EPA-540/1-86-037

Office of Research and Development
Office of Health and Environmental Assessment
Environmental Criteria and Assessment Office
Cincinnati OH 45268

Superfund

EPA

HEALTH EFFECTS ASSESSMENT FOR BENZENE

EPA/540/1-86-037
September 1984

HEALTH EFFECTS ASSESSMENT FOR BENZENE

U.S. Environmental Protection Agency
Office of Research and Development
Office of Health and Environmental Assessment
Environmental Criteria and Assessment Office
Cincinnati, OH 45268

U.S. Environmental Protection Agency
Office of Emergency and Remedial Response
Office of Solid Waste and Emergency Response
Washington, DC 20460

DISCLAIMER

This report has been funded wholly or in part by the United States Environmental Protection Agency under Contract No. 68-03-3112 to Syracuse Research Corporation. It has been subject to the Agency's peer and administrative review, and it has been approved for publication as an EPA document. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with benzene. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to September, 1984. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1978b. Estimation of Population Cancer Risk from Ambient Benzene Exposure. Prepared by the Carcinogen Assessment Group, OHEA, Washington, DC. Internal draft. (Cited in U.S. EPA, 1980b)

U.S. EPA. 1980b. Ambient Water Quality Criteria for Benzene. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 440/5-80-018. NTIS PB 81-117293.

U.S. EPA. 1982. Reportable Quantity for Benzene. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1983b. Review of Toxicologic Data in Support of Evaluation for Carcinogenic Potential of Benzene. Prepared by the Carcinogen Assessment Group, OHEA, Washington, DC for the Office of Solid Waste and Emergency Response, Washington, DC.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data was limited in scope tending to generate conservative (i.e. protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, the AIS or acceptable intake subchronic, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval which does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used, or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is

assumed. Animal data used for AIS estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure.

The AIC, acceptable intake chronic, is similar in concept to the ADI (acceptable daily intake). It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980a) for a discussion of this concept]. The AIC is route specific and estimates acceptable exposure for a given route with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CS) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities; the methodology for their development is explained in U.S. EPA (1983a).

For compounds for which there is sufficient evidence of carcinogenicity, AIS and AIC values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980a). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. Consequently, derivation of AIS and AIC values would be inappropriate. For carcinogens, q_1*s have been computed based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, the reader is referred to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of quantitative estimates presented.

Considerable human data are available linking inhalation exposure to benzene with leukemia. A carcinogenic potency for inhaled benzene of 2.59×10^{-2} $(mg/kg/day)^{-1}$ may be estimated using data from several epidemiological investigations. Animal data concerning the carcinogenicity of inhaled benzene are equivocal.

Data regarding cancer incidence in humans following oral exposure to benzene were not located. Only one animal bioassay for the carcinogenicity of orally administered benzene was located (Maltoni and Scarnato, 1979). Using the linearized multistage model (U.S. EPA, 1980a), a q_1^* of 4.4512×10^{-2} $(mg/kg/day)^{-1}$ was computed. This value compares favorably with the unit risk estimate of 5.2×10^{-2} $(mg/kg/day)^{-1}$ estimated from human inhalation data by U.S. EPA (1980b). For the purposes of the present assessment, the unit risk estimate of 5.2×10^{-2} $(mg/kg/day)^{-1}$ is proposed to represent the carcinogenic potency of benzene following oral exposure. As more complete data concerning the carcinogenicity of orally administered benzene are available, this estimate should be reviewed.

ACKNOWLEDGEMENTS

The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3112 for EPA's Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa and Karen Blackburn were the Technical Project Monitors and Helen Ball was the Project Officer. The final documents in this series were prepared for the Office of Emergency and Remedial Response, Washington, DC.

Scientists from the following U.S. EPA offices provided review comments for this document series:

Environmental Criteria and Assessment Office, Cincinnati, OH
Carcinogen Assessment Group
Office of Air Quality Planning and Standards
Office of Solid Waste
Office of Toxic Substances
Office of Drinking Water

Editorial review for the document series was provided by:

Judith Olsen and Erma Durden
Environmental Criteria and Assessment Office
Cincinnati, OH

Technical support services for the document series was provided by:

Bette Zwayer, Pat Daunt, Karen Mann and Jacky Bohanon
Environmental Criteria and Assessment Office
Cincinnati, OH

TABLE OF CONTENTS

	Page
1. ENVIRONMENTAL CHEMISTRY AND FATE	1
2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS	2
2.1. ORAL	2
2.2. INHALATION	2
3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS	3
3.1. SUBCHRONIC	3
3.1.1. Oral	3
3.1.2. Inhalation	3
3.2. CHRONIC	5
3.2.1. Oral	5
3.2.2. Inhalation	5
3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS	7
3.3.1. Oral	7
3.3.2. Inhalation	7
3.4. TOXICANT INTERACTIONS	9
4. CARCINOGENICITY	10
4.1. HUMAN DATA	10
4.1.1. Oral	10
4.1.2. Inhalation	10
4.2. BIOASSAYS	12
4.2.1. Oral	12
4.2.2. Inhalation	12
4.3. OTHER RELEVANT DATA	15
4.4. WEIGHT OF EVIDENCE	16
5. REGULATORY STANDARDS AND CRITERIA	17

TABLE OF CONTENTS (cont.)

	Page
6. RISK ASSESSMENT	20
6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)	20
6.2. ACCEPTABLE INTAKE CHRONIC (AIC)	20
6.3. CARCINOGENIC POTENCY (q_1*)	20
6.3.1. Oral	20
6.3.2. Inhalation	20
7. REFERENCES	22
APPENDIX A: Cancer Data Sheet for Derivation of q_1*	41
APPENDIX B: Summary Table for Benzene	42

LIST OF TABLES

No.	Title	Page
4-1	Incidences of Leukemia and Zymbal Gland and Mammary Gland Carcinomas in Sprague-Dawley Rats Given Benzene by Gavage	13
4-2	Incidences of Hematopoietic Tumors in Mice Exposed to Benzene Vapors by Inhalation.	14
5-1	National Occupational Exposure Limits for Benzene	18

LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
AIC	Acceptable intake chronic
AIS	Acceptable intake subchronic
bw	Body weight
CAS	Chemical Abstract Service
CS	Composite score
NOEL	No-observed-effect level
ppm	Parts per million
SMR	Standardized mortality ratio
STEL	Short-term exposure limit
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

The physical and chemical properties and environmental fate of benzene (CAS No. 71-43-3) are given below:

Chemical class:	monocyclic aromatic hydrocarbon
Molecular weight:	78.12 (Callahan et al., 1979)
Vapor pressure:	95.2 mm Hg at 25°C (Callahan et al., 1979)
Water solubility:	1750 mg/ℓ at 25°C (Banerjee et al., 1980)
Octanol/water partition coefficient:	132 (Banerjee et al., 1980)
Bioconcentration factor:	12.6 (MacKay, 1982)
Half-lives in:	
Air:	6 days (Singh et al., 1981)
Water:	1-6 days (estimated)

The half-life of benzene in aquatic media has been estimated from the reaeration rate ratio of 0.574 and the oxygen reaeration rate of 0.19 day^{-1} to 0.96 day^{-1} (Mabey et al., 1981).

An estimate for the half-life for benzene in soil was not located in the available literature. By analogy with its probable fate in aquatic media, evaporation is expected to be the predominant loss mechanism from the soil surface. Considering its reasonably high water solubility and reasonably low soil-water distribution coefficient (Chiou et al., 1983), benzene is expected to leach from soil. Coniglio et al. (1980) reported, however, only an 8.5% frequency of occurrence of benzene in groundwater samples throughout the United States, compared with a 70% frequency for chloroform. Therefore, both volatilization and biodegradation may account for the primary loss of benzene from soil before it has the chance to leach appreciably from soil to groundwater.

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

Although quantitative data regarding the rate and extent of benzene absorption from the gastrointestinal tract are not available, absorption can be inferred from oral toxicity and carcinogenicity studies (Chapters 3 and 4).

2.2. INHALATION

Although quantitative data regarding the rate and extent of pulmonary benzene absorption are not available, absorption can be inferred from studies reporting effects in humans and animals following exposure to benzene vapors (Chapters 3 and 4).

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Wolf et al. (1956) dosed groups of 10 female Wistar rats (~2.75 months old) with benzene at levels of 1, 10, 50 or 100 mg/kg by gavage 5 days/week for a period of 187 days. The control group, consisting of 20 matched animals, received only the vehicle, which was an olive oil solution emulsified with 5-10% aqueous solution of acacia. Hematopoietic effects were reported for all dose levels except the lowest one. No effect on the hematopoietic system was seen at the 1 mg/kg level, while very slight leukopenia was recorded at the 10 mg/kg level, and leukopenia and erythrocytopenia were noted at both the 50 and 100 mg/kg levels. From this study, the 1 mg/kg dose level of benzene can therefore be suggested as a NOEL for leukopenia and/or erythrocytopenia in female rats.

Pertinent data regarding the effects of subchronic oral exposure of humans to benzene were not located in the available literature.

3.1.2. Inhalation

In a series of experiments, Deichmann et al. (1963) exposed groups of ~40 male and female Sprague-Dawley rats to benzene vapors at levels of 15-831 ppm for 5-13 weeks. After 1-4 weeks of exposure, significant leukopenia was recorded for those animals exposed to $\geq$61 ppm for 5 hours/day, ~5 days/week over a period of 38-46 days. Rats exposed to benzene vapors at a level of 47 ppm for 7 hours/day on 180 days over a period of 245 days had slight or moderate leukopenia, which began at 7-8 weeks of exposure and persisted to the end of the study. Likewise, leukopenia was observed among rats exposed to 44 ppm benzene for 7 hours/day, 5 days/week, for 8 weeks. Leukopenia was not observed in groups of rats exposed to benzene levels $\leq$31 ppm for 7 hours/day, ~5 days/week for periods of 88-126 days. There were no

overt signs of toxicity, effects on body weight gain, anemia or gross pathologic changes at any exposure level (15-831 ppm of benzene). Rats exposed to either 61 or 831 ppm of benzene vapors were examined for bone marrow changes, but there were no differences when compared with control animals. No differences between treated and control animals were observed during extensive histopathological examination of control rats and those exposed to 15, 31 or 47 ppm of benzene. From this study, 31 ppm of benzene can be suggested as the NOEL for leukopenia in rats.

Wolf et al. (1956) exposed groups of 10-25 male and female Wistar rats, 5-10 male guinea pigs and 1-2 male rabbits to benzene vapors at levels of $\geq$88, 88 and 80 ppm, respectively, for 7 hours/day, 5 days/week for 204-269 days. Leukopenia was seen in all three species at the lowest exposure levels tested. In addition, rats exposed to 88 ppm of benzene had increased spleen weights; guinea pigs exposed to 88 ppm had depressed growth, increased spleen and testes weights and unspecified histopathologic changes in the bone marrow; and rabbits exposed to 80 ppm had unspecified histopathologic changes in the kidneys and testes. Rats exposed to benzene vapors at a level of 2200 ppm had signs of necrosis, depressed growth and unspecified histopathologic changes in the spleen and bone marrow, in addition to the effects also seen at the lower exposure level.

No hematologic effects were seen in rats, guinea pigs or dogs exposed to benzene vapors at a level of 17.6 ppm continuously for up to 127 days (Jenkins et al., 1970).

Green et al. (1981) exposed 11 or 12 male CD-1 mice to benzene vapors at a level of 302 ppm for 6 hours/day, 5 days/week for 26 weeks. Treatment-related effects included nearly 50% mortality by the end of the study, as well as marked lymphocytopenia, anemia and reduction of bone marrow, spleen cellularity and spleen weight.

Pertinent data regarding the effects of subchronic inhalation exposure of humans to benzene were not located in the available literature.

3.2. CHRONIC

3.2.1. Oral. Pertinent data regarding the chronic toxicity of benzene following oral exposure of either animals or humans were not located in the available literature.

