

DRAFT

81MR R1018

BENZENE

Thomas R. Bartman
March 1981

Graduate School of Industrial Administration,
Carnegie-Mellon University

This work was done under a contract with the American
Petroleum Institute.

	<u>Page</u>
Summary and Conclusions	i
I. Chronology	1
II. Health Effects of Benzene	
A. Summary	
B. Review	
C. Leukemogenicity	
Thorpe Study	
Infante Study	
Aksoy Study	
Ott Study	
D. Non-Malignant Blood Disorders	
Effects on Fetal Development	
E. Chromosomal Effects	
III. Agency Quantitative Risk Assessment	
A. OSHA	
EPA	
B. Critique: OSHA	
EPA	
Appendix A: Review of CAG Risk Assessment	
Appendix B: Risk Assessment in Reply Brief for the Federal Parties	
Appendix C: Outside Pressures on OSHA	
Appendix D: Background on EPA Risk Assessment	

DO 068061
CONFIDENTIAL

YZ0015898

Summary and Conclusions

Benzene, one of the most extensively used petrochemicals, has adverse effects on the formed elements of the blood, and damages chromosomes. In 1977, OSHA issued an Emergency Temporary Standard and then a permanent standard lowering exposure in the workplace from 10 to 1 ppm, based on what it termed new evidence of an excess incidence of leukemia among rubber workers. In 1977, EPA relied upon the same body of evidence to list benzene as a hazardous air pollutant.

OSHA's new standard never took effect. The Emergency Temporary Standard was stayed and the permanent standard was vacated. The Court of Appeals for the Fifth Circuit held in 1978 that OSHA had failed to show a reasonable relationship between the benefits sought and the cost of lowering the standard. In 1980 a divided Supreme Court affirmed, holding that OSHA had not shown that benzene exposure under the existing 10 ppm standard involved a significant risk; apparently, OSHA was required to show that significant benefits would result from lowering the standard. EPA subsequently held hearings on the first step of its regulation of atmospheric benzene exposure from various sources starting with maleic anhydride plants.

Extensive evidence links benzene to leukemia and various nonmalignant blood disorders in humans and some evidence indicates a connection to fetotoxic effects in rodents. The failure to observe a leukemic response in animals until recently means

DO 068062
CONFIDENTIAL

YZ0015899

that scientists have lacked until now an important link establishing carcinogenicity and some have been cautious in identifying benzene as a carcinogen. Excess leukemia has been found in several epidemiological studies; but unfortunately the meaning of these studies and those finding no significant effect are obscured by the failure to measure actual exposure levels. Quantitative risk analysis is complicated by the lack of knowledge concerning the physiological mechanisms by which benzene causes leukemia, by the lack of exposure data, by the possibility of exposure to benzene from other sources, and other leukemogens, and a latency period of up to twenty years. Studies of humans exposed to benzene for long periods show a reduction in the formed elements of the blood, a non-malignant blood disorder. This effect can develop into aplastic anemia and may promote the development of leukemia, but effects caused by low exposures appear to be reversible. Occupational studies appear to have found effects at 40 ppm and below, but exposure can only be guessed. There is also evidence of chromosomal damage that can persist for long periods of time.

Non-malignant blood effects are confirmed by animal bioassays. There is some evidence of blood changes at an exposure of 44 ppm. Benzene has not produced leukemia in laboratory experiments. Chromosomal changes in laboratory animals replicate human effects. There is limited evidence such damage occurs down to

about 2 ppm. The significance of chromosomal changes is uncertain. Benzene has been found to reduce litter size, retard embryonic development, and cause other fetotoxic effects in rodents. These effects appear to occur as low as 10 ppm.

Although OSHA had recently rejected suggestions that it revise the benzene standard, in 1976 the newly designated Assistant Secretary of Labor for OSHA, Eula Bingham, began to organize an effort to revise the standard. Dr. Bingham saw benzene as a symbolic issue and placed a high priority on tightening the standard. She influenced Dr. Infante to compile and publish a preliminary assessment of his epidemiological study of rubber workers. Based on this evidence, OSHA published an Emergency Temporary Standard and rushed to establish a permanent standard. Allowing political, rather than scientific forces to raise the issue and then proceeding with unseemly speed to publish a standard led OSHA to ignore any calculations concerning the risk to workers and to reject an analysis submitted during the hearing. Instead, OSHA argued that no level of exposure to a carcinogen could be considered safe and that the standard should be set at the lowest level that was technically feasible and would not put the affected industry out of business.

A quantitative examination of risk would have clarified the issues. Careful examination of the various epidemiological and bioassay studies would have avoided embarrassing misinterpretations. Using risk assessment to set priorities would have focused OSHA's resources on more serious hazards.

By contrast, EPA based its proposed maleic anhydride plant standard on a combination of reviewing health effects, estimating human exposures to atmospheric benzene, and quantitative risk assessment. While agreeing with OSHA that there is no safe level of exposure to a carcinogen, EPA used quantitative risk assessment to consider the risks and costs of exposure at various alternative standards. EPA's proposed final standard included an estimate of expected costs and benefits. While the analysis could have been improved in some aspects, EPA demonstrated the feasibility of a quantitative risk assessment for benzene and isolated many of the crucial issues in setting a standard. Whatever the ultimate fate of the proposed standard, the issues have been stated clearly, the scientific basis for the standard has been clarified, and both the scientific uncertainties and value conflicts can be addressed with greater clarity.

I. REGULATORY CHRONOLOGY

The present Occupational Safety and Health Administration (OSHA) standard for benzene was adopted from the consensus standard of the American National Standards Institute in 1971. Based on benzene's general toxic effects on the blood, the standard prescribes an 8-hour time weighted average (TWA) of 10 ppm and a ceiling concentration of 25 ppm, and permits excursions to a peak of 50 ppm for no more than 10 minutes per 8-hour period. In 1974, the National Institute for Occupational Safety and Health (NIOSH), the research complement of OSHA, compiled a criteria document on occupational exposure to benzene that recommended retention of the 10 ppm TWA and 25 ppm ceiling standard (NIOSH, 1976).

In a letter dated April 23, 1976, the United Rubber, Cork, Linoleum, and Plastic Workers of America urged the Secretary of Labor to issue an emergency standard regulating benzene (43 FR 5917). Secretary William J. Usery denied the request on May 18, 1976, noting the lack of sufficient scientific evidence to warrant a change in the standard and indicating that other means of controlling benzene exposure were being taken (Usery, 1976).

Later in 1976, a panel of scientists at the National Academy of Sciences reviewed for EPA the information on health effects of benzene and concluded that benzene should be considered a suspect leukemogen (Committee on Toxicology, 1976). In August 1976, NIOSH submitted a revised criteria document that found benzene to be a leukemogen (43 FR 5917). NIOSH recommended that since no safe level for benzene exposure could be established, no worker should

be exposed to more than 1 ppm. The Director of NIOSH recommended a 1 ppm emergency standard to the Secretary of Labor by letter dated October 27, 1976 (43 FR 5917 at 5919).

Based on the recommendations of NIOSH, OSHA issued voluntary "Guidelines for Control of Occupational Exposure to Benzene" on January 14, 1977 (43 FR at 5919). The guidelines, which were based on benzene's leukemogenicity, urged that the benzene concentration in the air not exceed an 8-hour TWA of 1 ppm per 8-hour shift. On April 15, 1977, NIOSH conveyed the preliminary findings of its epidemiological study of two Ohio rubber manufacturing plants to OSHA and again urged the setting of a 1 ppm emergency standard (43 FR at 5919).

On May 3, 1977, OSHA issued a 1 ppm Emergency Temporary Standard (ETS) for Occupational Exposure to Benzene (42 FR 22516) to take effect on May 17.^{1/} The Fifth Circuit Court of Appeals, ruling on legal challenges,^{2/} issued a temporary restraining order on May 20, 1977, and the ETS never went into effect.

On May 27, 1977, OSHA published a proposed permanent standard incorporating the 1 ppm ceiling (43 FR 5917). The standard

^{1/} Before issuing an ETS, OSHA must find "that employees are exposed to grave danger from exposure to substances determined to be toxic or physically harmful or from new hazards, and ... that such emergency standard is necessary to protect employees from such danger" 29 USC §655(c).

^{2/} Petitioners, including the American Petroleum Institute and other industry groups, attacked the reduction of the exposure standard to 1 ppm, the prohibition of dermal contact, and engineering and work practice prescriptions.

also prohibited any dermal contact with benzene. OSHA subsequently amended the standard to exempt operations where the only exposure was to liquids containing no more than 1% benzene and no more than .1% as of 1981. OSHA held hearings on the standard from July 19 through August 10 with witnesses from agencies, affected industries, unions, and other members of the public. OSHA also published a draft environmental impact statement for its standard on June 17 (42 FR 27455).

During the same period in 1977, EPA was petitioned by the Environmental Defense Fund (EDF) to list benzene as a hazardous air pollutant under Section 112 of the Clean Air Act (April 4). Following consultations with OSHA on its regulatory action and with NIOSH and in response to the EDF petition, EPA listed benzene as a hazardous air pollutant on June 8, 1977 (42 FR 29332). During 1978, EPA issued an "Assessment of Health Effects of Benzene Germane to Low-Level Exposure" (EPA 1978a), its Carcinogen Assessment Group's evaluation of benzene's leukemogenic risk and an "Assessment of Human Exposure to Atmospheric Benzene" (1978b). These documents formed the basis of EPA's plan to regulate benzene emissions from various sources, starting with a proposed benzene emission standard for maleic anhydride plants (1980).

The Fifth Circuit ruled on the challenges to OSHA's 1 ppm permanent standard on October 5, 1978 (American Petroleum Institute v. OSHA, 581 F.2d 493 (5th Cir. 1978)), setting aside the

standard. The court cited the absence of substantial evidence showing a reasonable relationship between the measureable benefits sought by reducing exposure and the significant cost of the regulation to the affected industries. The court also set aside OSHA's prohibition of any dermal contact, holding that the standard was based on dated and inconclusive data.

The Supreme Court heard oral argument October 10, 1979, in OSHA's appeal of the Fifth Circuit decision. The government argued that the benzene standard was based on the best available scientific evidence, which supported the no-threshold hypothesis. It further contended that both the lack of data on a safe level of exposure to benzene and the policy assumption that there is no safe level for a carcinogen required the standard to be set at the lowest feasible level, namely 1 ppm. The government argued further that the OSH Act did not require that a standard be based on a cost-benefit analysis. The American Petroleum Institute and associated groups argued that studies did not show there was an excess risk of leukemia at low concentrations of benzene and that OSHA had failed to show that the standard would produce material or appreciable benefits.

The Supreme Court affirmed the Fifth Circuit's decision on July 2, 1980 (Industrial Union Department, AFL-CIO v. American Petroleum Institute, 100 S. Ct. 2844). Two other justices joined in Justice Stevens' plurality opinion holding that OSHA had made no showing that a significant health risk was associated with the

existing 10 ppm standard. Rather, the court held that OSHA had lowered the benzene standard based on a series of assumptions about the risk at 10 ppm and about a reduction in risk that might result from a 1 ppm standard. The court found that OSHA lacks statutory authority to regulate to a completely risk-free 1 v 1. OSHA must show that appreciable benefits will result from reducing exposure. Three justices held that OSHA had made no attempt to show that chronic exposure to 10 ppm of benzene would more likely than not result in a significant risk of material health impairment.

Justice Powell stated in a separate opinion that while OSHA tried but failed to show by substantial evidence a hazard at 10 ppm, OSHA must also demonstrate that the economic effects of the standard bear a reasonable relationship to its expected benefits. Justice Rehnquist voted to vacate the standard because Congress had unlawfully delegated authority with no guiding principles. Justice Marshall's dissent, joined by three justices, asserted that the plurality's requirement of a threshold showing of significant risk at 10 ppm had no statutory basis.

As a first step in a program for reducing population exposure to benzene emitted into the atmosphere from a range of sources, EPA proposed an Emission Standard for Hazardous Air Pollutants, Benzene Emissions from Maleic Anhydride Plants (45 FR 26660) on April 18, 1980. The proposed standard would require 97 percent control (100 percent for new plants) of benzene

emissions from maleic anhydride plants.^{3/} Hearings on the proposed standard were held in August 1980. Comments by interested parties included the claim that using the same data and modified assumptions, EPA's risk assessment model shows that the risk of benzene exposure was not significant. EPA has subsequently not finalized its maleic anhydride standard but has proposed standards for other emission sources (Benzene Emissions from Benzene Storage Vessels, 45 FR 83952).

