plant in Baltimore. Washington, DC: U.S. Environmental Protection Agency, May (EPA-560/6-76-003).

Mattson ME, Pollack ES, Cullen JW (1987) What are the odds that smoking will kill you? Am J Pub Health 77:425-431.

McCabe M, Maguire D and Nowak M (1983) The effects of arsenic compounds on human and bovine lymphocyte mitogenesis in vitro. Environ Research 31:323-331.

McCann, J (1986) Personal communication. Scientific Review Panel on Toxic Air Contaminants, State of California.

McMichael AJ (1976) Standardized mortality ratios and the "healthy worker effect:" Scratching beneath the surface. J Occup Med 18:165-168.

McMichael AJ, Haynes SG, Tyroler HA (1975) Observations on the evaluation of occupational mortality data. J Occup Med 17:128-131.

Milham S Jr and Strong T (1974) Human arsenic exposure in relation to a copper smelter. Environ Res 7:176-182, as reviewed in EPA 1984.

Milner J (1969) The effect of ingested arsenic on methylcholanthrene-induced skin tumors in mice. Arch Environ Health 18:7.

Mohelska H, Bencko V, Smetana K and Hyncia V (1980) Ultrastructural changes in hepatocytes of mice exposed to arenic in drinking water. Exper Pathol 18:275-281.

Morris HF (1978) Testimony on Proposed Standard for Exposure to Inorganic Arsenic (Exhibit 28B). Occupational exposures to inorganic arsenic: Final standard. Federal Register 43:19584-19629

Morris JS, Schmid M, Newman S, Scheuer PJ, Path MRC and Sherlock S (1974) Liver Physiology and Disease: Arsenic and noncirrhotic portal hypertension. Gastroenterology 64:86-94.

Morrissey RE and Mottet NK (1983) Arsenic-induced exencephaly in the mouse and associated lesions occurring during neurulation. Teratology 28:399-411.

Murphy MJ, Lyon LW and Taylor JW (1981) Subacute arsenic neuropathy: Clinical and electrophysiological observations. J Neurol Neurosurg Psychiatry 44:896-900.

Mushak P (1985) Potential impact of acid precipitation on arsenic and selenium. Environ Health Perspect 63:105-113.

Nagymajtényi L, Selypes A and Berencsi G (1985) Chromosomal aberrations and fetotoxic effects of atmospheric arsenic exposure in mice. J Appl Toxicol 5:61-63.

Nakamuro K and Sayato Y (1981) Comparative studies of chromosomal aberration induced by trivalent and pentavalent arsenic. Mutation Res 88:73-80.

NAS (National Academy of Sciences) (1977) Medical and Biologic Effects of Environmental Pollutants: Arsenic. Washington, DC: NAS.

NAS (National Academy of Sciences) (1977b) Drinking Water and Health. Vol. 1. Washington, DC: NAS.

Nelson WC, Lykins MH, Mackey J, Newill VA, Finklea JF and Hammer DI (1973) Mortality among orchard workers exposed to lead arsenate spray: A cohort study. J Chron Dis 26:105-118, as reviewed in EPA 1984.

Neubauer O (1947) Arsenical cancer: A review. British Journal of Cancer 1:192-245.

Newman JA, Archer VE, Saccomanno G et al. (1976) Histological types of bronchogenic carcinoma among members of copper-mining and smelting communities. Ann NY Acad Sci 271:260-268, 1976, as reviewed in EPA 1984.

Nielson FH (1985) Ultratrace elements current status: In: Nutrition Update, vol. 2, Weininger J and Briggs GM eds. New York: John Wiley & Sons,pp. 107-123.

NIOSH (National Institute for Occupational Safety and Health) (1973) Criteria for a recommended standard: Occupational exposure to inorganic arsenic. Washington, DC: U.S. Department of Health, Education, and Welfare.

NIOSH (1975) Criteria for a recommended standard: Occupational exposure to inorganic arsenic: New Criteria--1975. Washington, DC: U.S. Department of Health, Education, and Welfare.

Nishioka H (1975) Mutagenic activities of metal compounds in bacteria. Mutation Res 31:185-189.