3.2.2. Inhalation. Snyder et al. (1980) examined the hematotoxic and carcinogenic effects of benzene to mice by exposing groups of 50 male AKR/J mice to filtered air or 100 ppm of benzene, and groups of 40 male C57Bl/6J mice to filtered air or 300 ppm of benzene, for 6 hours/day, 5 days/week for life (up to 505 days for C57Bl mice). For AKR mice, there was no significant difference in median survival or rate of weight gain between treated and control animals. From the first week of exposure through the end of the experiment, marked lymphocytopenia and slight but statistically significant anemia were reported for treated AKR mice relative to controls. Bone marrow hypoplasia was observed in 10/50 treated AKR mice and in 1/50 controls. Similar, but more severe, effects on these parameters in AKR mice were reported in an earlier study conducted at a higher exposure level of 300 ppm of benzene in the same laboratory (Snyder et al., 1978).

A decreased survival rate was reported for treated C57Bl mice, with a median survival of 41 weeks for the treated group and 75 weeks for the control group. Body weight gain of treated C57Bl mice was depressed relative to controls. From the first week of exposure through the end of the experiment, marked lymphocytopenia and anemia were observed in treated C57Bl mice relative to controls. Bone marrow hyperplasia was observed in 13/40 benzene-exposed C57Bl mice and in none of the corresponding control mice.

In an earlier experiment by Snyder et al. (1978), Sprague-Dawley rats, tested similarly at 300 ppm of benzene exhibited a trend toward anemia and had a milder lymphocytopenia than had either AKR mice (Snyder et al., 1978) or C57Bl mice (Snyder et al., 1980) at the same exposure level.

There are numerous reports of the effects of chronic inhalation exposure to benzene in humans. Chronic exposure of humans to benzene vapor causes pancytopenia, which is a reduction of blood erythrocytes, leukocytes and thrombocytes (platelets) (U.S. EPA, 1980b; IARC, 1982; ACGIH, 1980; NIOSH, 1974). In early (mild) cases of chronic benzene poisoning, a decrease in only one type of blood element may occur (i.e., anemia, leukopenia or thrombocytopenia), and the disease appears to be reversible on cessation of exposure. Severe pancytopenia (aplastic anemia) as a result of exposure to benzene is often associated with a marked reduction in bone marrow cellularity (U.S. EPA, 1980b; IARC, 1982). The best evidence for the causal relationship between benzene exposure and pancytopenia is derived from occupational studies in which the appearance of pancytopenia in workers occurred after the use of benzene was instituted, and ceased after benzene was replaced with another solvent (U.S. EPA, 1980b). According to NIOSH (1974), occupational exposures to benzene at 300-700 ppm have been linked consistently with blood dyscrasias (Greenburg, 1926; Savilahti, 1956; Vigliani and Saita, 1964). The lower limit of exposure that will result in hematologic effects in humans is not well defined, but is thought to be <100 ppm (Hardy and Elkins, 1948; Pagnotto et al., 1961; Pagnotto, 1972). There is some evidence for impairment of the immune system in humans chronically exposed to benzene (Lange et al., 1973; Smolik et al., 1973).

An additional consequence of chronic benzene exposure is the induction of acute myelogenous leukemia in humans (Section 4.1.) (U.S. EPA, 1980b; IARC, 1982). According to IARC (1982), there is sufficient evidence that benzene is carcinogenic to humans.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Pregnant mice were given gavage doses of benzene at levels of 0.3, 0.5 or 1.0 mg/kg/day on days 6-15 of gestation (Nawrot and Staples, 1979). Increased mortality among the dams and increased resorption of embryos occurred at all dose levels. At the 1 mg/kg/day dose level (given on days 6-15 or days 12-15 of gestation), there was no statistically significant change in the incidence of malformations.

3.3.2. Inhalation. In most inhalation teratogenicity experiments, benzene was not teratogenic and was fetotoxic only at levels of exposure that were also maternotoxic (U.S. EPA, 1980b; IARC, 1982). In one study, however, evidence of fetotoxicity was observed in mice in the absence of maternotoxicity (Murray et al., 1979), and in another study, suggestive evidence of teratogenic potential was observed in rats at maternotoxic exposure levels (Kuna and Kapp, 1981). Only the studies of Murray et al. (1979) and Kuna and Kapp (1981), summarized by U.S. EPA (1982), will be discussed here; further information is available in U.S. EPA (1980b) and IARC (1982).

Murray et al. (1979) exposed CF-1 mice and New Zealand rabbits to benzene vapors at a concentration of 500 ppm. Groups of 35 and 37 mice were exposed to room air or 500 ppm benzene, respectively, for 7 hours/day, on days 6-15 of gestation. Groups of 20 rabbits were exposed to room air or 500 ppm benzene for 7 hours/day, on days 6-18 of gestation. Changes in body weight and overt signs of toxicity were not observed in exposed animals of either species, nor were differences in numbers of resorptions or viable

fetuses observed. Mean fetal body weight was significantly lower ($p<0.05$) in litters from benzene-exposed mice, but not in litters from benzene-exposed rabbits. Litters of benzene-exposed mice had statistically significant increases in several minor skeletal variants considered to be indicative of delayed development, but not in major malformations. Treatment-related effects were not seen in litters of benzene-exposed rabbits.

Kuna and Kapp (1981) exposed pregnant Sprague-Dawley rats to benzene by inhalation on days 6-15 of gestation. Animals were exposed to 0 ppm (17 females), 10 ppm (18 females), 50 ppm (20 females) or 500 ppm (19 females) for 7 hours/day. No overt signs of toxicity were seen in any of the pregnant dams except for reduced weight gains on days 5-15 of gestation in the 50 and 500 ppm groups. No differences were seen in maternal erythrocyte, leukocyte or differential leukocyte counts, or in implantation efficiencies or number of resorptions. Mean crown rump length was significantly reduced ($p<0.05$) in litters of dams exposed to 500 ppm, and mean fetal body weights were reduced ($p<0.05$) in both the 50 and 500 ppm groups. Delayed ossification occurred at 50 and 500 ppm, and four fetuses (from four litters) of the 500 ppm group had skeletal variants or anomalies; one fetus had exencephaly, one had angulated ribs and two had out-of-sequence ossification of the forefeet. In addition, litters from the high dose group contained three fetuses with dilated lateral and third brain ventricles. Historical incidences of exencephaly, angulated ribs, out-of-sequence ossification of the forefeet, and dilated lateral and third brain ventricles were very low in control rats; these specific abnormalities had not previously occurred together in a single experiment. In the 50 ppm group, delayed ossification of the rib cage and extremities was seen. No anomalies were noted in the lowest dose or control litters. This study suggests a NOEL of 10 ppm for fetotoxic effects in rats.