II. HEALTH EFFECTS OF BENZENE

A. Summary

Epidemiological studies, animal bioassays, and other reports have implicated benzene, one of the most extensively used chemicals, in increased incidences of leukemia, non-malignant blood disorders, and effects on chromosomes and embryonic development. Exposure to benzene at high concentrations has been accepted as leukemogenic in humans on the basis of numerous individual medical reports, discovered coincidences between the introduction of benzene and increased leukemia rates in occupational settings, and epidemiological studies. Although there is some evidence of effects at lower exposures, leukemias have been generally shown following exposure to concentrations in the area of 100 ppm and

^{3/} While 80 percent of benzene in the ambient air results from mobile emissions, regulation of maleic anhydride plant emissions constituting 35 percent of emissions from chemical manufacturing was undertaken under §112 of the Clean Air Act, which covers only stationary sources.

over. Research, however, was until recently hampered by lack of an animal model and by uncertainties about the mechanism of benzene leukemogenicity. The significance of the few epidemiological occupational studies is limited by the lack of dosage data. The three studies relied upon by EPA in its quantitative risk assessment involve additional uncertainties about the size of the population at risk and the role of unknown prior histories of workers. In sum, the available dose-response data are limited.

The typical symptom of chronic benzene toxicity is reduction in the formed elements of the blood (pancytopenia). Blood effects can develop into fatal aplastic anemia and may participate in the development of leukemia, but effects caused by low exposures are apparently reversible. There is some evidence of blood changes in animals at an exposure of 44 ppm. Occupational studies lack accurate dosage data and have generally been based on small populations. They have offered some evidence of effects at 40 ppm and lower.

Specialized research into fetal malformation caused in rodents by benzene exposure has indicated that benzene is probably not teratogenic. Exposure by inhalation and other means has, however, shown fetotoxic effects in rodents, such as reduced litters, retarded embryonic development, and fetal resorptions. Dose-response correlations for these effects are inconsistent, with some evidence of effects around 10 ppm. The limited results

of related studies on humans suggest effects on reproductive organs in females. The meaning of the animal studies for research into benzene effects on humans is complicated by the obvious differences between man and animal in terms of fetal development.

Occupational and animal studies show that benzene, like other known carcinogens, causes chromosomal damage. Benzene exposure reduces DNA synthesis, an effect that evidently persists for considerable periods. Human studies have had to cope with small populations, uncertain dosages, and confounding factors such as age, the spontaneous occurrence of chromosomal changes, and damage resulting from laboratory techniques. There is some epidemiological evidence of chromosomal effects following occupational inhalation exposure of around 2 ppm. While the significance of effects on chromosome number and structure is quite uncertain, such effects may participate in the transition from a non-malignant blood disorder to leukemia.

B. Review of Health Effects

Benzene is a clear, colorless liquid used extensively in the petrochemical and refining industries. An estimated 11 billion pounds of benzene were produced domestically in 1976. It is used as the raw material for other organic chemicals, is found in detergents and pesticides (and formerly solvents), and is a constituent of gasoline, generally in concentrations of less than two percent (in the United States). OSHA estimates that 190,000

DO 068073
CONFIDENTIAL

YZ0015910

workers are occupationally exposed to benzene.^{4/} EPA estimates that 110 million people are exposed to atmospheric benzene at concentrations from a few parts per billion to .5 parts per million due to manufacturing processes and automobile emissions.^{5/}

Benzene,^{6/} which evaporates rapidly due to its low boiling point and high vapor pressure, enters the body primarily through inhalation. It diffuses rapidly through the lungs and is readily absorbed. Its primary effect is on the bloodforming organs and the classic finding is a reduction in the number of platelets and red and white blood cells (pancytopenia). Benzene has also been causally associated with damage to chromosomes and fetal development. Recent OSHA and EPA attempts at reducing benzene exposure have been based on its suspected leukemogenicity.

C. Leukemogenicity^{7/}

The association of benzene and leukemia is based on numerous individual case reports. Girard (1970) surveyed leukemia patients and found a significant number with histories of benzene

4/ Feasibility study by A.D. Little & Co.

5/ In contrast to occupational exposures (8 hours per day for a limited number of days) in low parts per million, ambient air concentrations in the low parts per billion involve both 24 hours exposure per day all year and a population including children and old people more sensitive than worker cohorts.

6/ For a general review of benzene's health effects, see Laskin 1977, EPA 1978a and Snyder 1975.

7/ For a review of benzene leukemogenicity, see Goldstein and Leong in Laskin 1978, and EPA 1978a.

DO 068074
CONFIDENTIAL

YZ0015911

exposure. Most importantly, instances of increased leukemia rates have been found to follow chronologically outbreaks of industrial benzene poisoning. For example, Aksoy (1974a) discerned an increased incidence of leukemia among Turkish shoe-workers that coincided with the introduction of benzene in adhesives (resulting in exposure to a maximum exposure of 210-650 ppm), an increase which also subsided with the substitution of toluene for benzene. Vigliani likewise noted an increased rate corresponding to specific outbreaks of benzene poisoning in Italian factories (at concentrations of 200-500 ppm) (1976a). Vigliani estimated a 20-fold excess risk of leukemia for the exposed population of 5,000.

Leukemia can be defined as a cancer of the white blood cells. It is characterized by the appearance of abnormal white cells in the circulating blood, replacement of the bone marrow with the leukemic cells, and widespread effects on the liver, spleen and other tissues. The occurrence of several different types of leukemia may relate to the duration of the disease (acute or chronic); the different types show differing incidences, clinical development and mechanisms. While the prognosis for different types of leukemia varies (one factor being the age at which it develops), adult acute leukemias, the type most often associated with benzene, are usually fatal.

The mechanism of benzene leukemogenicity is unknown and this uncertainty hampers research into dose-response relationships and

DO 068075
CONFIDENTIAL

YZ0015912

risks. Phenol and phenolic derivatives such as catechol and quinol are produced in the body as metabolites of benzene. It is hypothesized that a metabolite may be the actual leukemogen but this metabolite has not yet been isolated. Further uncertainty surrounds benzene's association with the various types of leukemia. European studies of substantial occupationally-exposed populations (Aksoy, Vigliani) have indicated a relationship between benzene and acute myelogenous and related (e.g., acute myelomonocytic) leukemias, and the association between benzene and acute forms seems well established. Other studies (Girard, 1979; Tareeff, 1963; McMichael, 1975) have found some correspondence with chronic lymphocytic leukemia. The discrepancy in findings may be related to differing environmental factors or different exposure duration or concentrations (Laskin, 1975).

Research has been seriously complicated by the unavailability, until recently, of bioassays showing benzene's leukemogenicity. Benzene was one of the two human carcinogens for which no analogous effect in animals had been established. The lack of animal data did not negate evidence of benzene's human leukemogenicity, since relatively few studies of chronic administration with long-term follow-up have been done and it was thought that there may be no analog in rodents of benzene leukemogenicity (Goldstein, 1977). However, this lack of confirmation from animal studies caused some scientists to hesitate in acknowledging benzene leukemogenicity. Maltoni (1979) has found a significant incidence of Zymbal gland tumors in benzene-exposed rats

and mice. The preliminary results of animal testing at New York University, which may show a leukemogenic effect in animals, have been recently published.

There are few large-scale epidemiological studies on benzene leukemogenicity. Studies of leukemogenicity have usually been in the form of individual medical reports, which provide a poor basis for calculating the incidence of leukemia. Similarly, the ubiquity of benzene complicates estimating the population at risk. It has been difficult to isolate benzene as the only contaminant, particularly in occupational settings (Aksoy, 1972; Vigliani, 1976). The potentially long latency period preceding leukemic manifestations -- periods of 15 and 27 years have been reported^{8/} -- complicates research, requiring retrospective studies covering long periods. Retrospective studies offer no means of confirming past diagnoses or of validating historic, technically inadequate measures of dose. Because benzene exposure could have resulted from any number of sources and might have occurred long before diagnosis of the effect, the link between benzene and mortality may be overlooked.

Past epidemiological studies have lacked precise measures of benzene exposure. They have confirmed the qualitative

^{8/} See for example, E.C. Vigliani, 1976b. By contrast, the latency period for leukemia from ionizing radiation is only 2-4 years (BEIR III). If the latency period for benzene leukemia is this short, the dose-response curve would be different from that estimated by EPA and other investigators.

association of benzene and leukemia. Since the ambient dose of benzene is so low, resulting in a normal incidence of leukemia of about 8 deaths per 100,000 persons per year, it would be hard to evaluate an isolated, possibly fortuitous case. Large sample sizes would be required for significant results. The unavailability of large samples for which there are controls of environmental factors, accurate dosage data, and a sufficient time period to take latency effects into account, contributes to the uncertainty of research into benzene leukemogenicity.

Thorpe Study

Among the limited number of epidemiological studies are several sponsored by the petroleum industry finding no increased incidence of leukemia and thus complicating the evaluation of benzene's effects (Stallones, 1977; Tabershaw, 1976). For example, Thorpe's study (1974) for Exxon on the refining industry and covering the 10-year period 1962-1971, examined employment records of eight Exxon affiliates in Europe with a combined population and duration of exposure of 380,000 man-years. He found 18 cases (23.23 expected) of diagnosed leukemia occurring at four of the plants, an incidence judged equivalent to that in the general population of comparable age.

Thorpe acknowledged several limitations of his study, including uncertainty in dosage data and the inadequacy of follow-up on retirees which might result in the under reporting of cases. Exposure levels were known only for certain job

categories and known only roughly as "much less than the recommended level of 25 ppm." Likewise, the duration of exposure and the extent of exposures to different levels as a result of job mobility are not known. In addition to the uncertainties not d by Thorpe, it seems likely that the eight different plants were subject to different environmental factors and population (ethnic-genetic) characteristics, and the reliability of the diagnosis of leukemia would vary. Finally, job mobility and lack of data made unclear how much of the population was chronically exposed to benzene at all.

The Thorpe study indicates at least that there was no outstanding leukemic incidence in the refining industry. While it does not eliminate a risk of leukemia due to benzene, the Thorpe study can be used to place an upper bound on the quantitative effect of benzene.

Infante Study

The epidemiological study by Peter F. Infante (1977a) of NIOSH involved a cohort combining workers from two Ohio plants producing a natural rubber cast film known as "Pliofilm" by "nearly identical" processes. Benzene was established to be the only significant airborne contaminant.^{9/}

^{9/} The Infante study was heavily relied on in OSHA's promulgation of an Emergency Temporary Standard and was a focus of industry attacks on the permanent standard in the 1978 OSHA hearings

The study cohort comprised 748 workers employed and exposed to benzene at Akron and St. Mary's between January 1, 1940 and December 31, 1949. Follow-up covered the period from first employment to June 30, 1975. The period covered would allow development of possible long term latent effects. Causes of death were derived from death certificates, but deaths before 1950 were excluded due to a lack of information on the cause of death. This exclusion, and the assumption that the 25 percent of the population not covered by the initial followup were alive, were judged to underestimate the risk of leukemia. As controls, Infante chose 1,447 white males from a fiberglass manufacturing factory situated in a geographically similar area and the United States white male population during the 1940s, adjusted for age.

Levels of exposure to benzene before 1946 are unknown (OSHA, 1978). In 1946, installation of an exhaust ventilation system significantly reduced exposure. After a survey of the Pliofilm process in 1946, the Industrial Commission of Ohio reported that "tests were made with benzol detectors and the results indicate that concentrations have been reduced to a safe level and in most instances range from zero to 10 or 15 parts per million."^{10/} A total of 112 surveys were conducted in one plant in the period between 1963 and 1974. Infante notes that these and earlier

^{10/} Industrial Commission of Ohio, Report, 1946, cited in Infante, 1977.

surveys indicate that employee exposure was generally within the recommended limits of the respective year.

Infante found 140 deaths from all causes compared to 187.6 expected from his U.S. white male control group. He attributed the lower mortality rate of the rubber workers to incomplete follow-up, and it may also be due to the "healthy worker effect," the select character of workers in terms of health compared to the heterogeneity of the general population. Infante found, however, a significant excess of hematopoietic malignancies, chiefly of leukemia deaths. Seven workers died from myelogenous or monocytic leukemias, as compared to an expected 1.38 deaths ($p < .002$) among all white males, a 5-fold excess risk, and an expected 1.48 ($p < .002$) deaths among the fiberglass workers.

In a supplemental letter to The Lancet Infante (1977b) referred to reports of additional leukemias among pliofilm workers. An Akron hematologist found two leukemias in workers who, he claimed, probably belonged in the Akron side of Infante's cohort. Infante did not include these additional deaths in his findings since they were not located by his own study. He indicated, however, that a more complete follow-up on his cohort and a recalculation of the years-at-risk reduced the number of expected deaths from 1.38 to 1.25 for white males.

Infante's report of a significant excess incidence of fatal leukemias in an industrial setting in which benzene was claimed to be the only contaminant, supports the qualitative association

of benzene and leukemia. The study's limited usefulness to the setting of standards and to estimation of a dose-response curve arises from the paucity of its dosage data. Infante gives no information on the duration of worker exposure. It is unclear why Infante did not determine the length of a worker's tenure in a Pliofilm production job from the same employment records by which he placed the worker in that process.^{11/} Infante supplies no information on the varying durations of exposure due to possibly considerable job mobility (McMichael, 1975). He evidently lacked records of prior employment that might have been the source of worker's exposure to benzene or other contaminants.