Nordenson I, Beckman G, Beckman L and Nordström S (1978) Occupational and environmental risks in and around a smelter in northern Sweeden: II. Chromosomal aberrations in workers exposed to arsenic. Hereditas 88:47-50.

Nordenson I, Sweins A and Beckman L (1981) Chromosome aberrations in cultured human lymphocytes exposed to trivalent and pentavalent arsenic. Scand J Work Environ Health 7:277-281.

Nordenson I and Beckman L (1982) Occupational and environmental risks in and around a smelter in northern Sweden: VII. Reanalysis and follow-up of chromosomal aberrations in workers exposed to arsenic. Hereditas 96:175-181.

Nordström S, Beckman L and Nordenson I (1978a) Occupational and environmental risks in and around a smelter in northern Sweden: I. Variations in birth weight. Hereditas 88:43-46.

Nordström S, Beckman L and Nordenson I (1978b) Occupational and environmental risks in and around a smelter in northern Sweden: III. Frequencies of spontaneous abortion. Hereditas 88:51-54.

Nordström S, Beckman L and Nordenson I (1979a) Occupational and environmental risks in and around a smelter in northern Sweden: V. Spontaneous abortion among female employees and decreased birth weight in their offspring. Hereditas 90:291-296.

Nordström S, Beckman L and Nordenson I (1979b) Occupational and environmental risks in and around a smelter in northern Sweden: VI. Congenital malformations. Hereditas 90:297-302.

Norpoth K, Gottschalk D, Gottschalk I et al. (1980) Influence of vinyl chloride monomer (VCM) and As_2O_3 on rat liver cell proliferation after partial hepatectomy. J Cancer Res Clin Oncol 97:41-50.

NRC (National Research Council, Committee on the Biological Effects of Ionizing Radiation) (1980) The Effects on Populations of Exposure to Low Levels of Ionizing Radiation: 1980, Chapter 5: Somatic effects. Washington, DC: National Academy Press, pp. 135-148.

NTP (National Toxicology Program) (1985) Fourth Annual Report on Carcinogens. Washington, DC: U.S. Department of Health and Human Services.

Nunoshiba T and Nishioka H (1975) Sodium arsenite inhibits spontaneous and induced mutations in Escherichia coli. Mutation Res 184:99-105.

Oberly TJ, Piper CE and McDonald DS (1982) Mutagenicity of metal salts in the L5178Y mouse lymphoma assay. J Toxicol Environ Health 9:367-376.

Ohyama S, Ishinishi N, Hisanaga A and Yamamoto A (1988) Comparative chronic toxicity, including tumorigenicity, of gallium arsenide and arsenic trioxide intratracheally instilled into hamsters. Applied Organometallic Chemistry 2:333-337.

Okada S, Yamanaka K, Ohba H and Kawazoe Y (1983) Effect of inorganic arsenics on cytotoxicity and mutagenicity of ultraviolet light on Escherichia coli and the mechanism involved. J Pharm Dyn 6:496-504.

Oladimenji AA, Quadri SU and deFreitas ASW (1984) Long-term effects of arsenic accumulation in rainbow trout, Salmo gairdneri. Bull Environ Contam Toxicol 32:732-741.

Osato K (1977) Effects of oral administration of arsenic trioxide during the suckling stage of rats. Fukuoka Acta Med 68:464-491.

Osborne P (1984) Additional analysis of arsenic exposure in a copper smelter and its possible relation to respiratory cancer combining air and urine data. Submitted to the Graduate School of Public Health, University of Pittsburgh (Enterline P, faculty committee chairperson).

OSHA (Occupational Safety and Health Administration) (1978) Occupational exposure to inorganic arsenic. Federal Register 43:19584-19631.

OSHA (1983) Occupational exposure to inorganic arsenic. Federal Register 48:1864-1903.

Osswald H and Goerttler K (1971) Arsenic-induced leucoses in mice after diaplacental and postnatal application. Verh Dtsch Ges Path 55:289-293, as reviewed in EPA 1984.