3.4. TOXICANT INTERACTIONS

Benzene metabolism, and therefore benzene toxicity, is altered by simultaneous exposure to some other solvents (e.g., xylene, toluene) because these aromatic solvents are oxidized by many of the same hepatic enzyme systems (Ikeda et al., 1972; U.S. EPA, 1980b). Reported hematotoxic effects of benzene in humans may be a synergistic result of simultaneous exposure to other solvents (e.g., xylene, toluene), as benzene itself does not induce leukemia in animals (NAS, 1976; U.S. EPA, 1980b). Since benzene metabolites rather than the parent compound are suspected of inducing bone marrow toxicity, inhibition of benzene metabolism (hydroxylation) by toluene may result in increased toxic effects of the parent compound instead of benzene metabolites (Andrews et al., 1977; U.S. EPA, 1980b).

4. CARCINOGENICITY

4.1. HUMAN DATA

4.1.1. Oral. Pertinent data regarding the carcinogenicity of benzene via oral exposure to humans were not located in the available literature.

4.1.2. Inhalation. IARC (1982) has summarized many case studies that suggest a causal relationship between exposure to benzene by inhalation and leukemia in humans (Delore and Borgomano, 1928; Bowditch and Elkins, 1939; Hunter, 1939; Mallory et al., 1939; DeGowin, 1963; Tareeff et al., 1963; Vigliani and Saita, 1964; Goguel et al., 1967; Aksoy et al., 1971, 1972; Aksoy, 1980; Ludwig and Werthemann, 1962; Galavotti and Troisi, 1950; Nissen and Soeborg Ohlsen, 1953; Di Guglielmo and Iannaccone, 1958; Rozman et al., 1968; Bryon et al., 1969; Forni and Moreo, 1969; Girard and Revol, 1970; Goldstein, 1977). Because these studies are secondary to several epidemiology studies for assessing human cancer risk associated with inhalation exposure to benzene, these case studies will not be discussed further. Instead, the reader is referred to the reviews by IARC (1982) and Goldstein (1977).

A number of epidemiology studies have associated occupational exposure to benzene (either alone or in conjunction with other organic solvents) by inhalation with an increased incidence of leukemia (Aksoy, 1977; Infante et al., 1977a,b; Ott et al., 1978; Ishimaru et al., 1971; Vigliani, 1976; Fishbeck et al., 1978; Thorpe, 1974; McMichael et al., 1975; Monson and Nakano, 1976; Tyroler et al., 1976; Brandt et al., 1978; Flodin et al., 1981; Hardell et al., 1981; Greene et al., 1979; Rushton and Alderson, 1980, 1981; Tabershaw and Lamm, 1977; Rinsky et al., 1981). Since the U.S. EPA (1980b) used the studies of Aksoy et al. (1974), Infante et al. (1977a,b) and Ott et al. (1978) to derive a human cancer-based criterion for exposure

to benzene, only these studies will be discussed further. The other epidemiology studies are reviewed in IARC (1982) and U.S. EPA (1978a, 1980b).

Aksoy et al. (1974) examined the effect of benzene exposure on the incidence of leukemia or "preleukemia" among a group of 28,500 workers employed in the shoe industry of Turkey. The mean duration of employment and mean age of this cohort were 9.7 years (range, 1-15 years) and 34.2 years, respectively. Benzene exposure was reported to have occurred in small, poorly ventilated work areas, with peak exposures of 210-650 ppm (670-2075 mg/m^3). Of the 28,500 subjects studied, 26 were reported to have leukemia (34 cases of leukemia or preleukemia were identified). This corresponds to an annual leukemia incidence of ~13/100,000 workers, which yields a relative risk of ~2 when compared with the annual estimate of 6/100,000 for the general population. In a later follow-up study, eight additional cases of leukemia were reported, and there was suggestive evidence of an increase in other malignant diseases (Aksoy, 1980).

Infante et al. (1977a,b) examined the leukemogenic effects of benzene exposure on a cohort of 748 white males exposed to the solvent during the manufacture of a rubber product from 1940-1949. Vital statistics were obtained for the cohort through mid-1975. When compared with either of two separate control populations, the general American population and workers in another industry not using benzene, a statistically significant ($p \leq 0.002$) excess of leukemia was found. Infante et al. (1977a) reported a 5-fold excessive risk of all leukemia and a 10-fold excessive risk of myelocytic and monocytic (probably myelomonocytic) leukemias combined. The lag period for chronic myelocytic leukemia (one case) was 2 years from initial benzene exposure, while the lag period for acute myelocytic and monocytic leukemia (six cases) was 10-21 years. The work environment was reported to be free

of contamination by solvents other than benzene. The air concentrations of benzene were generally below the recommended limits in effect during the period of the study (i.e., 100 ppm in 1941, 50 ppm in 1947, 35 ppm in 1948, 25 ppm in 1957 and 10 ppm in 1969).

Ott et al. (1978) used a retrospective cohort analysis to examine the mortality experience of 594 individuals occupationally exposed to benzene in chemical manufacture during the period 1940-1973. Three deaths attributable to leukemia (one myelogenous and one myeloblastic) and one to aplastic anemia were reported among the 594 workers. Only 0.8 deaths from leukemia (excluding lymphocytic or monocytic cell types) were expected, based on incidence data from the third National Cancer Survey (SMR=375); the difference had marginal statistical significance ($p<0.05$). The TWA benzene concentration to which the three subjects who died of leukemia were exposed was estimated to be <10 ppm.

4.2. BIOASSAYS

4.2.1. Oral. Maltoni and Scarnato (1979) observed increases in zymbal gland and mammary gland carcinomas in female Sprague-Dawley rats and leukemia in male rats administered benzene by gavage. Three groups of 30 or 35 animals of each sex were treated 4-5 times/week for 52 weeks at dose levels of either 50 or 250 mg/kg bw. The control group, consisting of 30 male and 30 female rats, received olive oil only. The tumor incidences for this study are summarized in Table 4-1.