Exposure data are limited and uncertain. Exposure levels before 1946 were not recorded. The Ohio Industrial Commission reported an exposure level of 10-15 ppm in most places and "safe" levels everywhere. These "safe" levels were those recommended for the various years, a level of 100 ppm from 1941-1946, 50 ppm TWA in 1947 and 35 ppm in 1948. The fact that recommended exposure levels decreased over the period of study is no guarantee that the actual exposure declined. The total of 112 air surveys in one plant between 1963-1974 amount to less than one sampling per month. Further, though uniform exposure could be determined for most production areas, certain sites in the production process were subject to significantly higher exposures. Use of

^{11/} Indeed the OSHA hearings indicated that workers were included in the study on the basis of as little as one day of employment exposure.

respirators was recommended for such sites but there is no assurance that respirators were used at these times. There was testimony of unrecorded temporary excursions significantly above the recommended safe level, up to 350 ppm and beyond, resulting, for example, from accidental drenching. Finally, there is some doubt about whether sampling and measurement techniques in the 1940s were capable of accurately measuring levels as low as 10 ppm.

Infante's cohort of white men directly exposed to benzene was poorly defined. The use of populations from two separate plants with different amounts of available exposure data leaves some doubt on the comparability of environmental and occupational exposure data.^{12/} Infante plausibly justified the combining of two separate plants as a means of significantly enlarging the study population with workers all involved in essentially identical processes.

Infante's definition of his cohort also excluded the group of "dry side" employees whose jobs involved some regular, though not constant, benzene exposure. Infante explained that this job category was outside the intended scope of the study and that there had been no figures showing any possible benzene exposures in these non-production line jobs. However, mention of the leukemia incidence in this population exposed at a lower level would

^{12/} Tabershaw (1977), point out that one plant also manufactured products other than Pliofilm, and that turnover was greater at one plant than at the other.

have expanded the significance of his findings. Infante does not describe the job categories used or his criteria for eliminating other jobs.^{13/}

Infante's estimate of the exposure levels of workers in his study was low. The Infante study documents the qualitative association of benzene and leukemia, but provides little evidence on doses that may be associated with leukemia.

Aksoy Study

Dr. Muzaffer Aksoy (1971, 1972a, 1972b, 1974a, 1974b, 1976, 1977, 1978a, 1978b) has published a series of studies of health effects among Turkish shoeworkers using benzene-based adhesives.^{14/} Observing leukemic patients in Istanbul hospitals, his primary conclusion was that an increase in cases coincided with the introduction of benzene as a solvent for adhesives. He has reported (1971) that of 217 apparently healthy shoeworkers selected at random and compared to a matched group of 100 medical personnel and students, there were 51 cases of haematological abnormalities associated with acute benzene poisoning. The

^{13/} Critics further noted a failure to account for the fact that the worker population must have been reduced in the number of healthy males due to the draft that took place during the study period. This reduction in the number of healthy workers was likely small. There was also some question about the nosological accuracy in the study's recording of death certificate figures, which again, is likely a small element of uncertainty.

^{14/} Aksoy's findings were relied on by both OSHA and EPA in setting standards and Aksoy was presented as an OSHA witness at its 1978 administrative hearings.

exposure was between 30 and 210 ppm for three months to 17 years.^{15/}

In the study specifically used in EPA's risk assessment for its large sample size and quantitative importance, Aksoy (1974b) reported 26 cases of leukemia among shoeworkers admitted to Istanbul hospitals during the period 1967-1973.^{16/} He considered this figure conservative since he had not seen all the leukemia cases in Istanbul and not all cases would be reported in an area with a low level of health care. The concentration of benzene resulting from the use of adhesives in poorly ventilated workshops was estimated to be as much as 210-650 ppm. The duration of exposure ranged from four months to 15 years, with a mean exposure period of 9.7 years. The range in ages at the time of diagnosis was 16-58 (average 34.2). Official records indicated that 28,500 workers were involved in shoe manufacturing, leading Aksoy to calculate an incidence of leukemia of 13 per 100,000, a significant excess over six per 100,000, which he accepted as the incidence for Western nations, or 2.5-3, the estimated incidence of leukemia for Turkey.

Aksoy's large cohort and significant, perhaps even conservative number of cases, support the qualitative association between

^{15/} Matching workers with medical personnel does not, however, control well for differences in income and lifestyle.

^{16/} Three cases were acute lymphoblastic leukemia, which are as yet inconclusively associated with benzene (Goldstein, 1977).

DO 068085
CONFIDENTIAL

YZ0015922

benzene exposure and leukemia. However, his rough dosage figures are difficult to quantify in establishing a dose response relationship. Also, comparison of these results to an American occupational setting is problematic.

Aksoy's exposure data are likely based on his examining the workplace and history of a small fraction of the shoeworker population. There is thus no information on the duration of exposure which must vary in this heavily populated, unregulated industry. The lack of data on length of exposure and employment makes it difficult to judge the role of latent effects that may occur after the study's completion. The possibility of undiscovered effects may contribute to an underestimation of incidence. Indeed, Aksoy's 1979 follow-up reported a number of additional leukemia cases and thus a higher incidence.

Aksoy gives only a rough range, a minimum of 210-650 ppm, for the workshop concentration of benzene. Excursions at high levels (possibly 5,000 ppm in a hot climate) in the form of drenchings are likely in workshops described as "not hygienic and poorly ventilated" (Aksoy, 1974) but there are no data. Finally, there are no figures on the change in benzene concentration as the use of the solvent began, peaked, and faded during the period of observation. Thus, Aksoy's estimate of exposure levels is rough and possibly underestimated, but this possibility is hard to judge.

Aksoy's results are difficult to apply to the American occupational and general populations due to the differing exposure experiences that presumably differ between the populations. For example, Aksoy has estimated the benzene level in the shoeworkers' shops to be 15-30 ppm outside of working hours. It is likely that a great many shoeworkers labor in their living quarters or in the immediate vicinity. The 15-30 ppm concentration would approximate a background exposure to which Turkish shoeworkers are exposed for much of the period outside of working hours. Background exposure for the general population might well differ importantly from that of the U.S. in a context where benzene was not banned or regulated until 1969. By contrast, ambient benzene levels in the U.S. generally peak at under 10 ppb.

It would seem even more difficult to isolate benzene as the only source of carcinogenic exposure. Indeed, Aksoy described the workshops as "not hygienic," though he himself could find no other contaminant in the workplace. His actual survey of shops was evidently limited.

Aksoy's calculation of the incidence of leukemia is uncertain. His figure of 13 per 100,000 is based on a population at risk that is difficult to quantify. The figure of 28,500 documented shoeworkers is likely a rough, conservative estimate: if the actual number were twice as high, the incidence rate for his worker population would be halved. His figure of 6 to 8 expected

leukemia deaths per 100,000 is that for the general population; since the incidence of leukemias increases with age, this figure is high for a younger, worker aged population, and 13 per 100,000 is conservative.

The lack of figures on exposure level and duration is crucial. Aksoy gives no details about how his estimate of a maximum range of 210-650 ppm was reached^{17/} and, in view of likely excursions, his range may be conservative. The probable under-reporting of leukemia cases (suggesting a higher incidence) and the great uncertainty regarding dose magnify the uncertainty of Aksoy's calculation of leukemia incidence.

Ott Study

Dr. M. Gerald Ott's (1978) epidemiological study^{18/} of workers exposed to benzene in the petrochemical industry examined 594 workers at a Dow Chemical plant. The study covered employment between 1940 and 1973. Ott notes that since 355 workers entered employment before 1950, sufficient allowance was made for the development of latent effects. On the basis of employment records, Ott located workers in particular departments and

^{17/} Indeed, Aksoy uses different exposure levels in other studies of shoeworkers (e.g., 150-210 ppm in 1972b). H does not specify whether these figures are based on closer examination of a fewer number of workplaces.

^{18/} This industry-sponsored study was published after the Infante results and the OSHA ETS promulgation. It was cited by industry in the OSHA hearings as a negative study and was used by EPA to broaden the data base in its calculation of the benzene risk assessment.

DO 068088
CONFIDENTIAL

YZ0015925

associated them with particular durations of exposure and ranges of benzene concentration (from 2 to 25 ppm).^{19/} Ott found no statistically significant excess rate of death from any cause other than leukemia. He identified two deaths due to leukemia, and a third in which leukemia was noted as a significant condition, the primary cause of death being broncho-pneumonia. This result, compared to an expected incidence of .8, based on the U.S. white male rate^{20/} yielding a result of borderline statistical significance ($p < .047$).^{21/}

Ott's access to work histories and industrial hygiene records gives a better estimate of benzene dosage than the other studies and Ott has tabulated his findings in detail. Ott points out the uncertainty due to the likelihood that long-term employees were exposed to a wide range of chemicals and exposure levels; two of the leukemia cases had had previous exposure to potentially carcinogenic chemicals.

^{19/} Fifty-three workers were excluded from dose-response calculations due to known exposure to arsenicals, asbestos, and high vinyl chloride levels.

^{20/} He presumably adjusted the figures for the white male population for the age of the workers and for the period of the study. Ott used no other occupationally or geographically comparable control.

^{21/} Evaluation of two of the leukemia cases is, in fact, complicated by documented exposure of one to vinyl chloride and an exposure level up to 200 ppm of benzene, while the other had worked in veneer manufacturing which is associated with increased risk of myelocytic leukemia. Also, the cause of death in the third case was given on the certificate as bronchopneumonia with leukemia as a significant concurrent condition.

Ott does not discuss air sampling methods. His historic records of hygienic surveys are presumably subject to doubt based on the limited technical capability of measuring low concentration in the 1940s, the difficulty of accounting for temporary excursions, and the possibly inadequate number of air samples. The major limit on the study's utility arises from its small sample size. While the resultant leukemia deaths are suggestive, their statistical inconclusiveness makes use of the study's figures difficult. This study has both the lowest concentration of benzene and the smallest worker population of the three studies. The low incidence of leukemia reported by the study is not necessarily surprising or significant. The Ott study is important because it is the only one with documented exposures below 25 ppm.

D. Non-Malignant Blood Disorders

The effects of benzene on the hematopoietic tissue, which have been recognized for 100 years and which served as the basis for past benzene standards, can be readily produced in laboratory animals (Leong, 1977). An acute dose affects the central nervous system, quickly inducing a light anesthesia followed by depression and respiratory failure. The narcotic threshold is 1,000 ppm and acute toxic effects follow exposure to concentrations below 10,000 ppm. Studies have shown that a subacute, chronic dose produces changes first in the bone marrow, slowing the maturation process of red blood cells, and next inhibits the production of white blood cells (Leong, 1977).

DO 068090
CONFIDENTIAL

YZ0015927

Attempts to correlate concentration and effect in chronic inhalation studies have had inconsistent results.^{22/} Wolf et al. exposed rats, rabbits and guinea pigs for seven to eight hours per day, five days per week, to benzene concentrations of 80 and 88 ppm. The study found a significant incidence of leukopenia and testicular and splenic degeneration. Exposing rats to mean levels of 47 ppm (range 33-55) and 44 ppm (range 40-50) for seven hours a day, Deichmann et al. (Deichmann, 1963) found a significant reduction in the white blood cell count, with females apparently more sensitive. The study, however, lacked parallel controls and the animals were subject to significant variability in weight and age.

By contrast, Jenkins et al. (Jenkins, 1970), exposing various species to benzene levels of 256, 30 and 17.6 for eight hours a day, 5 days a week, 30 exposures total, found no statistically significant changes at any level.

The evaluation of these results is complicated by the problem of extrapolating from animal to human effects.^{22/} The blood counts normal to different laboratory animals will vary, and hormonal changes and even the time of day may distort blood counts, but such factors have generally not been recorded in past

^{22/} The studies briefly cited are representative of research into dose-response relationships. More complete surveys are found in Goldstein and Leong, 1977, and in EPA 1978a.

^{23/} For a general discussion of this problem see Risk Assessment document.

studies (Leong 1977). Animal studies have given insight into the mechanism of benzene effects on the blood, but in view of their inconsistent results and their uncertainties, past animal studies have presented inconclusive dose response data.

The results of human epidemiological studies are complicated by a worker's likely exposure to multiple agents in the workplace. [As in the case of research into benzene leukemias, however, the correlation between benzene and blood effects is based on a strong temporal correspondence between the incidence of pancytopenia with benzene use.] Benzene has also been isolated as the common denominator in various occupational settings where blood effects were found. Benzene has induced in animals blood effects not reproducible with other chemical agents (Goldstein 1977).

Chronic benzene exposure is associated with the occurrence of pancytopenia, the reduction of all formed elements in the blood and interference with cell production in the marrow. Some evidence suggests that exposure shortens the survival of circulating cells (EPA, 1978a). Benzene exposure also reduces the counts of particular cell types or combinations of cell types. Symptoms of mild pancytopenia are lassitude, tiredness, dizziness, headaches, and shortness of breath. Recovery is likely in a mild case of pancytopenia if benzene exposure is halted, although there have been reports of leukemia developing after apparent full recovery (EPA 1978a).