Ott MG, Holder BB and Gordon HL (1974) Respiratory cancer and occupational exposure to arsenicals. Arch Environ Health 29:250-255.

Padney K and Shukla JP (1982) Deleterious effects of arsenic on the growth of fingerlings of a freshwater fish, Colisa fasciatus (Bl. & Sch.) Acta Pharmacol Toxicol 50:398-400.

Pagano G, Esposito A, Bove P et al. (1982) Arsenic-induced developmental defects and mitotic abnormalities in sea-urchin development. Mutation Res 104:351-354.

Passino DRM and Kramer JM (1980) Toxicity of arsenic and PCBs to fry of deepwater ciscoes (Coregonus). Bull Environ Contam Toxicol 24:527-534.

Passino DRM and Novak AJ (1984) Toxicity of arsenate and DDT to the cladoceran Bosmina longirostris. Bull Environ Contam Toxicol 33:325-329.

Paton GR and Allison AC (1972) Chromosome damage in human cell cultures induced by metal salts. Mutation Res 16:332-336.

Pearce N, Checkoway H, Shy C (1986) Time-related factors as potential confounders and effect modifiers in studies based on an occupational cohort. Scand J Work Environ Health 12:97-107.

Perry K, Bowler RG, Buckell HM, Druett HA and Schilling RSF (1948) Studies in the incidence of cancer in a factory handling inorganic arsenic compounds of arsenic: II. Clinical and environmental investigations. Brit J Indust Med 5:6.

Pershagen G (1981) The carcinogenicity of arsenic. Environ Health Perspect 40:93-100.

Pershagen G (1985) Lung cancer mortality among men living near an arsenic-emitting smelter. Am J Epidemiol 122:684-94.

Pershagen G (1990) Personal communication (letter). Karolinska Institutet, Stockholm, Sweden.

Pershagen G and Björklund N-E (1985) On the pulmonary tumorigenicity of arsenic trisulfide and calcium arsenate in hamsters. Cancer Letters 27:99-104.

Pershagen G, Elinder C-G and Bolander A-M (1977) Mortality in a region surrounding an arsenic-emitting plant. Environ Health Perspect 19:133-137, as reviewed in EPA 1984.

Pershagen G, Wall S, Taube A et al. (1981) On the interaction between occupational arsenic exposure and smoking and its relationship to lung cancer. Scand J Work Environ Health 7:302-309.

Pershagen G et al. (1983) (Pershagen G et al. 1984, as cited in EPA 1984).

Pershagen G, Nordberg G and Björklund N-E (1984) Carcinomas of the respiratory tract in hamsters given arsenic trioxide and/or benzo[a]pyrene by the pulmonary route. Environ Res 34:227-241.

Peto R (1978) Carcinogenic effects of chronic exposure to very low levels of toxic substances. Environ Health Perspect 22:155-159.

Peto J (1979) Dose-response relationships for asbestos-related disease: Implications for hygiene standards, Part 2: Mortality. Ann NY Acad Sci 330:195-203.

Phalen RF (1976) Inhalation exposure of animals. Environ Health Perspect 16:17-24.

Phalen RF and Oldham MJ (1983) Tracheobronchial airway structure as revealed by casting techniques. Am Rev Respir Dis 128:S1-S4.

Phalen RF, Oldham MJ, Beaucage CB et al. (1985) Postnatal enlargement of human tracheobronchial airways and implications for particle deposition. Anat Res 212:368-380.

Pinto SS and Bennett BM (1963) Effect of arsenic trioxide exposure on mortality. Arch Environ Health 7:583-591.

Pinto SS and McGill CM (1953) Arsenic trioxide exposure in inudustry. Indust Med Surg 22:281.

Pinto SS, Varner MO, Nelson KW, Labbe AL and White LD (1976) Arsenic trioxide absorption and excretion in industry. J Occup Med 18:677.

Pinto SS, Enterline PE, Henderson V and Varner MO (1977) Mortality experience in relation to a measured arsenic trioxide exposure. Environ Health Perspect 19:127-130.

Pinto SS, Henderson VH and Enterline PE (1978) Mortality experience of arsenic-exposed workers. Arch Environ Health 33:325.