4.2.2. Inhalation. Slight increases in hematopoietic neoplasms were reported for male C57Bl mice (N=40) exposed by inhalation to 300 ppm of benzene for 6 hours/day, 5 days/week for 488 days (Snyder et al., 1980). These tumor incidences are summarized in Table 4-2. In the same study, there was no increase in tumors in 50 male AKR mice exposed to 100 ppm of benzene under the same exposure schedule. Snyder et al. (1980) also failed

TABLE 4-1

Incidences of Leukemia and Zymbal Gland and Mammary Gland Carcinomas in Sprague-Dawley Rats Given Benzene by Gavage[a]

Sex	Dose or Exposure	Duration of Treatment (weeks)	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)
M	0.0 mg	NA	lifespan	NA	olive oil	hematopoietic	leukemia	0/30
M	50 mg/kg 4-5 times/week	52	lifespan	NR	olive oil	hematopoietic	leukemia	0/30
M	250 mg/kg 4-5 times/week	52	lifespan	NR	olive oil	hematopoietic	leukemia	4/35
F	0.0 mg	NA	lifespan	NA	olive oil	zymbal gland mammary gland	carcinoma carcinoma	0/30 (NA) 3/30
F	50 mg/kg 4-5 times/week	52	lifespan	NA	olive oil	zymbal gland mammary gland	carcinoma carcinoma	2/30 (NS)[b] 4/30
F	250 mg/kg 4-5 times/week	52	lifespan	NA	olive oil	zymbal gland mammary gland	carcinoma carcinoma	8/35 ($p<0.05$)[b] 7/35

[a]Source: Maltoni and Scarnato, 1979

[b]Fisher exact test

NA = Not applicable; NR = not recorded; NS = not significant

TABLE 4-2

Incidences of Hematopoietic Tumors in Mice Exposed to Benzene Vapors by Inhalation[a]

Strain	Sex	Dose or Exposure	Duration of Treatment (days)	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)
C57Bl	M	0.0 ppm	NA	lifespan	NA	NA	hematopoietic	all tumors	2/40
C57Bl	M	300 ppm 6 hours/day, 5 days/week	488	lifespan	NR	vapor	hematopoietic	all tumors	8/40
AKR	M	0.0 ppm	NA	lifespan	NA	NA	hematopoietic	all tumors	NR
AKR	M	100 ppm 6 hours/day, 5 days/week	505	lifespan	NR	vapor	hematopoietic	all tumors	NS

[a]Source: Snyder et al., 1980

[b]Lymphomas occurred in two of the control and six of the treated C57Bl mice.

NA = Not applicable; NR = not reported; NS = not significant

to find a statistically significant increased incidence in tumors in male Charles River CD-1 mice (number not specified) exposed to 100 or 300 ppm of benzene under the same exposure schedule previously described; however, myelogenous (myeloid) leukemia was observed in two CD-1 mice exposed to 300 ppm of benzene. A leukemic response was not observed in 45 male Sprague-Dawley rats exposed to benzene vapors at a level of 300 ppm for 6 hours/day, 5 days/week for life (Snyder et al., 1980).

4.3. OTHER RELEVANT DATA

Benzene has been tested extensively for genotoxic properties. Benzene was not mutagenic in several bacterial and yeast systems, including Salmonella typhimurium both in the presence and absence of an exogenous metabolic activating system (Lyon, 1976; Dean, 1978; Shahin and Fournier, 1978; Lebowitz et al., 1979; Kaden et al., 1979), Saccharomyces cerevisiae (Cotruvo et al., 1977) and Escherichia coli (Rosenkranz and Leifer, 1980). Benzene was also negative in the sex-linked recessive lethal mutation assay with Drosophila melanogaster (Nylander et al., 1978) and the mouse lymphoma forward mutation assay (Lebowitz et al., 1979). Equivocal results have been obtained in assays for clastogenic effects of benzene in vitro, but it appears that benzene metabolites are responsible in those cases with positive results (IARC, 1982; Koizumi et al., 1974; Morimoto, 1976; Gerner-Smidt and Friedrich, 1978; Diaz et al., 1979; Morimoto and Wolff, 1980). Several investigators have reported positive results for benzene in mouse micronucleus assays (Lyon, 1976; Diaz et al., 1980; Hite et al., 1980; Meyne and Legator, 1980). Benzene induced chromosomal aberrations in bone marrow cells from rabbits (Kissling and Speck, 1971), mice (Meyne and Legator, 1978, 1980) and rats (Dean, 1969; Philip and Krogh Jensen, 1970; Lyapkalo, 1973; Lyon, 1976; Dobrokhotov and Enikeev, 1977; Anderson and Richardson, 1979).

Numerous investigators have examined the effect of benzene on the chromosomes of bone marrow cells and peripheral lymphocytes from both symptomatic and asymptomatic workers with either a current or a past history of exposure to benzene. Many of these investigators found significant increases in chromosomal aberrations in both symptomatic and asymptomatic groups, some of which persisted for years after cessation of exposure (IARC, 1982; Pollini and Colombi, 1964a,b; Pollini et al., 1964, 1969; Pollini and Biscaldi, 1976, 1977; Forni et al., 1971a,b; Forni and Moreo, 1967, 1969; Hartwich et al., 1969; Sellyei and Kelemen, 1971; Erdogan and Aksoy, 1973; Hudak and Gombosi, 1977; Van den Berghe et al., 1979; Tough and Court Brown, 1965; Tough et al., 1970; Funes-Cravioto et al., 1977; Picciano, 1979; Hartwich and Schwanitz, 1972; Khan and Khan, 1973; Fredga et al., 1979).

4.4. WEIGHT OF EVIDENCE

The case reports reviewed by IARC (1982) and Goldstein (1977) relating carcinogenicity in humans with exposure to benzene, coupled with the epidemiological studies by Aksoy et al. (1974), Infante et al. (1977a,b) and Ott et al. (1978) provide sufficient evidence for the carcinogenicity of benzene to humans.

Animal bioassays, which demonstrate increased incidence of zymbal and mammary gland carcinoma in orally exposed rats (Maltoni and Scarnato, 1979) and suggest increased incidence of hematopoietic tumors in C57Bl mice exposed via inhalation, may be considered corroborative data supportive of a carcinogenic role for benzene. Applying the criteria for weight of evidence proposed by the Carcinogen Assessment Group of the U.S. EPA (Federal Register, 1984), benzene is most appropriately designated a Group A human carcinogen.