DO 068092
CONFIDENTIAL

YZ0015929

Severe pancytopenias may be accompanied by hemorrhagic effects due to thrombocytopenia (reduction in platelets necessary to clotting), with the possibility of fatal bleeding. Aplastic anemia, which has a 50 percent mortality rate, may result, generally at high exposure levels. The influence of benzene on blood forming tissues may affect the human immunological system, potentially resulting in immunological defenses being overwhelmed by other disease. Finally, it is possible that benzene-induced blood disorders are related to the development of leukemia. Viqiani (1976a) has speculated that leukemia is the terminal stage of pancytopenia. It is possible that leukemia is in fact always preceded by pancytopenia. Benzene's effects on the blood may allow the development of acute leukemia by hampering the blood's immune surveillance function that normally weeds out abnormal cells. However, Goldstein (1977) notes evidence that a relatively small percentage of workers with pancytopenia will develop serious effects, particularly if occupational conditions improve.

Dose response data are limited as in the case of benzene leukemia studies. Goldstein (1977) has suggested that the true incidence of benzene-induced pancytopenia may be underreported because mild blood disorders will not be noticed unless they are looked for. Similarly, benzene's role in a particular hematological case may be overlooked, due to the ubiquitousness of benzene.

DO 068093
CONFIDENTIAL

YZ0015930

Goldwater (1941) studied 332 male rotogravure workers who were exposed to benzene levels of 11-160 ppm for at least six months and generally about three years. He found six cases of benzene poisoning severe enough to require hospitalization.

Goldwater found hematological abnormalities in various tests of the blood of benzene workers compared to a control group of 81 unexposed workers. Aksoy's (1971) study of 217 apparently healthy shoeworkers, exposed to a maximum of 210-650 ppm for uncertain periods, found 51 with benzene-associated abnormalities, including 41 cases of leukopenia. In one of the only studies of long-term effects, Pagnotto (1977) did a follow-up of an earlier survey of 38 workers in the rubberworking industry exposed from one to 24 years to average concentrations between five and 50 ppm (90 ppm in the case of one worker). Pagnotto found a small number of cases with abnormal blood changes and one case of mild benzene poisoning at an exposure level averaging 40 ppm. There were, thus, no significant effects 13 years after the use of solvents containing benzene had been discontinued. Finally, a Korean study (Chang, 1972) of 119 workers at low benzene levels found hematological effects at 20 ppm and attempted to extrapolate down to effects at 10 ppm. The study, however, is very difficult to evaluate due to insufficient information on exposures and on the work force, aside from difficulties of comparing its Korean population to an American occupational cohort. In sum, epidemiological studies have generally lacked data on dosage and have been based on small populations.

DO 068094
CONFIDENTIAL

YZ0015931

While the association of benzene and changes in the human hematopoietic system seems well established, with some evidence of effects at relatively low doses, the data are insufficient for a dose-response curve. The relationship of benzene-induced blood changes to leukemic developments is unclear and there is little study of long term effects of slight blood changes. The mild disorders that result from low doses appear reversible.

Effects on Fetal Development

Teratological studies have examined the effects of benzene on fetal development.^{24/} The usual protocol involves exposure of rodents during the middle trimester of gestation, the period of organ formation. The fetus is examined on the 20th day of development for external, skeletal, and visceral malformation.

The significance of teratological studies in animals for research into the effects of benzene on humans is complicated by the difference in metabolism and embryonic development in animals, specifically rodents, which are used for reasons of cost and practicality. Rats and mice have respiratory rates five to 10 times the rate of humans, which may mean that an ambient concentration gives the animals a higher dose. In rats, the maternal blood does not mix with that of the fetus to the extent it does in humans; the different placenta further complicates

^{24/} For a review of teratological studies, see Consumer Products Safety Commission, 1980. This is a new area of research; little data was available to EPA's assessment of health effects and OSHA did not cover it.

comparing findings in rats to human effects.^{25/} Finally, rats and mice show spontaneous abnormalities similar to effects caused by benzene. A sizeable control population is required to determine the role of these abnormalities, which may result from environmental factors like fasting.

Watanabe (1970) subcutaneously injected pregnant mice with a benzene dose of three ml/kg of body weight during organogenesis and found numerous abnormalities, including cleft jaw and missing lower jaw. These effects may be due to the acute dose of benzene and a method of exposure that does not correspond to the way humans are exposed. The study also lacked a control group. Nawrot (1979), having introduced doses of benzene from .3 to 1 ml/kg into the stomachs of mice (gavage) during the period of organogenesis, reported significant lethal maternal effects and fetal resorptions at .5 and 1 ml. Fetal weight gain was significantly reduced at all doses. He found no statistically significant change in the incidence of malformations. Though the method of exposure, gavage, would give a less acute dose than an injection, it differs from inhalation and complicates evaluation of the results.

Inhalation studies have produced inconsistent findings. The Hazelton Laboratories study of rats (1977) reported a significantly lower fetal and maternal weight gain at benzene concentrations of 50 to 500 ppm, a significant incidence of reduced

^{25/} And there is evidently no human equivalent to the finding of fetal resorptions in rats.

DO 068096
CONFIDENTIAL

YZ0015933

crown-rump distance at 500 ppm, and retarded fetal ossification. At 500 ppm it also found a statistically insignificant incidence of skeletal malformations, suggesting a teratogenic potential.^{26/} Two studies undertaken by Litton Bionetics exposed rats to 10 and 40 ppm (1977), and 8.7 and 43.4 ppm (1978) for six hours per day. The investigators found a significant increase in fetal resorptions (a sensitive measure of fetotoxicity) at the 40, 10 and 8.7 ppm levels, but no other significant fetal or maternal effects.

By contrast, research by Green (1978) exposed pregnant rats to benzene levels of 100, 300 and 2,200 ppm for six hours per day and found a significant reduction of crown-rump length only at the highest level. Green noted an increased incidence of skeletal abnormalities at the middle and high dose levels and particularly in female fetuses. The study found no increase in resorptions at any level. Similarly, Murray (1979) found a significant increase in minor skeletal abnormalities in mice and rabbits at a benzene concentration of 500 ppm, a level which caused some maternal toxicity. Murray notes that malformations occur in mice spontaneously at a low incidence rate.

Results of these studies must be considered in light of the technical parameters of teratological study. Exposure is focused on the period of organogenesis for the purpose of studying abnormal growth. This ten-day exposure during the period of

^{26/} Critics have suggested that the control groups used were improperly small.

gestation is unlikely to have any close correspondence to human occupational exposure, which would occur before and after as well as during pregnancy. The duration of exposure is not long enough to produce the hematological effects of benzene exposure,^{27/} such as dyscrasias, that might well be dangerous to in utero development in cases of aplastic anemia. (Deichmann (1963), for example, required five weeks exposure at 40 ppm to produce blood changes in mice.) Human exposure to benzene would likely occur before as well as during pregnancy.^{28/} In an animal study involving exposure prior to pregnancy, Gofmekler (1968) exposed female rats inhaled benzene levels of 6.3 to 209.7 ppm for 10-15 days before impregnation. Gofmekler found that litter size dropped proportionally with increased exposure at 19.5 ppm and above and found no pregnancies at the highest dose. He found no significant effect on fetal weight or survival, or on the incidence of external fetal abnormalities. He noted that weights of fetal organs varied with the dose and found one case in ten of fetal resorption at 19.8 ppm.

In sum, studies of benzene's effect on embryonic development indicate that benzene is apparently not a teratogen in rats at exposure levels under 500 ppm. Benzene's fetotoxic effects seem well established and occur at lower levels, possibly as low as 10

^{27/} Deichmann (1963)

^{28/} Pregnant rats are not exposed before organogenesis because the fetus may be killed, vitiating the teratological study.

ppm. The fact that this line of research must rely on animals complicates its significance for the study of benzene effects on humans.

EPA (1980) has cited two studies related to reproductive effects. Hett and Maak (1938) found degeneration of ovarian follicles and effects on ova in mice at exposure levels at which blood dyscrasias were produced. These were apparently toxic levels. Vara and Kinnunen (1946) studied gonadal effects in 30 occupationally exposed females. Twelve workers reported menstrual peculiarities that they themselves attributed to their employment. The researchers also gave chronic injections of benzene to rabbits until blood changes occurred and found similar effects on reproductive organs, including reduced ovary size in some animals. Neither the occupational reports nor the animal tests offer dosage data. While these reports suggest areas for further study, and roughly correlate with general findings of fetotoxicity in animals, they are insufficiently described and have no dose-response significance.

E. Chromosomal Effects

The study of the effects of benzene exposure has turned more recently to the examination of its potential cellular and chromosomal effects.^{29/} The theory of somatic mutation has been

^{29/} For a more complete survey, see Wolman, 1977. This area of research is relatively new. OSHA's review of benzene health effects did not explore it in depth.

associated with the initiation or maintenance of malignant change. There are, in fact, indications that many agents causing chromosomal damage (like radiation, viruses, and chemicals) are carcinogenic. There is indirect evidence in that the three human syndromes of chromosomal instability are both highly sensitive to clastogenic (causing chromosomal breakage) agents and are characterized by "unstable" chromosomal changes such as ring structures and fragments, the type of changes most often associated with the toxicity of chemicals like benzene (Vogel, 1979). The significant latency period that can precede benzene's effect would be consistent with original damage done to the genetic system by benzene.

The effect of benzene as a mitotic poison has been well documented (Wolman, 1977). Experiments with labeled thymidine have shown a reduced uptake and thus a decreased rate of DNA synthesis in vivo in rat and rabbit bone marrow.^{30/} This effect corresponds to a depressed formation of marrow cells resulting from benzene toxicity and has been demonstrated in vitro in human marrow.

The most common finding of benzene cytogenetic studies has involved chromosomal alterations. Kissling (1972) found a significantly increased rate of chromosomal aberrations in rabbit lymphocytes after 18 weeks of chronic subcutaneous injections of

^{30/} The results in rabbit studies were variable but still significant.

.2 ml/ kg of body weight per day. They noted an increase in the number of aberrations from 5.9 percent at the outset to 58 percent at the end of the injections. The study found a 36 percent incidence of such effects persisting two months after the end of the treatment. They compared their cytogenetic findings to those associated with dyscrasias induced by ionizing radiation.

The significance of an increased incidence of chromosomal breaks is not certain: breaks may be repaired, but a larger incidence may increase the possibility of mutation. The persistence of changes after exposure at least suggests that damage has occurred (Forni, 1971a). Chromosome changes have also been associated with specific cancers. For instance, 50 percent of patients with acute myelogenous leukemia and a history of solvent exposures have been found to have cytogenetic alterations (Mitelman, 1978). But the incidence of aberrations accompanying specific cancers has been only lately discovered and its meaning is not precisely known. Finally, effects have so far been found only in somatic rather than germinal cells, so a relation of benzene to hereditary damage is not known.

Most relevant to the human effects of benzene are cytogenetic studies of occupational exposure at subacute dosages. So far, however, these tend to involve small samples with detailed medical reports that support the qualitative association of benzene exposure and chromosomal change. Hartwich (1972)

DO 068101
CONFIDENTIAL

YZ0015938

examined nine seemingly healthy refinery workers three to seven years after exposure to benzene. They found an aberration rate of eight to 12 percent with a mean of 10.4 percent, significantly higher than the 5.1 percent in the matched controls ($p < 0.1$). They noted that the incidence of alterations was at the outer limit of normal rates but pointed to the low exposure level, well under 25 ppm.

Forni (1977b) examined cytogenetic effects in patients with various degrees of benzene poisoning. Of the twenty-five subjects who had suffered benzene poisoning with bone marrow impairment one to 18 years before the chromosomal study were almost all found to have normal blood counts indicating recovery. An examination of peripheral blood, however, showed that 18 patients had more than one percent unstable chromosomal changes and 17 had one percent or more stable changes.^{31/} This compared with only one patient with more than one percent unstable and one with one percent stable changes among the controls. Follow-up studies showed that the chromosomal effects persisted long after exposure and recovery. The rate of breakages had decreased in many cases while changes in chromosome number showed a definite increase in some cases, a finding that Forni compared to the symptoms of individuals with past exposure to ionizing radiation. It is hard to compare this occupational study to others due to the differing degrees of hematotoxicity in the subjects.

^{31/} Mutational or "stable" change occurs in chromosome number; change in structure is toxic or "unstable".

Tough (1965, 1970) studied three factory cohorts. In the first, with exposure levels between 25 and 150 ppm of benzene, Tough found a significant increase in the percentage of aberrant cells.^{32/} While he found no correlation between the duration of exposure and the number of cytogenetic changes, he did determine an increased proportion of effects in older workers. Twenty men from factory #3 were exposed intermittently to around 12 ppm for two to 26 years (exact and relative exposures are not known). They were compared to a matched control group comprising general population and on-site unexposed workers. The survey found about the same aberration rate in the exposed and unexposed workers, which did not significantly differ from that of the general population.^{33/}

Dr. Dante Picciano (1979) did a cytogenetic evaluation of 52 workers exposed to low levels of benzene in a chemical plant, the first occupational study of chromosomal effects to try to measure dose. The benzene concentration was calculated on the basis of personnel sampling, area air samples, and urine levels of phen 1, a benzene metabolite considered a good measure of exposure. The time-weighted average exposure was estimated to be 2.1 ppm and

^{32/} He found 1.5 percent stable and two percent unstable changes compared to .6 percent stable and .4 percent unstable changes in the controls.