Piper CE, McCarroll NE and Oberly TJ (1979) Mutagenic activity of an organic arsenical compound detected with L5178y mouse lymphoma cells. Environ Mutagenesis 1:165.

Piscator M (1981) Toxic metals of clinical importance. In: Nutrition in Health and Disease and International Development, symposia from the XII International Congress of Nutrition, pp. 209-217.

Piscator M (1986a) Personal communication (conversation). Karolinska Institute, Stockholm, Sweden.

Piscator M (1986b) Personal communication (letter). Karolinska Institute, Stockholm, Sweden.

Plopper CG (1983) Comparative morphologic features of bronchiolar epithelial cells: The Clara cell. Am Rev Respir Dis 128:S37-S41.

Poma K (1984) No synergism between caffeine and arsenic in the induction of chromosomal aberrations in bone-marrow cells and spermatogonia of mice. Mut Res 130:202.

Poma K, Kirsch-Volders M and Susanne C (1984) Lack of synergistic effect between arsenic, mercury and ethyl methane sulfonate on the frequency of chromosomal aberrations in mice. J Appl Toxicol 4:293-296.

Poma K, Degraeve N, Kirsch-Volders M and Susanne C (1981) Cytogenetic analysis of bone marrow cells and spermatogonia of male mice after in vitro treatment with arsenic. Experientia 37:129-130.

Puzanova L (1980) Teratogenic effect of different toxic elements on young chick embroyos. Folia Morphologica 28:354-356.

Rencher AC, Carter MW and McKee DW (1977) A retrospective epidemiological study of mortality at a large western copper smelter. J Occup Med 19:754-758.

Robins J (1986) A new approach to causal inference in mortality studies with a sustained exposure period -- application to control of the healthy worker survivor effect. Mathematical Modeling 7:1393-1512.

Rom WN, Varley G, Lyon JL, and Shapkow S (1982) Lung cancer mortality among residents living near the El Paso smelter. Br J Ind Med. 39:269-272, as reviewed in EPA 1984.

Rosen P (1971) Theoretical significance of arsenic as a carcinogen. J Theor Biol 32:425-426.

Rosin MP (1985) *In vitro* synergistic effects of combinations between cigarette smoke and arsenic, chromium, or formaldehyde. In: *Carcinogens and Mutagens in the Environment*, Vol. 4, Stich HF ed. Boca Raton, FL: CRC Press, Inc., pp. 127-133.

Rosner MH and Carter DE (1987) Metabolism and excretion of gallium arsenide and arsenic oxides by hamsters following intratracheal instillation. Fundamental and Applied Toxicology 9:730-737.

Rossman TG, Stone D, Molina M, and Troll W (1980) Absence of arsenite mutagenicity in *E. coli* and Chinese hamster cells. Environ Mutagenesis 2:371-379.

Rossman TG (1981a) Enhancement of UV-mutagenesis by low concentrations of arsenite in *E. coli*. Mutation Res 91:207-211.

Rossman TG (1981b) Effect of metals on mutagenesis and DNA repair. Environ Health Perspect 40:189-195.

Roth F (1958) Uber den bronchialkrebs arsengeschodigter winzer. Virchows Arch 331:119-137 (The sequelae of chronic arsenic poisoning in Moselle Vintners. Ger Med Mon 2:172-175, 1957).

Rothman KJ, Greenland S and Walker AM (1980) Concepts of interaction. Am J Epidemiol 112:467-470.

Rozenshtein IS (1970) Sanitary toxicological assessment of low concentrations of arsenic trioxide in the atmosphere. Hygiene and Sanitation 35:16.

Rudnai P and Börzönyi M (1981) Tumor-inducing effect of arsenic trioxide treatment in CFLP mice (translated title). Magyar Onkológia 25:73-77, as reviewed in EPA 1984.

Ruth RC and Weglicki WB (1982) Effects of ATP on lysosomes: Inhibition of the loss of latency caused by cooling. Am J Physiol 242:C192-C199.

Sanderson KV (1961) Arsenic as a cocarcinogen in mice. British Empire Cancer Campaign, 39th Annual Report, pp. 628-629.