5. REGULATORY STANDARDS AND CRITERIA

Regulations and recommended guidelines have been reported by 15 countries for limiting occupational exposure to benzene (IARC, 1982). These regulations and guidelines are summarized in Table 5-1. Six countries (Finland, the Federal Republic of Germany, Italy, Japan, Sweden and Switzerland) recognize benzene as being carcinogenic to humans, and two others (Australia, the United States) have designated benzene as a suspected human carcinogen (IARC, 1982).

The U.S. EPA (1980b) has estimated water criteria for the consumption of benzene through water andd life time contaminated fish for increased risk levels of 10^{-7}, 10^{-6} and 10^{-5} of 0.066, 0.66 and 6.6 μg/ℓ, respectively.

TABLE 5-1

National Occupational Exposure Limits for Benzene[a]

Country	Year	Concentration (mg/m³)	Concentration (ppm)	Interpretation	Status
Australia	1978	30	10	TWA[b]	guideline
Belgium	1978	30	10	TWA[b]	regulation
Czechoslovakia	1976	50	NR	TWA	regulation
		80	NR	ceiling (10 minutes)	regulation
Finland	1975	32	10	TWA[b]	regulation
Hungary	1974	20	NR	TWA[c]	regulation
Italy	1978	30	10	TWA[b]	guideline
Japan	1978	80	25	ceiling	guideline
The Netherlands	1978	30	10	TWA[b]	guideline
Poland	1976	30	NR	ceiling[b]	regulation
Romania	1975	50	NR	maximum[b]	regulation
Sweden	1978	15	5	TWA[b]	guideline
		30	10	maximum (15 minutes)	guideline
Switzerland	1978	6.5	2	TWA[b]	regulation
United States					
OSHA	1980	NR	10	TWA	regulation
		NR	25	ceiling	regulation
		NR	50	peak[d]	regulation
ACGIH	1983	30	10	TWA	guideline
		75	25	STEL	guideline
NIOSH	1980	3.2	1	ceiling (60 minutes)	guideline

TABLE 5-1 (cont.)

Country	Year	Concentration (mg/m³)	Concentration (ppm)	Interpretation	Status
USSR	1980	5	NR	ceiling[b]	regulation
Yugoslavia	1971	50	15	ceiling[b]	regulation

[a]Sources: ACGIH, 1983; International Labour Office, 1980; NIOSH, 1980; OSHA, 1980; IARC, 1982

[b]Skin irritant notation added

[c]May be exceeded 5 times/shift as long as average does not exceed value

[d]Peak limit above ceiling -- 10 minutes

NR = Not recorded

6. RISK ASSESSMENT

6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

Benzene is a known carcinogen for which data are sufficient for computing a q_1*. Therefore, it is inappropriate to calculate an oral or inhalation AIS for benzene.

6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

Benzene is a known carcinogen for which data are sufficient for computing a q_1*. Therefore, it is inappropriate to calculate an oral or inhalation AIC for benzene.

6.3. CARCINOGENIC POTENCY (q_1*)

6.3.1. Oral. In the only oral cancer bioassay, Maltoni and Scarnato (1979) observed an increased incidence of zymbal gland carcinoma in female rats given benzene by gavage in olive oil at levels of 0, 50 or 250 mg/kg bw (equivalent to 0, 11.6 or 58.0 mg/kg/day, respectively), 4-5 days/week for 52 weeks. The incidences of zymbal gland carcinoma were 0/30 controls, 2/30 low dose and 8/35 high dose. Using the cancer data from this study, a quantitative risk criterion can be derived for benzene. Based on the zymbal gland carcinoma response of female rats, and using the linearized multistage model adopted by the U.S. EPA (1980a), a carcinogenic potency factor (q_1*) of 4.4512×10^{-2} $(mg/kg/day)^{-1}$ can be derived for humans. The human q_1* is calculated from the animal q_1* by applying the cube root of the ratio of the body weight of humans to rats. Complete data for derivation of this q_1* are presented in Appendix A.

This value compares favorably with the unit risk estimate developed for oral exposure based upon human occupational exposure (U.S. EPA, 1980b). This inhalation-based oral estimate of 5.2×10^{-2} $(mg/kg/day)^{-1}$ was derived as described in section 6.3.2. of this document with the additive of

an absorption factor of 0.5 to estimate oral exposure from enhalation data It is proposed that the unit risk value of 5.2×10^{-2} $(mg/kg/day)^{-1}$ as estimated by U.S. EPA (1980b) be used as an estimate of the oral carcinogenic potency of benzene for the purposes of the present assessment.

6.3.2. Inhalation. The U.S. EPA (1980b) derived a cancer-based criterion for human exposure to benzene from the epidemiology studies of Infante et al. (1977a,b), Ott et al. (1978) and Aksoy et al. (1974), in which a significantly increased incidence of leukemia was observed for workers exposed to benzene principally by inhalation. Using these epidemiology studies, the U.S. EPA Carcinogen Assessment Group (U.S. EPA, 1978b) calculated a dose-response curve with a slope of 0.024074 units of lifetime risk/unit (ppm) of continuous exposure to atmospheric benzene. This corresponds to a unit risk of 7.52×10^{-3} $(mg/m^3)^{-1}$. Assuming an inhalation rate of 20 m^3/day for a 70 kg man, the unit risk also may be expressed as 3.76×10^{-4} mg/day^{-1} or 2.6×10^{-2} $mg/kg/day^{-1}$.

7. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values for Substances in Workroom Air. Fourth edition with supplements through 1982. Cincinnati, OH. p. 37-40.

ACGIH (American Conference of Governmental Industrial Hygienists). 1983. Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1984. Cincinnati, OH.