^{33/} The sample from factory #2 comprised 12 men exposed for six to 25 years to about 25 to 150 ppm and on-site unexposed workers. The frequency of aberrations was high in the exposed group compared to the general population but also in the controls, possibly due to ambient air exposure.

the duration was one month to 26 years (average exposure 56.6 months with an average of 39.3 months). The control group comprised 44 pre-employment individuals with an average age of 26.6 years. Picciano examined 200 cells per subject. He found the same number of abnormal cells as in the controls but twice the percentage of chromosome breaks (.67 percent compared to .35 percent in controls), three times the percentage of marker chromosomes (1.6 percent compared to 0.6 percent in controls) and 10 times the percentage of controls showing both aberrations. Analysis for the age difference found no significant difference in aberrations.

Picciano's attempt to correlate dose with chromosomal response is subject to uncertainties. Picciano acknowledges that the discovered damage may be due to a worker's prior exposure to higher levels of benzene which recent phenol samples would not indicate. He had access to records of only five years of prior employment.^{34/} Picciano's cohort was the combined benzene-exposed populations of three plants;^{35/} it is unclear why only 52 workers were available during an employment period of 26 years. His control group is small and its comparability with his benzene-exposed subjects is uncertain, for example as regards age. Despite his finding the age difference insignificant, other

^{34/} Picciano, personal communication.

^{35/} Picciano, personal communication.

studies (Tough, 1970) have associated age with an increased incidence of benzene-induced chromosomal aberrations.

The significance of cytogenetic studies of occupational exposure is limited by lack of data on dosage, the generally small size of populations, an inability to control for possible varied degrees of latency in the subjects, and by the often low number of aberrations in workers (around one percent). Court Brown (1965) has noted that the incidence of chromosomal aberrations in the general population is 2.6 in males and 3.0 in females. This evidently spontaneous incidence of aberrations might also result from the complexities of laboratory techniques.^{36/}

The association of benzene with cytogenetic damage is subject to further uncertainty due to the still early stage of research. Some non-carcinogens and non-mutagens (e.g., caffeine) produce chromosomal damage. Conversely, carcinogens do not necessarily damage cultured chromosomes in vitro. Finally, the significance of such aberrations is uncertain: it is not clear whether chromosomal alterations are causative or whether they are perhaps accidental or exceptional occurrences such as accompany the attack of any disease.

Evidence shows that benzene causes cytogenetic damage. The research is new and the dose-response relationship is unclear. More importantly, the meaning of chromosomal effects are not known, though these effects bear some resemblance to those of

^{36/} Goldstein, personal communication.

documented carcinogens, particularly ionizing radiation, and may have a role in the development of leukemia. Chromosomal damage has been shown to persist long after exposure. There is no known correlation between the persistence or extent of chromosomal aberrations and benzene dose.

III. Agencies/Quantitative Risk Assessment^{37/}

OSHA

The Occupational Safety and Health Act requires that in regulating toxic materials, the agency "set the standard which most adequately assures, to the extent feasible, on the basis of the best available evidence, that no employee will suffer material impairment of health or functional capacity" (§6(b)(5)). Under this authority, OSHA promulgated its benzene regulations based on a review of the scientific evidence summarized above and a feasibility study of the 1 ppm standard.

^{37/} This and subsequent sections were based in part on interviews with: Dr. Peter F. Infante, OSHA; Dr. Jim Vail, Chemical Specialties Manufacturers Association, former project director for benzene at OSHA; Grover Wrenn, Clement Associates, former Health Standards Director OSHA; Dr. Robert E. McGaughy, Deputy Director, CAG; Diane Berkley, Solicitor's Office, OSHA; Ed Klein, Solicitor's Office, OSHA; Morton Corn, Johns Hopkins University, former Administrator of OSHA; Richard Johnson, Environmental specialist, EPA, formerly project manager for benzene; Dr. Bernard Goldstein, Rutgers University; Dr. Dante Picciano; Barbara Bankoff, Special Assistant to the Administrator for Air Quality, EPA; Robert Kelham, EPA, RTP; Michael Dusetzina, EPA, RTP.

OSHA did not base its standard on any quantitative risk assessment for benzene exposure. The primary basis of OSHA's standard was the evidence of benzene leukemogenicity. Its review of the scientific literature showed the range of effects associated with benzene and pointed to evidence of effects at low levels. OSHA acknowledged unanswered questions about benzene's malignancy but noted that under the OSH Act it could not wait for answers while workers were exposed to a life-threatening substance. Because of benzene's chronic toxicity and the unknown range of human susceptibility, OSHA could not "conclude that 10 ppm provide[d] sufficient protection ... to all workers" (43 FR 5925). Thus the limiting criterion was feasibility.

OSHA commissioned a consultant, A.D. Little & Co., to study the feasibility of the 1 ppm standard. The report considered in detail the use and the estimated levels of occupational exposure to benzene in various industries. Its study of the standard's economic impact assessed effects on price, productivity and market structure. It also listed as benefits of the standard an expected reduction in potential leukemia cases and blood abnormalities; a better-informed workforce resulting from a training program required by the standard; and increased medical knowledge due to detailed recordkeeping. The report concluded that the 1 ppm standard was feasible and that compliance would impose capital investment costs of around \$266 million, first year operating costs of about \$187 million and annual costs of \$34 million (43 FR 5934).

DO 068107
CONFIDENTIAL

YZ0015944

In answer to legal challenges that it should perform a quantitative risk assessment, OSHA argued repeatedly that there was insufficient data to engage in risk assessment. It stated that it was not in principle opposed to quantitative risk assessment, particularly in setting priorities, but it would not use it in setting exposure levels. In the absence of contrary evidence, the Agency adhered to its policy that there is no safe level for a carcinogen and that protection of the worker dictated reduction of exposure to the lowest feasible level.

Indeed, OSHA interpreted the OSH Act as precluding a balancing of benefits and costs.^{38/} Relying on the one-hit dose-response model that assumes there is no safe level for a carcinogen, OSHA understood its mandate to be setting a standard assuring "to the extent feasible" that "no employee will suffer material impairment of health" (29 U.S.C. §655(b)(5)); thus, the standard for a carcinogen could not be set higher than the constraints of feasibility, technology and economics would allow. OSHA perceived as well that interpreting its mandate to allow consideration of different achievable levels of exposure would involve dealing with the methodological uncertainties of risk analysis. Prior to the benzene case, courts had upheld OSHA's interpretation of feasibility as economic cost and as the engineering capability of the industry as a whole.^{39/}

^{38/} Industrial Union Dept., Brief for the Federal Parties.

^{39/} E.g., D.C. Circuit in Industrial Union Dept. v. Hodgson, 499 F2d 467 (1974).

OSHA argued before the Supreme Court that in making judgments about specific hazards, the agency has the duty to set a standard at the level which assures the greatest protection (Brief for Federal Parties, 1979). Given its policy that there is no safe level for a carcinogen, feasibility would be the only limit to OSHA's standard. Reasons for selecting 1 ppm as the "lowest feasible level" include limits to the technical capability of measuring low concentrations (OSHA, 1977). Also, OSHA claimed that 1 ppm approaches the level at which benzene occurs in nature; an even lower standard would require cleaning the ambient air (OSHA 1977). Furthermore, OSHA felt that the 10 ppm standard had no intrinsic foundation. It was adopted in 1971 from the American National Standards Institute consensus standard which was established in 1969 when the scientific data on benzene was less than that available. The past standard was also based on the association of benzene with non-malignant blood disorders, not on its leukemogenicity (43 FR at 5918). Finally, OSHA was motivated in its choice of a 1 ppm standard by its conviction that that level was readily achievable. The A.D. Little study, in fact, concluded that the majority of 98,000 refinery workers were exposed to levels actually under 1 ppm. OSHA asserted that if A.D. Little had found 1 ppm in fact not feasible, it would have explored other standards.

OSHA did offer a quantitative risk assessment in its Supreme Court brief after the Fifth Circuit had criticized its failure to

engage in a balancing of costs and benefits.^{40/} This example seemed intended primarily to show the crude nature of risk assessment and how different assumptions could produce a significantly different result based on the same data.

OSHA's current position on risk assessment is enunciated in its generic policy for the "Identification, Classification, and Regulation of Potential Occupational Carcinogens" (45 FR 5001). After extensively reviewing the uncertainties of risk assessment and proposing models for extrapolating from animal studies, OSHA concludes that the uncertainties of extrapolating from high doses in animals to low doses in humans are too great to be useful to a risk-benefit balancing and setting exposure limits. Quantitative risk analysis has a role in setting priorities by comparing relative risks, and it can be used to estimate the reduction of risk that has resulted from a regulatory action. OSHA further suggests that risk assessment should not rely on single numbers but state the range of risk based on cautious assumptions about the uncertainty.

EPA

On April 4, 1980, EPA proposed an emission standard of 97 percent control for existing maleic anhydride plants as a first step in reducing benzene in the ambient air. EPA has authority under §112 of the Clean Air Act to regulate "hazardous air pollutants" which, "in the judgment of the Administrator may

^{40/} See Appendix B for a short review of the OSHA risk assessment.

cause or contribute to an increase in mortality or in serious irreversible or incapacitating reversible illness" (42 FR 29332). The proposed standard was based on EPA's report "Health Effects of Benzene Germane to Low Level Exposure (1978a), an "Assessment of Human Exposure to Atmospheric Benzene" (1978b) and calculation of a dose response curve by its Carcinogen Assessment Group (1978c).

The scientific basis for EPA's regulation, exhaustively reviewed in its Health Effects Document, comprised the same studies on which the OSHA benzene standard was based. EPA recognized that this evidence primarily involved research into occupational exposure at levels higher than those found in the ambient air, but noted the Administrator's "generic determination that, in view of the existing state of scientific knowledge, prudent public health policy requires that carcinogens be considered for regulatory purposes to pose some finite risk of cancer at any exposure level above zero" (45 FR 58646).

Finally, EPA used the quantitative risk assessment in a general balancing of the risks and costs of options to arrive at its final standard (45 FR 58646). The comparison of options considered environmental impact (the degree of reduction in benzene emissions), the energy impact of particular methods of controls (such as carbon adsorption and thermal incineration), and aspects of economic impact. The option chosen, 97 percent control with best available technology (and 100 percent control

in new plants), is expected to result in only .03 to .19 deaths per year.^{41/} It was estimated to cost \$6.6 million in capital, \$2.5 million in additional annual costs, possibly one plant closing, and a 1.2 percent price increase for maleic anhydride.

EPA's June 1977 decision to list benzene as a hazardous air pollutant under Section 112 followed OSHA's promulgation of an Emergency Temporary Standard. During 1978, the agencies had numerous meetings. OSHA evidently considered EPA's risk assessment but did not formally respond to it. After the decision of the Fifth Circuit requiring a risk assessment, OSHA's counsel appended CAG's risk assessment to its brief but evidently only for the purpose of showing the crudeness of the technique. OSHA modified its regulation to exempt gasoline stations (and industries using liquids containing less than one percent benzene) in recognizing service stations as a borderline case between occupational and ambient air exposure and in expectation of appropriate coverage by EPA's action. Neither agency has yet moved to regulate service stations.

EPA has specified the general role of risk assessment in setting ambient air standards in its "National Emission Standards for Identifying, Assessing and Regulating Airborne Substances Posing a Risk of Cancer" (44 FR 58642). Citing the uncertainties of risk assessment, EPA limits the use of risk assessment to

^{41/} CAG estimated 3.39 deaths would result from emissions from chemical manufacturing in general (EPA, 1979).

providing supplementary evidence in support of a finding of significant risk: the assessment cannot be ignored if it shows risk, but is too crude to be the basis for not listing a substance. Thus, EPA will conduct a quantitative risk assessment for agents listed as carcinogens under Section 112. The risk assessment will be used to set priorities for regulations of particular source categories and to determine the degree of control required in final emission standards for those source categories.^{42/}

B. Critique: OSHA

The Occupational Safety and Health Act does not require a quantitative risk assessment. While the Act may mandate quantitative methods in the setting of priorities (Industrial Union Department), the basic limit it sets to OSHA standards is one of "feasibility" the meaning of which is loose and ambiguous. OSHA argued in court that there was too little data on which to base a risk assessment for benzene. It has also stated that it did use risk assessment generally in setting priorities and in showing the benefits of a standard once the lowest feasible level had been chosen. (Industrial Union Department, Brief.) Other elements in its rejection of risk analysis included the policy concern that the Secretary of Labor, who has a highly defined constituency -- a benzene or vinyl chloride standards affects

^{42/} Appendix D briefly reviews the background of the initial EPA regulation of benzene.

known individuals -- could not be associated with any quantitative method that approached cost-benefit analysis and the setting of a dollar value on life.^{43/} There were also significant political pressures for a new benzene standard.^{44/} Finally, the agency, in 1977, was regulating in an atmosphere of judicial deference to administrative discretion.^{45/} While OSHA may have made a less substantial showing of the standard's basis than it had in past regulations, no legal precedent provided any basis for expecting that once it had detailed its safety concerns it would have to show more.