Sandstrom AIM, Wall SGI, Taube A (1989) Cancer incidence and mortality among Swedish smelter workers. Brit J Indust Med 46:82-89.

Schneiderman MA, Decouflé P and Brown CC (1979) Thresholds for environmental cancer: biologic and statistical considerations. Ann NY Acad Sci 329:92-130.

Schoolmeester WL and White DR (1980) Arsenic poisioning. Southern Med J 73:198-208.

Schrauzer GN and Ishmael D (1974) Effects of selenium and of arsenic on the genesis of spontaneous mammary tumors in inbred C3H mice. Ann Clin Lab Sci 4:441-447.

Schrauzer GN, White DA and Schneider CJ (1977) Cancer mortality correlation studies--IV: Associations with dietary intakes and blood levels of certain trace elements, notably Se-antagonists. Bioinorganic Chem 7:35-56.

Schrauzer GN, White DA, McGinness, JE, Schneider CJ and Bell LJ (1978) Arsenic and cancer: Effects of joint administration of arsenite and selenite on the genesis of mammary adenocarcinoma in inbred female C3H/St Mice. Bioinorganic Chemistry 7:245-253.

Schroeder HA and Balassa JJ (1967) Arsenic, germanium, tin and vanadium in mice: Effects on growth, survival, and tissue levels. J Nutrition 92:245-252.

Schroeder HA and Mitchener M (1971) Toxic effects of trace elements on the reproduction of mice and rats. Arch Environ Health 23:102-106.

Shabad LM, Pylev LN and Kolesnichenko TS (1964) Importance of the deposition of carcinogens for cancer induction in lung tissue. J Natl Cancer Inst 33:135.

Shariatpanahi M and Anderson AC (1985) Fate of sodium arsenate in dairy sheep and goats. Biol Trace Element Res 8:37-46.

Shimp D (1986, 1987) Personal communication. Air Resources Board, State of California.

Shirachi DY, Tu S-H and McGown JP (1982) Effect of prolonged exposure to arsenic compounds on rat hepatic gamma-glutamyltranspeptidase (GGTASE) activity. Federation Proceedings 41:Abstr. 6082.

Shirachi DY, Johansen MG, McGowan JP and Tu S-H (1983) Tumorigenic effect of sodium arsenite in rat kidney. Proc West Pharmacol Soc 26:413-415.

Shukla JP and Pandey K (1984a) Impaired ovarian functions in arsenic-treated freshwater fish, Colisa fasciatus (Bl. and Sch.). Toxicol Letters 20:1-3.

Shukla JP and Pandey K (1984b) Impaired spermatogenesis in arsenic treated freshwater fish, Colisa fasciatus (Bl. and Sch.). Toxicol Letters 21:191-195.

Shukla JP and Pandey K (1984c) Arsenic-induced cellular and biochemical changes during the testicular cycle of a freshwater perch, Colisa fasciatus (Bl. and Sch.). Cell Molec Biol 30:227-231.

Shunichi A, Hiroshi A and Katsuyuki M (1986) Adjustment of urinary concentration to urinary volume in relation to erythrocyte and plasma concentrations: An evaluation of urinary heavy metals and organic substances. Arch Environ Health 41:3

Simmon VP, Mitchell AD and Jorgenson TA (1977) Evaluation of selected pesticides as chemical mutagens: In vitro and in vivo studies. U.S. EPA, Office of Research and Development, Health Effects Research Laboratory, Research Triangle Park, NC 27711 (EPA-600/1-77-028).

Singh I (1983) Induction of reverse mutation and mitotic gene conversion by some metal compounds in Saccharomyces cerevisiae. Mutation Res 117:149.

Smith DC, Sandi E and Leduc R (1972) Pesticide residues in the total diet in Canada II--1970. Pesticide Sci 3:207-210.

Smith DC, Leduc R and Charbonneau C (1973) Pesticide residues in the total diet in Canada III--1971. Pesticide Sci 4:211-214.

Smith GH, Lloyd OL and Hubbard FH (1986) Soil arsenic in Armadale, Scotland. Arch Environ Health 41(2):120-122.