Aksoy, M. 1977. Leukemia in workers due to occupational exposure to benzene. New Istanbul Contrib. Clin. Sci. 12: 3-14. (Cited in IARC, 1982)

Aksoy, M. 1980. Different types of malignancies due to occupational exposure to benzene: A review of recent observations in Turkey. Environ. Res. 23: 181-190. (Cited in IARC, 1982)

Aksoy, M., K. DinCol, T. Akgun, S. Erdem and G. DinCol. 1971. Haematological effects of chronic benzene poisoning in 217 workers. Br. J. Ind. Med. 28: 296-302. (Cited in IARC, 1982)

Aksoy, M., K. DinCol, S. Erdem, T. Akgun and G. DinCol. 1972. Details of blood changes in 32 patients with pancytopenia associated with long-term exposure to benzene. Br. J. Ind. Med. 29: 56-64. (Cited in IARC, 1982)

Aksoy, M., S. Erdem and G. DinCol. 1974. Leukemia in shoe workers exposed chronically to benzene. Blood. 44: 837-841. (Cited in U.S. EPA, 1980b)

Anderson, D. and C.R. Richardson. 1979. Chromosome gaps are associated with chemical mutagenesis (Abstract No. Ec-9). Environ. Mutagen. 1: 179. (Cited in IARC, 1982)

Andrews, L.S., E.W. Lee, C.M. Witmer, J.J. Kocsis and R. Snyder. 1977. Effects of toluene on the metabolism, disposition and hemopoietic toxicity of ^{3}H-benzene. Biochem. J. Pharmacol. 26: 293-300. (Cited in U.S. EPA, 1980b)

Banerjee, S., S.H. Yalkowsky and S.C. Valvani. 1980. Water solubility and octanol/water partition coefficients of organics. Limitations of the solubility-partition coefficient correlation. Environ. Sci. Technol. 14: 1227-1229.

Bowditch, M. and H.B. Elkins. 1939. Chronic exposure to benzene (benzol). I. The industrial aspects. J. Ind. Hyg. Toxicol. 21: 321-330. (Cited in IARC, 1982)

Brandt, L., P.G. Nilsson and F. Mitelman. 1978. Occupational exposure to petroleum products in men with acute non-lymphocytic leukemia. Br. Med. J. i: 553-554. (Cited in IARC, 1982)

Bryon, P.-A., P. Coeur, R. Girard, O. Gentilhomme and L. Revol. 1969. Acute erythromyelosis with benzene etiology. (Fre.) J. Med. Lyon. 50: 757-759. (Cited in IARC, 1982)

Callahan, M.A., M.W. Slimak, N.W. Gabel, et al. 1979. Water-Related Environmental Fate of 129 Priority Pollutants, Vol. II. Office of Water Planning and Standards, Office of Water and Waste Management, U.S. EPA, Washington, DC. EPA 440/4-79-029-b.

Chiou, C.T., P.E. Porter and D.W. Schmedding. 1983. Partition equilibrium of nonionic organic compounds between soil, organic matter and water. Environ. Sci. Technol. 17: 227-231.

Coniglio, W.A., K. Miller and D. MacKeever. 1980. The occurrence of volatile organics in drinking water. Briefing prepared for Deputy Assistant Administrator for Drinking Water Criteria and Standards Division, Science and Technology Branch, U.S. EPA, Washington, DC.

Cotruvo, J.A., V.F. Simmon and R.J. Spanggord. 1977. Investigation of mutagenic effects of products of ozonation reactions in water. Ann. NY Acad. Sci. 298: 124-140. (Cited in IARC, 1982)

Dean, B.J. 1969. Chemical-induced chromosome damage. Lab. Anim. 3: 57-174. (Cited in IARC, 1982)

Dean, B.J. 1978. Genetic toxicity of benzene, toluene, xylenes and phenols. Mutat. Res. 47: 75-97. (Cited in IARC, 1982)

DeGowin, R.L. 1963. Benzene exposure and aplastic anemia followed by leukemia 15 years later. J. Am. Med. Assoc. 185: 748-751. (Cited in IARC, 1982)

Deichmann, W.B., W.E. MacDonald and E. Bernal. 1963. The hemopoietic tissue toxicity of benzene vapors. Toxicol. Appl. Pharmacol. 5: 201-224. (Cited in U.S. EPA, 1982)

Delore, P. and C. Borgomano. 1928. Acute leukemia following benzene poisoning. On the toxic origin of certain acute leukaemias and their relation to serious anaemias. (Fre.) J. Med. Lyon. 9: 227-233. (Cited in IARC, 1982)

Diaz, M., N. Fijtman, V. Carricarte, L. Braier and J. Diez. 1979. Effect of benzene and its metabolites on SCE in human lymphocytes cultures (Abstract No. 23). In Vitro. 15: 172. (Cited in IARC, 1982)

Diaz, M., A. Reiser, L. Braier and J. Diez. 1980. Studies on benzenes mutagenesis. I. The micronucleus test. Experientia. 36: 297-299. (Cited in IARC, 1982)

Di Guglielmo, G. and A. Iannaccone. 1958. Inhibition of mitosis and regressive changes of erythroblasts in acute erythropathy caused by occupational benzene poisoning. Acta Haematol. 19: 144-147. (Cited in IARC, 1982)

Dobrokhotov, V.B. and M.I. Enikeev. 1977. Mutagenic effect of benzene, toluene and a mixture of these hydrocarbons in a chronic experiment. (Rus.) Gig. Sanit. 1: 32-34. (Cited in IARC, 1982)

Erdogan, G. and M. Aksoy. 1973. Cytogenetic studies in thirteen patients with pancytopenia and leukemia associated with long-term exposure to benzene. New Istanbul. Contrib. Clin. Sci. 10: 230-247. (Cited in IARC, 1982)

Federal Register. 1984. Environmental Protection Agency. Proposed Guidelines for Carcinogenic Risk Assessment. Federal Register. 49: 46294-46299.