Courts reviewing Emergency Temporary Standards have been concerned with the actual probability that an asserted hazard poses an actual hazard and with the gravity or severity of the harm threatened. The Court of Appeals for the Third Circuit has held that OSHA must show more than "some probability" that a

^{43/} This is in contrast to EPA which has a diffuse constituency as large as the United States. Noted by Morton Corn, personal communication.

^{44/} Background to the benzene standard is reviewed in Appendix C.

^{45/} Courts have required that OSHA be explicit in its rationale for a particular standard. See, Dry Colors Manuf. Assoc. v. Dept. of Labor, 486 F2d 98 (3d Cir. 1973). See also, Industrial Union Dept. v. Hodgson, 499 F2d 467 (D.C. Cir. 1973): "where that choice [of a regulatory course] purports to be based on the existence of certain determinable facts, the Secretary must ... find those facts from evidence in the record. By the same token, when the Secretary is obliged to make policy judgments where no factual certainties exist ... he should so state and go on to identify the considerations he found persuasive."

substance is carcinogenic and that OSHA need not show actual harm, but simply that harm would result.^{46/}

While OSHA has consistently argued against the use of benefit-cost analysis in the actual setting of a benzene standard, the 1 ppm standard represents an implicit weighing of cost and benefit. It is unclear from OSHA's promulgation of the standard and from interviews with agency personnel, how 1 ppm was arrived at as the "lowest feasible level," rather than 5 ppm or, in view of the A.D. Little conclusion that 1 ppm was easily feasible, .5 ppm.^{47/} Instead of comparing a number of levels to find the "lowest feasible", OSHA evidently selected a level that would be reasonable in terms of economic cost and political feasibility. OSHA's protestations to the contrary, this element of balancing appears inevitable in standard setting.^{48/}

OSHA has argued that it could have applied a safety factor of 10 or 100 to the demonstrated effects of benzene at high

^{46/} Dry Colors Manuf. Assoc. v. Dept. of Labor, 486 F2d 98 (3d Cir. 1973) (reviewing an ETS for 14 carcinogens).

^{47/} Discussions with OSHA personnel indicate that A.D. Little either considered the feasibility of 10, 5 and 1 ppm levels or such an examination was discussed in the contract stage. But the final A.D. Little document gives no hint of this nor a reason for not discussing other levels.

^{48/} The Supreme Court noted the balancing implicit in the benzene standard: "... OSHA adopted an action level [of 0.5 ppm below which monitoring was not required], largely because the insignificant benefits of ... performing the necessary monitoring did not justify the substantial cost." Industrial Union Department, 00 S.Ct. 2844 at 2868.

DO 068115
CONFIDENTIAL

YZ0015952

levels to justify a standard of 1 ppm.^{49/} The safety margin would be justified by the uncertainties of benzene research and the nonsensitive nature of epidemiological studies, as well as by the potentially important factor of individual susceptibility which research has not tried to measure. However, even this roughly quantitative approach was not used in its promulgation of the standard.

OSHA's review of the research on benzene's health effects was, with the exception of its initial reliance on the Infante study as quantitatively significant, thorough and accurate.^{50/} OSHA issued the new exposure standard based on benzene leukemogenicity because the Infante study represented strong qualitative evidence of this link which was not considered in setting past standards^{51/} and because in contrast to leukemia, blood disorders caused by low level exposure are apparently reversible. OSHA also considered the slight evidence of benzene's cytogenetic effects, but little research on these effects and on fetotoxicity was available at the time.

^{49/} Industrial Union Dept. v. American Petroleum Institute, Brief for the Federal Parties, p.21, n.25.

^{50/} OSHA's assessment that the results were significant or indicative or risk is a matter of policy-based judgment.

^{51/} OSHA, however, issued its ETS under the impression that the Infante study offered data about low benzene concentrations, and the association of benzene and leukemia was reasonably well-established prior to the Infante study.

Finally, the uncertainty associated with OSHA's argument that there is no safe level for a carcinogen should be noted. The linear no-threshold theory assumes that one molecule of a carcinogen hitting a cell at the right site can cause cancer. It is a subject of ongoing debate but is, in any case, accepted government policy. (Nelson, 1978; Lave, 1978).

In sum, OSHA did not use risk assessment even to set priorities before deciding to regulate benzene. To add quantitative substantiation to its case, OSHA could have pointed to evidence of benzene leukemogenicity at exposure levels around 100 ppm and used a safety factor based on the recognized scientific uncertainties about benzene's effects and about extrapolation. Since the 1 ppm standard ostensibly based on feasibility itself involved some sort of balancing (known familiarly as turning the screws until the screaming gets too loud), it could have explicitly considered other levels of feasibility or cost, including 5 and .5 ppm. Finally, it could have adapted to its own showing of health effects a quantitative risk assessment like that produced by EPA finds health effects at levels in the low parts per billion. In the wake of the Supreme Court's ruling on benzene, OSHA will have to confront quantitative means of substantiating health effects.

EPA

CAG's risk assessment model for benzene is plausible and CAG generally made reasonable assumptions in the face of limited

evidence. A review of the risk assessment, as detailed in Appendix A, indicates that CAG might have been more explicit about the uncertainties of its assumptions. It would have been helpful for CAG to have considered several values, for example in the estimation of dosage, to indicate a range for the calculated risk. Also, its estimated confidence interval (95 percent from 34 to 235 assuming a precision of within two fold in the exposure estimate) must be interpreted carefully; it refers only to the standard error in the estimate, calculated using standard assumptions. No account is taken of the uncertainties that arise from the unknown exposure levels in each case, misdiagnosed cases (both false positives and false negatives), exposure to other leukemogens, and failure to take into account of latency periods.

The CAG quantitative risk assessment extrapolates down to low exposures on the basis of the linear non-threshold model. As the Table below indicates, the highest response to exposure and effectively all the expected leukemias occur at levels below the lowest concentrations, that is, below 4ppb. Less extreme functional forms for a dose-response relation would, by contrast, indicate almost zero deaths below 10 ppb.

Annual Average Benzene Concentrations (ppb)	People Exposed	Million of ppb- Person-Years	Expected Number of Benzene-Caused Leukemia Deaths/year
10.0	80,000	1.2	0.41
4.1-10.0	200,000	1.4	0.47
1.1- 4.0	115,000,000	287.5	97.50
0.1- 1.0	7,000,000	3.85	1.30
			99.70 Total

This table is a modification of Table 1-2 in the "Assessment of Human Exposure to Atmospheric Benzene" (EPA, 1978) with the expected leukemias calculated following the CAG quantitative risk assessment (see Table 5, CAG risk assessment).

The "Assessment of Human Exposure to Atmospheric Benzene" (1978b) commissioned by EPA from the Stanford Research Institute, is subject to uncertainty due to the paucity of information on which it was based. Data from actual samples of benzene concentrations have subsequently become available.^{52/} While any updating of the risk assessment should utilize these more accurate measures of benzene emissions, it appears that the difference between the old and new estimates does not significantly affect the risk assessment.

As a final point on the scientific basis of the risk assessment, it should be noted that due to the long association of benzene and hematotoxicity, this chemical is one of the most extensively researched. There have been several epidemiological studies of benzene. While dosage data are scarce, such studies

^{52/} A detailed critique of the Exposure Assessment was submitted by API in its comments on the Draft Health Assessment, December 9, 1977.

are a better indicator of human effects than any research on animals^{53/} (Risk Assessment document). Deputy Director of CAG, Dr. Robert McGauhy, has noted on the basis of CAG's significant experience with risk assessment (on over 60 chemicals so far) that the data on benzene are nearly as extensive as that available for any substance.^{54/}

Despite the amount of research on benzene, the unsettled uncertainties, the cost and problems of providing large samples, and the possible lack of occupational settings in which benzene can be isolated as the only contaminant, will hamper the production of more precise, quantifiable information in the future. Given, in addition, the low incidence of leukemia (still relatively low even when induced by benzene), it is unlikely that a well-designed study could show a significant increase in the incidence of leukemia from low-level exposure. It would be impossible to find thousands of workers exposed to 5-15 ppm of benzene over several decades, being sure that exposure was never higher and that exposure to other leukemogens was controlled at 10 ppm. For a quantitative supplement to its finding of health effects, OSHA must turn to extrapolation from epidemiological and toxicological studies. Such extrapolations cannot be

^{53/} See the Quantitative Risk Assessment Document.

^{54/} Conversation per telephone, July 24, 1980. This evaluation is based on the availability of several epidemiological studies on the effects of benzene while data on most toxic substances is limited to animal tests.

mathematical straitjackets, as the Supreme Court recognized. But used with explicit awareness of their limitations, they offer a significant basis for regulatory decision as EPA's use of risk assessment suggests.

The subsequent history of EPA's quantitative risk assessment indicates the ultimate limit on the use of quantitative methods. Commenters at EPA's maleic anhydride hearings, having criticized specific assumptions underlying EPA's calculations, concluded that EPA's risk assessment would show on the same data, but under somewhat modified assumptions, that there is in fact no risk associated with atmospheric exposure to benzene.^{55/} However, once the quantitative showing of risk has been factored into the decisionmaking process, the decision to regulate is a matter of policy.

^{55/} Appendix A suggests modifications of EPA's interpretations of the data, emphasizing objective rather than policy-based criteria for modifying the calculation.

Review of CAG Risk AssessmentMathematical Model Employed

The CAG assumes that for low exposures, the lifetime probability of leukemia may be represented by the linear equation

$$P = A + B x,$$

where

A = the leukemia rate in the absence of benzene,

x = the average lifetime background benzene exposure in ppm,

and

B = the change in the leukemia rate per 1 ppm benzene.

Assuming that the relative leukemia risk, R, of benzene-exposed workers compared to the general population is independent of the length or age of exposure but depends only on the total exposure, it follows that

$$R = \frac{P_2}{P_1} = \frac{A + B(x_1 + x_2)}{A + Bx_1}$$

or

$$RP_1 = A + B(x_1 + x_2),$$

$$P_1 = A + Bx_1$$

so that

$$B = \frac{P_1(R - 1)}{x_2}$$

where

x_1 = ambient air level of benzene

x_2 = industrial level of benzene

P_1 = lifetime probability of dying of benzene with no or negligible benzene exposure.

DO 068122
CONFIDENTIAL

Estimates of R and x_2 are obtained from the epidemiological studies. The exposure values for x_1 are obtained from the Assessment of Human Exposure to Atmospheric Benzene.

The estimation of the lifetime probability, P_1 , of death due to various forms of leukemia for a member of the general population is based on data from the "Vital Statistics of the United States," 1973, Volume II. Age-specific rates are estimated by dividing the number of deaths due to a particular leukemia by the total number of people in that age class. CAG estimates these probabilities on a "constant segmented model" and gives the results in a table.

Infante

Estimation of Relative Risk

CAG accepted Infante's recalculation, based on his more complete followup, of the expected incidence of leukemia from 1.38 to 1.25 per 100,000. CAG also added to Infante's seven leukemia cases two additional ones reported by Dr. Marvin Sakol which were "probably" in Infante's cohort. (See Infante et al., Letter to The Lancet, October 22, 1977, p.868).^{1/} CAG calculates

$$R = \frac{7+2}{1.25} = 7.2$$

Since the additional leukemias were not discovered in the framework of the original study (indeed Infante omits them from his

^{1/} CAG was persuaded by Dr. Sakol's conviction that leukemia deaths were consistently under-reported for reasons associated with workman's compensation, according to Bob McGaughy of CAG.

own calculation of the leukemia incidence - in his letter to the Lancet), we omit them from the calculation of relative risk:

$$R = \frac{7}{1.25} = 5.6$$

Estimation of Average Occupational Exposure

There are no air monitoring records covering 1940 to 1946. A new ventilation system installed in 1946 resulted in a reported range of zero to 15 ppm in "most areas" of the plant. All areas were reportedly within the maximum safe limit of 100 ppm (Baier Testimony, OSHA hearings). CAG assumes on the basis of this information that exposure before 1946 was at least 15 ppm and less than or equal to 100 ppm.

In the absence of any data on pre-1946 exposure levels, though, it is likely that they were higher before 1946 than afterwards. There is no data on man hours spent at particular locations.

There was also testimony of occasional excursions above 1,000 ppm and of uncertainty about the actual use of respirators during duty in areas of unusual concentrations. Also, CAG assumes that actual concentrations were within the recommended levels during the 36 year period; there is no guarantee of this. In addition to the uncertainty about pre-1946 exposures, there is also doubt about technical accuracy in measuring low doses of benzene in the 1940s.

Based on the assumption that the recommended levels were the actual levels for the years of the study,^{2/} CAG estimates a continuous lifetime exposure level of 40.36 ppm for workers starting before 1946, when the level was reduced by improved ventilation, and an exposure duration of 35 years. CAG assumes an exposure of 23.7 ppm for workers starting after 1946, and an exposure duration of 25 years. This and the following calculations assume, non-conservatively, that a worker starting in 1940 or in 1946 stayed in Pliofilm during his whole working life. The group includes workers who may have been employed as little as one day. CAG produced the following two estimates:

Employed prior to 1946	$40.36 \times \frac{240}{365} \times \frac{1}{3} \times \frac{35}{70} = 4.4 \text{ ppm}$
Employed after 1946	$23.7 \times \frac{240}{365} \times \frac{1}{3} \times \frac{25}{70} = 1.8 \text{ ppm}$

CAG calculates the geometric mean of these continuous exposures,

$$4.4 \times 1.8 = 2.81$$

I, however, will use both high and low estimated lifetime averages in subsequent calculations to indicate the range of exposures.