Smith TJ, Crecelius EA and Reading JC (1977) Airborne arsenic exposure and excretion of methylated arsenic compounds. Environ Health Perspect 19:89-93.

Sobel W, Bond GG, Baldwin CL, Ducommun DJ (1988) An update of respiratory cancer and occupational exposure to arsenicals. Am J Indust Med 13:263-270.

Sorensen EMB, Ramirez-Mitchell R, Harlan CW and Bell JS (1980) Cytological changes in the fish liver following chronic, environmental arsenic exposure. Bull Environ Contam Toxicol 25:93-99.

Sorensen EMB and Smith N (1981) Hemosiderin granules: Cytotoxic response to arsenic exposure in channel catfish. Bull Environ Contam Toxicol 27:645-653.

Spath D (1987) Personal communication. Department of Health Services, State of California.

Spehar RL, Fiandt JT, Anderson RL, and DeFoe DL (1980) Comparative toxicity of arsenic compounds and their accumulation in invertebrates and fish. Arch Envirionm Contam Toxicol 9:53-63.

Spicer SS, Schulte BA and Thomopoulos GN (1983) Histochemical properties of the respiratory tract epithelium in different species. Am Rev Respir Dis 128:S20-S26.

Sram RJ (1976) Relationship between acute and chronic exposures in mutagenicity studies in mice. Mutation Res 41:25-42.

Sunderman FW Jr. (1976) A review of the carcinogenicities of nickel, chromium and arsenic compounds in man and animals. Preventive Med 5:279-294.

Sunderman FW Jr. (1978) Carcinogenic effects of metals. Federation Proceedings 37:40-46.

Symons MJ and Taulbee JD (1981) Practical considerations for approximating relative risk by the standardized mortality ratio. J Occup Med 23:413-416.

Tam GHK, Charbonneau SM, Bryce F, Pomroy C, and Sandi E (1979) Metabolism of inorganic arsenic (^{74}As) in humans following oral ingestion. Toxicol Appl Pharmacol 50:319-322.

Taylor PR, Qiao Y-L, Schatzkin A, Yao S-X, Lubin J, Mao B-L, Rao J-Y, McAdams M, Xuan X-Z, Li J-Y (1989) Relation of arsenic exposure to lung cancer among tin miners in Yunnan Province, China. Brit J Indust Med 46:881-886.

Taylor RT, Stewart SA and Hanna ML (1984) Cocytotoxicity/comutagenicity of arsenic in a chinese hamster ovary triple auxotroph. In: Trace Substances in Environmental Health--XVIII, Hemphill DD ed. Columbia, MO: University of Missouri, pp. 64-77.

Thienes CH and Haley TJ (1972) Clinical Toxicology, 5th ed. Philadelphia: Lea & Febiger.

Thomson VE, Jones A, Haemisegger E and Steigerwald B (1985) The air toxics problem in the United States: An analysis of cancer risks posed by selected air pollutants. J Air Pollution Control Assn 35:535-540.

Tokudome S and Kuratsune M (1976) A cohort study on mortality from cancer and other causes among workers at a metal refinery. Int J Cancer 17:310-317.

Tola S and Hernberg S (1983) Healthy worker effect. In: Methods and Issues in Occupational and Environmental Epidemiology, Chiazze L, Lundin FE and Watkins D eds. Ann Arbor, MI: Ann Arbor Science pp. 85-92.

Travis LB and Arndt KA (1986) Occupational skin cancer: Four major carcinogens that put workers at risk. Postgrad Med 79:211-217.

Tseng W-P (1977) Effects and dose-response relationships of skin cancer and blackfoot disease with arsenic. Environ Health Perspect 19:109-119.

Tseng WP, Chu HM, How SW, Fong JM, Lin CS and Yeh S (1968) Prevalence of skin cancer in an endemic area of chronic arsenicism in Taiwan. J Nat Cancer Inst 40:453-463.

Tsukamoto H, Parker HR, Gribble DH, Mariassy A and Peoples, SA (1983) Nephrotoxicity of sodium arenate in dogs. Am J Vet Res 44:2324-2330.