^{2/} CAG tabulates the recommended exposure-limits for the particular years, e.g. 1940-46, 100-15 ppm; 1947, 50 ppm; 1948-56, 35 ppm. CAG arrives at a time weighted average of 23.3-39.3 ppm.

Estimation of Lifetime Probability of Leukemia Per Unit Exposure

Using the calculation of relative risk (R), the lifetime probability of dying from a particular type of leukemia (P), and the model discussed previously, CAG estimates:

$$B = \frac{P_1(R - 1)}{x_2}$$

$$B = .006732 \times \frac{(7.20 - 1)}{2.81} = .014854$$

Using the lower number of deaths (7) found by Infante (resulting in the relative risk estimate of 5.6) and using both the high and low estimates of lifetime exposure arrived at above, I calculate estimates 1/4 to 1/2 those of CAG:

$$\text{High: } B = .006732 \times \frac{(5.6 - 1)}{4.4} = .00738$$

$$\text{Low: } B = .006732 \times \frac{(5.6 - 1)}{1.8} = .00374$$

AksoyEstimation of Relative Risk

In calculating the leukemia rate per unit of benzene exposure using Aksoy's results, CAG first estimates the incidence of leukemia using the figure of 25 cases out of a population of 28,500 shoeworkers at risk during the 6-2/3 years of observation. CAG, eliminating the cases of lymphoblastic leukemia, "not thought to be associated with benzene exposure" (1978c, p.15), estimates the incidence among shoeworkers to be 13.15 per

100,000. Modifying the available estimate of the incidence of all leukemias in the Turkish population (2.5 to 3.0 per 100,000), CAG calculates an expected incidence of non-lymphoblastic leukemia of .66 per 100,000. There is uncertainty about the actual incidence of leukemia in the general Turkish population; industry witnesses at the OSHA hearings pointed to higher European incidences. But the cancer rate in less developed Turkey is presumably lower and CAG's estimated number of expected deaths is reasonably conservative.

CAG arrives at the incidence of leukemia associated with occupational benzene exposure as

$$R = \frac{13.15}{.66} = 19.92$$

Estimation of Lifetime Average Exposure

CAG uses Aksoy's estimate that the benzene concentration in the shop outside of working hours was 15 to 30 ppm and the level during working hours was 150 to 210 ppm. CAG takes the geometric mean of these exposures:

$$x_2 = \frac{(15 + 30)}{2} \times \frac{(150 + 210)}{2} = 63.6 \text{ ppm} \quad (a)$$

Assuming a ten hour working day, 300 day working year, average age at the end of observation of 50, and average period of exposure of 9.7 years, CAG calculates lifetime average exposure

$$x_2 = 63.6 \times \frac{(10)}{24} \times \frac{(300)}{365} \times \frac{(9.7)}{50} = 4.22 \text{ ppm}$$

DO 068127
CONFIDENTIAL

Computation (a) above assumes that the duration of the non-working hour concentration was equal to that of the higher working hour concentration. This results in an estimate of average exposure, 63.6, that is lower than the mean of the working hour exposure, which would be 180 ppm.

In the calculations that follow, CAG does not take into account this non-working hour workshop concentration. But considering that the shoeworkers' shops are likely attached to their abodes, this exposure level represents a background exposure that must be distinguished from the background ambient air exposure of American workers, which is on the order of a few parts per billion. Instead of taking the mean of these exposures and weighting them for 10 hours of work per day, we assume a 10 hour working exposure at the high level and add a 10 hour non-working hour exposure to the background level. Also, the figures used by CAG are low. Aksoy has noted the poor ventilation of the shoeworkers' shops; the low boiling point of benzene would lead to higher concentrations in a warm climate. In any case, Aksoy himself uses the range of 210 to 650 ppm.^{3/} We use these modified assumptions and figures in calculating lifetime average exposure:

$$\left(\frac{15 + 30}{2} \right) \left(\frac{10}{24} \right) + \left(\frac{210 + 650}{2} \right) \left(\frac{10}{24} \right) \times \left(\frac{300}{365} \right) \times \left(\frac{9.7}{50} \right) = 30.06 \text{ ppm}$$

^{3/} Aksoy, "Leukemia in Shoeworkers Chronically Exposed to Benzene."

DO 068128
CONFIDENTIAL

To indicate the range of possible exposure, we also calculate lifetime exposure on the basis of CAG's more conservative figure for working hour exposure.

$$\left(\frac{15 + 30}{2} \right) \left(\frac{10}{24} \right) + \left(\frac{150 + 210}{2} \right) \left(\frac{10}{24} \right) \times \left(\frac{300}{365} \right) \times \left(\frac{9.7}{50} \right) = 30.06 \text{ ppm}$$

Estimation of Lifetime Probabilities of Levels per Unit Exposure

CAG applies its average exposure figure to the equation given earlier:

$$B = \frac{P_1(R - 1)}{x_2}$$

$$B = .04517 \times \frac{(19.92 - 1)}{4.22} = 0.20252$$

I calculate with the higher exposure figure and accounting for the relatively high background exposure

$$B = .04517 \times \frac{(19.92 - 1)}{28.0095} = .00342$$

Ott

Estimation of Relative Risk

3 deaths with .8 expected ($p < 0.047$)

$$R = \frac{3}{.8} = 3.75$$

Estimation of Lifetime Average Exposure

Ott estimated the ppm/months of exposure of each worker from records and plant benzene measurements (in ranges from high

(25+ ppm TWA) and low (2 to 9 ppm TWA) exposure) (high (1,000+ ppm months) low (zero to 499 ppm months)) observed and expected deaths and tabulated them in terms of observed and expected deaths corresponding to duration of exposure (see Ott, Table 7). CAG took the average of each exposure level and weighted averages by expected deaths.

$$\frac{(250 \times 65.1 + 750 \times 16.2 + 1250 \times 32.8)}{65.1 + 16.2 + 32.8} = 608.46 \text{ ppm months}$$

CAG then calculated the average lifetime exposure on the assumptions of an 8-hour day, a 240-day working year, and an average age at the end of observation period of 65 years.

$$\frac{(608.46)}{(12)} \times \frac{(8)}{(24)} \times \frac{(240)}{(365)} \times \frac{(1)}{(65)} = .171 \text{ ppm}$$

The object of weighting exposure by expected mortality values is to introduce an element of duration and proportionality (deaths correspond to level of exposure and time) but exposure can be correlated more directly with time by weighting the mean exposure level in a production area by duration of exposure in that area.

In Table 5, Ott gives the number of workers who spent a certain number of years in a particular production area:

	<u><1 year</u>	<u>1-9 years</u>	<u>10-19 years</u>	<u>20+ years</u>
I	9	36	20	43
II	21	64	23	27
III	96	139	39	24

DO 068130
CONFIDENTIAL

The average number of years spent in a particular production area is derived from the table by weighting the mean number of years in a range by the number of workers in that range

$$I \quad (9 \times 1 + 36 \times 5 + 20 \times 15 + 43 \times 30) / (9 + 36 + 20 + 43) = 16.47$$

$$II \quad (3 \times 1 + 12 \times 5 + 1 \times 15 + 5 \times 30) / (3 + 12 + 1 + 5) = 10.85$$

$$III \quad (1 \times 1 + 13 \times 5 + 13 \times 15 + 10 \times 3) / (1 + 13 + 13 + 10) = 15.16$$

These figures for the average number of years spent in a production area are used to weight the mean exposure level for each production area, to derive the average occupational exposure. Ott gives the ranges of exposure level for the production areas on pp.3-4:

I Low (2-9 ppm TWA), very low (<2 ppm TWA)

II High (25+ ppm TWA) moderate (10-24 ppm TWA), low, very low

III High

$$\frac{(3 \times 16.47 + 13 \times 10.85 + 30 \times 15.16)}{16.47 + 10.85 + 15.16} = 15.19 \text{ ppm average occupational exposure}$$

Using CAG's assumption of an 8-hour day and 240-day working year, and estimating the average duration of years on the job to be 15.5, we calculate the average lifetime exposure

$$15.19 \times \frac{240}{365} \times \frac{1}{3} \times \frac{(15.50)}{70} = .737 \text{ ppm}$$

Estimation of Lifetime Probability of Leukemia per unit Exposure

Using the equation

$$B = \frac{P_1(R-1)}{x_2}$$

DO 068131
CONFIDENTIAL

CAG calculates the lifetime probability of leukemia per unit exposure to be

$$B = .002884 \times \frac{(3.75 - 1)}{.171} = .04638$$

Substituting our value for the lifetime average exposure, we estimate

$$B = .002884 \times \frac{(3.75 - 1)}{.737} = .01076$$

Finally, CAG takes the geometric mean of its values for B to compute the total probability of deaths due to 1 ppm of benzene in the air breathed over a lifetime:

$$B = \sqrt[3]{.014854 \times .020252 \times .046380} = .024074$$

However, because the studies vary considerably in population size and thus should not be accorded equal statistical weight, we weight our estimates of the lifetime probability of leukemia per unit of benzene (B) by the square root of the population on which the probability is calculated:

$$B = \frac{(.00738 \times 748) + (.00342 \times 28,500) + (.01076 \times 594)}{748 + 28,500 + 594} = .0047193$$

Expected Number of Leukemia Deaths Due to Environmental Exposure to Benene

With D representing units in 10^6 ppb person years, the expected number of leukemia deaths per year may be estimated approximately by the relationship

DO 068132
CONFIDENTIAL

YZ0015969

$$M_D = \frac{.024074 \times D \times 10^3}{70.96} = .33962 D$$

where .24074 is the geometric mean of the slope parameters of the three studies and 70.96 is the average life expectancy in the U.S. By this equation and using our weighted average of the slope parameters, we calculate

$$M_D = \frac{.0047193 \times D \times 10^3}{70.96} = .066506 D$$

Using exposure figures for sources from the "Assessment of Human Exposures" document, CAG calculates expected deaths:^{4/}

<u>Sources of Exposure</u>	<u>Exposure in 106 ppb-person years</u>	<u>CAG Expected Number of Benzene Leukemia Deaths per year</u>	<u>Our recalculation of expected deaths</u>
Chemical Manufacturing	8.5	2.88	.57
Coke Ovens	.2	.07	.01
Petroleum Refineries	2.5	.85	.17
Automobile Emissions	150.0	50.89	9.98
Gasoline Service Stations	19.0	6.44	1.26
Self-Service Gasoline	1.6	.54	.11
		<u>61.67</u>	<u>12.10</u>

CAG also uses exposure figures based on a second model that instead of assuming a static population tries to follow the typical individual through a typical day, a primary factor of which is the location of his residence. CAG then calculates deaths:^{5/}

^{4/} This is Table 4 in the CAG risk assessment, with our calculations added.

^{5/} Table 5, CAG risk assessment (EPA 1978c).

<u>Vicinity of Residence</u>	<u>Exposure in 106 ppb-person years</u>	<u>CAG Expected Number of Benzene Leukemia Deaths per year</u>	<u>Our recalculation of expected deaths</u>
Chemical Manufacturing	10.0	3.39	.67
Coke Ovens	.2	.07	.01
Petroleum Refineries	4.5	1.53	.29
Urban Areas	<u>250.0</u>	<u>84.80</u>	<u>16.63</u>
	264.7	89.80	17.60

We thus calculate that about 18 leukemia deaths per year can be expected from ambient benzene exposure, compared to 90 found by CAG.

Risk Assessment in Reply Brief for the
Federal Parties, Appendix, Industrial Union
Department v. American Petroleum Institute

The appendix to the OSHA reply brief is a review of the uncertainties of risk assessment compiled in response to the Fifth Circuit decision requiring an agency risk assessment before setting a standard. OSHA presented a risk assessment in conclusion to its critique as a counter example.

In its example, OSHA uses only the Infante study, taking the figures of 5.6 excess leukemias in a population of 748 and an exposure level of 10 ppm. OSHA assumes an exposure duration of five years (resulting from a five year turnover) and calculates that a follow-up over the lifetime of the cohort would find 17 leukemias resulting from the constant leukemia rate. Assuming that 30,000 workers are exposed to 10 ppm of benzene, then 690 leukemias would result every five years.

OSHA uses only one study. It makes the unfounded assumption that the Infante study involved average exposures of 10 ppm. While it is correct in trying to account for turnover, duration of exposure is unknown and an average of only five years seems low. OSHA makes an exaggerated speculation that a follow-up of the remaining 25 percent of the cohort would result in a total of 17 leukemias assuming the rate of observed over expected leukemias of the first 75 percent remained constant over the lifetime of the cohort. While it is appropriate to account for latent effects and thus to expect that some leukemias will yet

develop in the future, 27 years had already elapsed since the period of exposure involved in the study, an ample space for the development of latent leukemias.