Tsutsui T, McLachlan JA, Hesterberg TW, Oshimura M, Lamb P and Barrett JC (1984) Correlation between mutagenicity and cell transformation. In: Proceedings of the 75th Annual Meeting of the American Association for Cancer Research, vol. 25. Toronto: American Association for Cancer Research, p. 392.

Tsutsumi S, Takako T, Kawaguchi M, Ishizuka S and Matsumoto Y (1980) Effects of arsenic trioxide (As_2O_3) on the uptake of ^{3}H-Thymidine in lymphocytes of mice. Bull Tokyo Dent Coll 21:63-70.

Tyler WS (1983) Small airways and terminal units: Comparative subgross anatomy of lungs: Pleuras, interlobular septa, and distal airways. Am Rev Respir Dis 128:S32-S36.

Ungers LJ, Jones JH, McIntyre AJ and McHenry CR (1985) Release of arsenic from semiconductor wafers. Am Indust Hyg Assoc J 46:416-420.

U.S. Borax (1989) An analysis of the potential of arsenic as a carcinogen and reproductive toxicant. Anaheim, CA: U.S. Borax Research Corporation, March. Submitted to the Undersecretary, Health and Welfare Agency, State of California (1600 Ninth Street, Sacramento, CA 95814), by the United States Borax & Chemical Corporation (3075 Wilshire Blvd., Los Angeles, CA 90010), with a letter from Eugene D. Smith, Vice President, Government & Public Affairs, dated May 2, 1989.

U.S. Department of Health and Human Services (1986) Vital Statistics of the United States 1982, Volume 2, Mortality, Part A. Hyattsville, MD: National Center For Health Statistics.

U.S. Department of Health and Human Services (1985) Health United States 1985, DHHS Pub. No. (PHS) 86-1232, Hyattsville, MD: National Center for Health Statistics.

Uthus EO, Cornatzer WE and Nielsen FH (1983) Consequences of arsenic deprivation in laboratory animals. In: Arsenic: Industrial, Biomedical, Environmental Perspectives, Lederer WH and Fensterheim RJ eds. New York: Van Nostrand Reinhold Company, pp. 173-189.

Vahter M and Envall J (1983) In vivo reduction of arsenate in mice and rabbits. Environ Res 32:14-24.

Vahter M and Marafante E (1985) Reduction and binding of arsenate in marmoset monkeys. Arch Toxicol 57:119-124.

Vahter M and Norin H (1980) Metabolism of ^{74}As-labeled trivalent and pentavalent inorganic arsenic in mice. Environ Res 21:446-457.

Vahter M, Friberg L, Rahnster B, Nygren A and Nolinder P (1986) Airborne arsenic and urinary excretion of metabolites of inorganic arsenic among smelter workers. Int Arch Occup Environ Health (1986) 57:79-91.

Valentine JL, Kang HK and Spivey G (1979) Arsenic levels in human blood, urine, and hair in response to exposure via drinking water. Environ Res 20:24-32.

Valkonen S, Savolainen H and Jarvisallo J (1983) Arsenic distribution and neurochemical effects in peroral sodium arsenite exposure of rats. Bull Environ Contam Toxicol 30:303-308.

Vallee BL, Ulmer DD and Wacker WEC (1960) Arsenic toxicology and biochemistry. Arch Indust Health 21:132.

Van Ryzin J (1983) Quantitative risk assessment. J Occup Med 22:321-326.

Von Glahn WC, Flinn FB and Keim WF (1938) Effect of certain arsenates on the liver. Arch Pathol 25:488-505.

Vos JG (1977) Immune suppression as related to toxicology. CRC Crit Rev Toxicol 5:67-101.

Walder BK, Robertson MR and Jeremy D (1971) Skin cancer and immunosuppression. Lancet, Dec. 11, p. 1282.

Wall S (1980) Survival and mortality pattern among Swedish smelter workers. Int J Epidemiol 9:73-87.

Wan B, Christian RT and Soukup SW (1982) Studies of cytogenetic effects of sodium arsenicals on mammalian cells in vitro. Environ Mutagenesis 4:493-498.

Waters MD, Garrett NE, Covone-de Serres CM, Howard BE and Stack HF (1983) Genetic toxicology of some known or suspected human carcinogens. In: Chemical Mutagens: Principles and Methods for Their Detection, Vol. 8, de Serres FJ, ed. New York: Plenum Press.

Watrous RM and McCaughey MB (1945) Occupational exposure to arsenic. Indust Med 14:639-646.

Weiler RR (1986) Personal communication. Ministery of the Environment, Ontario, Canada.

Weinberg SL (1960) The electrocardiogram in acute arsenic poisoning. Am Heart J 60:971-975.

Weiss W (1983) Letter to the editor. Arch Environ Health 38:189-190.

Welch K, Higgins I, Oh M and Burchfiel C (1982) Arsenic exposure, smoking, and respiratory cancer in copper smelter workers. Arch Environ Health 37:325-335.

Wen WN, Lieu TL, Chang H-J et al. (1981) Baseline and sodium arsenite-induced sister chromatid exchanges in cultured lymphocytes from patients with Blackfoot disease and healthy persons. Human Genet 59:201-203.

Wester PO, Brune D and Nordberg G (1981) Arsenic and selenium in lung, liver, and kidney tissue from dead smelter workers. Brit J Indust Medicine 38:179-184.

Wicklund KG, Daling JR, Allard J, Weiss NS (1988) Respiratory cancer among orchardists in Washington State, 1968 to 1980. J Occup Med 30:561-564.

Willhite CC (1981) Arsenic-induced axial skeletal (dysraphic) disorders. Exper Molecu Path 34:145-158.

Willhite CC (1985, 1986a) Personal communication. Department of Health Services, State of California.

Willhite CC and Ferm VH (1984) Prenatal and developmental toxicology of arsenicals. In: Nutritional and Toxicological Aspects of Food Safety Friedman M, ed. New York: Plenum Publishing Corporation, pp. 205-228.

Winship KA (1984) Toxicity of inorganic arsenic salts. Adv Drug React Ac Pois Rev 3:129-160.

Woods JS and Fowler BA (1977) Effects of chronic arsenic exposure on hematopoietic function in adult mammalian liver. Environ Health Perspect 19:209-213.

Wu W (1988) Occupational cancer epidemiology in the People's Republic of China. J Occup Med 30:968-974.

Yamauchi H and Yamamura Y (1984a) Metabolism of orally administered dimethylarsinic acid in the hamster. Toxicol Appl Pharmacol 74:134-140.

Yamauchi H and Yamamura Y (1984b) Metabolism of orally ingested trimethylarsenic in man. Bull Environ Contam Toxicol 32:682-687.

Yamauchi H and Yamamura Y (1985) Metabolism of orally administered arsenic trioxide in the hamster. Toxicology 34(2):113-121.

Zakour RA, Kunkel TA and Loeb LA (1981) Metal-induced infidelity of DNA synthesis. Environ Health Perspect 40:197-205.

Zaldívar R and Gullier A (1977) Environmental and clinical investigations on endemic chronic arsenic poisoning in infants and children. Zbl Bakt Hyg, I Abt Orig B 165:226-234.

Zaldívar R and Ghai A. (1980) Mathematical model of mean age, mean arsenic dietary dose and age-specific prevalence rate from endemic chronic arsenic poisoning: A human toxicology study. Zbl Bakt Hyg, I Abt Orig B 170:402-408.

Zaldívar R, Villar I, Wetterstrand WH and Robinson H (1978) Epidemiological, dietary, toxicological and clinical nutrition studies on low-income population groups from a geographical area with endemic chronic arsenic poisoning. Zbl Bakt Hyg, I Abt Orig B 167:242-247.

Zanzoni F and Jung EG (1980) Arsenic elevates the sister chromatid exchange (SCE) rate in human lymphocytes in vitro. Arch Dermatol Res 267:91-95.

Zeise L, Wilson R and Crouch EAC (1987) Dose-response relationships for carcinogens: A review. Environ Health Perspect 73:259-308.