Finally, the calculation used here is simplistic. Whereas CAG factors in several elements to arrive at a relatively narrow range of slope parameters, OSHA's calculation (10 ppm = 7 deaths in 748 workers) will give one data point that cannot be readily compared to another derived from Aksoy or Ott.^{1/} OSHA's critique of risk assessment in its brief is reasonable; its list of uncertainties should have been incorporated in its risk assessment.

^{1/} OSHA's risk assessment is, however, no more simplistic than that of Richard Wilson (direct testimony before OSHA, In re Proposed Standard for Occupational Exposure to Benzene, OSHA Docket No. H-059, 1977), a risk assessment that evidently persuaded the Fifth Circuit that risk analysis was feasible. OSHA answered with the above assessment and pointed out that Wilson had not explained his calculation. OSHA, however, did not respond to the more detailed analysis prepared by CAG.

Outside Pressure on OSHA

The following is a brief review of the background of the OSHA benzene standard to suggest the political pressures involved.^{1/}

Benzene had long been of concern to the Rubberworkers Union; a number of studies had found excess leukemia deaths associated with solvent use in that industry. But OSHA had rejected pressures for a benzene standard for three years after the chemical was designated a "suspected leukemogen" in the 1974 NIOSH Criteria Document in the absence of data to warrant changing the standard. In 1976, the Secretary of Labor had again directly rejected urgings of the Rubberworkers for a new standard.

In 1976, the Assistant Secretary for OSHA, newly designated but not yet confirmed, began to immediately organize an emergency standard for benzene. Dr. Eula Bingham was a toxicologist and knew the scientific data on benzene. She strongly felt it should be regulated to the lowest feasible level. Dr. Bingham was also interested in the advocacy function of OSHA. OSHA's past refusal to regulate benzene in the face of union concern, was seen as symbolic of its past failure to regulate toxic chemicals.^{2/}

^{1/} This account is based on several interviews that are not cited individually.

^{2/} Union pressure aside, OSHA was criticized in 1977 in a GAO report to a House oversight hearing for its slowness in promulgating health, as opposed to safety, standards, as a result of new interest in OSHA health standards generated by Bingham's predecessor, Dr. Morton. Hearings before a subcomm., Comm. on Gov. Operations, House of Representatives, 95th Cong., 1st Sess., April 27, 1977.

Thus, a benzene regulation would be a sign of OSHA's concern about toxic agents.

Promulgation of a new benzene standard could be sufficiently justified by evidence of benzene's association with leukemia: past regulations had been based on benzene's general toxicity and relation to non-malignant blood disorders and OSHA had a policy holding that there is holding that no level of a carcinogen is safe. An ETS, however, is a relatively extraordinary measure. To justify it, OSHA would have to find a new scientific basis for regulating benzene after having refused to do so for three years. Dr. Bingham, who knew Dr. Infante personally and was aware of his study of benzene then in progress, sought his results as a new basis for an ETS. The study was subsequently rushed into print in The Lancet with the follow-up only 75 percent complete. OSHA relied heavily on the Infante study in its ETS promulgation and apparently attributed to it quantitative significance concerning the effects of low benzene dosage. As OSHA subsequently recognized the basically qualitative focus of the study, it relied less on the study and in the proposed permanent standard emphasized the standard's foundation in the whole scientific record in the proposed permanent standard.

OSHA's scientific staff made clear the problems, primarily the lack of new data, with the proposed standard. It felt that it was not consulted to any extent because the decision had already been made to set the new standard.

Background on EPA Risk Assessment

In 1975, benzene was listed among 10 high volume industrial chemicals for which limited budget, fast assessments were undertaken by EPA in prioritizing air borne pollutants. These assessments considered the sources of emissions, the populations exposed, and potential technological controls. Subsequently, EPA collated priority lists based on the biological hazards and environmental impacts of pollutants, of various agencies and bodies and identified benzene as a high priority. In 1977, the recommendation of NIOSH that an emergency standard should be issued for benzene added momentum to EPA's handling of benzene. Finally, the Environmental Defense Fund's petition precipitated the listing of benzene as a hazardous air pollutant.

The scientific staff dealing with benzene at EPA did not notice political pressure for the listing of benzene, though policymakers might have. EPA's constituency is not as focused as OSHA's and likely had less influence over specific programs.

EPA's compiling of a human exposure survey and quantitative risk assessment in addition to the usual health effects document was an innovation intended to establish the parameters of risk associated with benzene. The actual role of the risk assessment in regulating benzene emissions is unclear. The health effects and human exposure documents were evidently considered the substantial bases for action. The risk assessment, based on benzene leukemogenicity, does not cover the other effects to

which the general population is exposed. Although the listing of benzene as a hazardous air pollutant in 1977 signifies only the identification of a potential hazard, no substance so listed has subsequently been removed from the list. Thus, the preliminary stages evaluating the health effects of benzene largely determined its regulation. The quantitative risk assessment, developed after the listing of benzene in 1977, was used as supplementary evidence of a hazard. It evidently was a factor in prioritizing benzene sources and thus in regulating maleic anhydride. It was an element in the risk-benefit balancing on which the choice of a regulatory option was based.

REFERENCES

- Aksoy, M., et al. Hematological effects of chronic benzene poisoning in 217 workers. 1971. Br. J. Ind. Med. 28: 296-302.
- Aksoy, M., et al. Details of blood changes in 32 patients with pancytopenia associated with long-term exposure to benzene. 1972a. Br. J. Ind. Med. 29: 56-64.
- Aksoy, M., et al. Acute leukemias due to chronic exposure to benzene. 1972b. Am. J. Med. 52: 160.
- Aksoy, M. et al. Acute leukemia in two generations following chronic exposure to benzene. 1974a. Hum. Hered. 24: 70.
- Aksoy, M., et al. Leukemia in shoe-workers exposed chronically to benzene. 1974b. Blood. 44: 837.
- Aksoy, M., et al. Types of leukemia in chronic benzene poisoning. A study in 34 patients. 1976. Acta Haemat. 55: 65.
- Aksoy, M. Leukemia in workers due to occupational exposure to benzene. 1977. New Istanbul Centris. Clin. Sci. 12: 3-14.
- Aksoy, M. Letter "Benzene and leukemia." 1978a. Lancet. 1: 441.
- Aksoy, M., and Erdem, S. Follow-up study on the mortality and the development of leukemia in 44 pancytopenic patients with chronic exposure to benzene. 1978 b. Blood. 52: 285.
- Chang, Im Won. Study on the threshold limit value of benzene and early diagnosis of benzene poisoning. 1972. J. Cath. M d. Coll. 23: 429-434. Cited in EPA, 1978a.
- Committee on Toxicology, NAS. Health effects of benzene, a review. 1976.
- Consumer Product Safety Commission Report. Review and analysis of the literature pertaining to the reproductive effects of exposure to benzene. 1980.
- Court Brown, W. Human Population Genetics. 1967.
- Deichmann, W., et al. The hemopoietic tissue toxicity of benzene vapors. 1963. Toxicol. Appl. Pharmacol. 5: 201-224.
- EPA, Assessment of Health Effects of Benzene Germane to Low-level Exposure. September 1978a.
- EPA, Assessment of Human Exposure to Atmospheric Benzene. June 1978b.

- EPA, Cancer Assessment Group, Report on population risk from ambient benzene exposure, 1979.
- EPA, Initial evaluation of Exxon's 8(e) submission of benzene teratology, 1980.
- Forni, A.M., et al. Chromosome changes and their evolution in subjects with past exposure to benzene. 1971. Arch. Environ. Health. 23: 385-391.
- Forni, A.M., et al. Chromosome studies in workers exposed to benzene, toluene, or both. 1977. Arch. Environ. Health. 22: 373-378.
- Girard, R., et al. Hydrocarbures, benzeniques et hemopathies graves. 1979. Arch. Malad. Prof. 31: 625-635.
- Gofmekler, V.A. Effect on embryonic development of benzene and formaldehyde. 1968. Hyg. Sant. 33: 327-332.
- Goldstein, B.D. Hematotoxicity in humans. 1977, in Laskin, 69-107.
- Green, J.D., et al. Inhaled benzene fetotoxicity in rats. 1978. Toxicol. Appl. Pharmacol. 46: 9-18.
- Hartwich, G., Schwanitz, G. Chromosomenuntersuchungen nach chronischer Benzol-Exposition. 1972. Deutsche Med. Woch. 97: 45-51.
- Hazelton Laboratories Study, 1977.
- Hett, J., Maak, H. 1938. Klinische Wochenschrift. 17: 1376.
Cited in Consumer Products Safety Commission.
- Industrial Union Dept. v. American Petroleum Institute. 100 S.Ct. 2844, 1980.
- Industrial Union Dept. v. American Petroleum Institute. Brief for the Federal parties in the Supreme Court, 1979.
- Infante, P.F., et al. Leukemia in benzene workers. 1977. Lancet. 2: 76-78.
- Infante, P.F. Reply. 1977. Lancet. 2: 868.
- Jenkins, L.J., Jr., et al. Long-term inhalation screening studies of benzene, toluene, o-xylene and cumene on experimental animals. 1970. Toxicol. Appl. Pharmacol. 16: 818-823.

- Kissling, M., Speck, B. Chromosome aberration in experimental benzene intoxication. 1972. Helv. Med. Acta. 36: 59-66.
- Laskin, S., Goldstein, B.D. Benzene Toxicity, A Critical Evaluation. 1977. J. Tox. Env. Health. Supp. 2.
- Lave, L. Health benefits of abating air pollutants. 1978. Bull. N.Y. Acad. Med. 54: 1235-1244.
- Leong, B.L. Experimental benzene intoxication. 1977, in Laskin. 45-63.
- A.D. Little & Co. Economic Impact Statement. Dept. of Labor, 1977.
- Litton Bionetics, A teratology study in rats. 1977, 1978.
- McMichael, A.J., et al. Solvent exposure and leukemia among rubber workers, an epidemiologic study. 1975. J. Occ. Med. 17: 234-239.
- Maltoni, C., Scarnato, C. The first experimental proof of the carcinogenic action of benzene. 1979. Med. Lavoro. 5: 332-357.
- Mitelman, F., Levan, G. Clustering of aberrations to specific chromosomes in human neoplasms, III. Incidence and geographic distribution of chromosome aberrations in 856 cases. 1978. Hereditas. 89: 207.
- Murray, F.J., et al. Embryotoxicity of inhaled benzene in mice and rabbits. 1979. Am. Ind. Hyg. Assoc. J. 40: 993-998.
- Nawrot, P.S., Staples, R.E. Embryofetal toxicity and teratogenicity of benzene and toluene in the mouse. 1979. Teratology. 19(2): 41A.
- Nelson, N. Discussion of paper by Vaun A. Newill, R. Wyzga and James R. McCarroll. 1978. Bull. N.Y. Acad. Med. 54: 1245-1256.
- NIOSH, Occupational Exposure to Benzene. 1974.
- Occupational Safety and Health Administration. Transcript of Proceedings, Informal hearing on proposed standard for exposure to benzene. 1977.
- Ott, M.G., et al. Mortality among individuals occupationally exposed to benzene. 1978. Arch. Occ. Health. 31: 3-10.

- Picciano, D. Cytogenetic study of workers exposed to benzene. 1979. Env. Res. 19: 33-38.
- Snyder, R., Kocsis, J.J. Current concepts of benzene toxicity, June 1978. CRC Critical Reviews in Toxicology. 265-288.
- Stallones, R.A. Report on mortality from leukemia, Shell Oil Co. 1977.
- Tabershaw, I., Mortality study among refinery workers. 1974.
- Tabershaw, I., Lamm, S., Letter, Lancet 2, 867 (1977).
- Tareeff, E.M., et al. Benzene leukemias. 1963. Acta. Unio. Int. Contra. Cancrum. 19: 751-755.
- Thorpe, J.J. Epidemiological survey of leukemia in persons potentially exposed to benzene. 1974. J. Occ. Med., 16: 375-382.
- Tough, I.M., Court Brown, W. Chromosome aberrations and exposure to ambient benzene. 1965. Lancet. 1: 684-689.
- Tough, I.M., et al. Chromosome studies in workers exposed to atmospheric benzene. 1970. Europ. J. Cancer. 6: 49-55.
- Usery, W.J., Jr. Letter to P. Bommarito, May 14, 1976.
- Vara, P. and Kinnunen, O. 1946. Acta Obstet. Gynecol. Scand. 26: 433-452. Cited in Consumer Products Safety Commission.
- Vigliani, E.C. Leukemia associated with benzene exposure. 1976a, Ann. N.Y. Acad. Sci. 271: 143-151.
- Vigliani, E.C., Occupational Animal factors, Proc. XI Intern, Congr. Cancer., 1976b.
- Vigliani, E.C. Benzene and leukemia, 1976, Env. Res., 11: 122-127.
- Vogel, P. and Motulsky, A.G., Human Genetics, 1979, 320-322.
- Watanabe, G.I., Yoshida, S. The teratogenic effect of benzene in pregnant mice, 1970, Acta Med. Biol., 17(4): 285-291.
- Wolman, S.R. Cytologic and cytogenetic effects of benzene, 1977, in Laskin, 63-66.