Fishbeck, W.A., J.C. Townsend and M.G. Swank. 1978. Effects of chronic occupational exposure to measured concentrations of benzene. J. Occup. Med. 20: 539-542. (Cited in IARC, 1982)

Flodin, U., L. Andersson, C.G. Anjou, U.B. Palm, O. Vikrot and O. Axelson. 1981. A case-referent study on acute myeloid leukemia, background radiation and exposures to solvents and other agents. Scand. J. Work Environ. Health. 7: 169-178. (Cited in IARC, 1982)

Forni, A. and L. Moreo. 1967. Cytogenetic studies in a case of benzene leukemia. Eur. J. Cancer. 3: 251-255. (Cited in IARC, 1982)

Forni, A. and L. Moreo. 1969. Chromosome studies in a case of benzene-induced erythroleukaemia. Eur. J. Cancer. 5: 459-463. (Cited in IARC, 1982)

Forni, A.M., A. Cappellini, E. Pacifico and E.C. Vigliani. 1971a. Chromosome changes and their evolution in subjects with past exposure to benzene. Arch. Environ. Health. 23: 385-391. (Cited in IARC, 1982)

Forni, A., E. Pacifico and A. Limonta. 1971b. Chromosome studies in workers exposed to benzene or toluene or both. Arch. Environ. Health. 22: 373-378. (Cited in IARC, 1982)

Fredga, K., J. Reitalu and M. Berlin. 1979. Chromosome studies in workers exposed to benzene. In: Genetic Damage in Man Caused by Environmental Agents. Academic Press, NY. p. 187-203. (Cited in IARC, 1982)

Funes-Cravioto, F., B. Kolmodin-Hedman, J. Lindsten, et al. 1977. Chromosome aberrations and sister-chromatid exchange in workers in chemical laboratories and a rotoprinting factory and in children of women laboratory workers. Lancet. p. 322-325. (Cited in IARC, 1982)

Galavotti, B. and F.M. Troisi. 1950. Erythroleukemia myelosis in benzene poisoning. Br. J. Ind. Med. 7: 79-81. (Cited in IARC, 1982)

Gerner-Smidt, P. and U. Friedrich. 1978. The mutagenic effect of benzene, toluene and xylene studied by the SCE technique. Mutat. Res. 58: 313-316. (Cited in IARC, 1982)

Girard, R. and L. Revol. 1970. The incidence of exposure to benzene in severe haemopathies. Nouv. Rev. Fr. Hematol. 10: 477-484. (Cited in IARC, 1982)

Goguel, A., A. Cavigneaux and J. Bernard. 1967. Benzene leukemias. (Fre.) Bull. Inst. Natl. Sante Rech. Med. 22: 421-441. (Cited in IARC, 1982)

Goldstein, B.D. 1977. Hematotoxicity in humans. J. Toxicol. Environ. Health Suppl. 2: 69-105. (Cited in IARC, 1982)

Green, J.D., C.A. Snyder, J. LoBue, B.D. Goldstein and R.E. Albert. 1981. Acute and chronic dose/response effect of benzene inhalation on the peripheral blood, bone marrow, and spleen cells of CD-1 male mice. Toxicol. Appl. Pharmacol. 59(2): 204-214. (Cited in U.S. EPA, 1982)

Greenburg, L. 1926. Benzol poisoning as an industrial hazard. VII. Results of medical examination and clinical tests made to discover early signs of benzol poisoning in exposed workers. Public Health Reports. 41: 1526-1539. (Cited in NIOSH, 1974; U.S. EPA, 1982)

Greene, M.H., R.N. Hoover, R.L. Eck and J.F. Fraumeni, Jr. 1979. Cancer mortality among printing plant workers. Environ. Res. 20: 66-73. (Cited in IARC, 1982)

Hardell, L., M. Eriksson, P. Lenner and E. Lundgren. 1981. Malignant lymphoma and exposure to chemicals, especially organic solvents, chlorophenols and phenoxy acids: A case-control study. Br. J. Cancer. 43: 169-176. (Cited in IARC, 1982)

Hardy, H.L. and H.B. Elkins. 1948. Medical aspects of maximum allowable concentrations -- Benzene. J. Ind. Hyg. Toxicol. 30: 196-200. (Cited in NIOSH, 1974; U.S. EPA, 1982)

Hartwich, G. and G. Schwanitz. 1972. Chromosome studies after chronic benzene exposure. (Ger.) Dtsch. Med. Wochenschr. 97: 45-49. (Cited in IARC, 1982)

Hartwich, G., G. Schwanitz and J. Becker. 1969. Chromosomal aberrations in a leukaemia due to benzene. (Ger.) Dtsch. Med. Wochenschr. 94: 1228-1229. (Cited in IARC, 1982)

Hite, M., M. Pecharo, I. Smith and S. Thornton. 1980. Effect of benzene in the micronucleus test. Mutat. Res. 77: 149-155. (Cited in IARC, 1982)

Hudak, A. and K. Gombosi. 1977. Chromosome impairment of workers in research laboratories under uncontrolled benzene exposure. (Hung.) Munkavedelem. 23: 50-51. (Cited in IARC, 1982)

Hunter, F.T. 1939. Chronic exposure to benzene (benzol). II. The clinical effects. J. Ind. Hyg. 21: 331-354. (Cited in IARC, 1982)

IARC (International Agency for Research on Cancer). 1982. Benzene. In: Some Industrial Chemicals and Dyestuffs. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. IARC, WHO, Lyon, France. Vol. 29. p. 93-148.

Ikeda, M., H. Ohtsuji and T. Imamura. 1972. In vivo suppression of benzene and styrene oxidation by co-administered toluene in rats and effects of phenobarbital. Xenobiotica. 2: 101-106. (Cited in U.S. EPA, 1980b)

Infante, P.F., R.A. Rinsky, J.K. Wagoner and R.J. Young. 1977a. Leukemia in benzene workers. Lancet. 2: 76. (Cited in U.S. EPA, 1980b)

Infante, P.F., R.A. Rinsky, J.K. Wagoner and R.J. Young. 1977b. Benzene and leukemia. Lancet. 2: 867-869. (Cited in U.S. EPA, 1980b)

International Labour Office. 1980. Occupational Exposure Limits for Airborne Toxic Substances, 2nd (rev.) ed. Occupational Safety and Health Series No. 37. Geneva. p. 48-49, 271-290. (Cited in IARC, 1982)

Ishimaru, T., H. Okada, T. Tomiyasu, T. Tsuchimoto, T. Hoshino and M. Ichimaru. 1971. Occupational factors in the epidemiology of leukemia in Hiroshima and Nagasaki. Am. J. Epidemiol. 93: 157-165. (Cited in U.S. EPA, 1980b)

Jenkins, L.J., R.A. Jones and J. Siegel. 1970. Long-term inhalation screening studies of benzene, toluene, o-xylene, and cumene on experimental animals. Toxicol. Appl. Pharmacol. 16: 818-823. (Cited in IARC, 1982; U.S. EPA, 1980b, 1982)

Kaden, D.A., R.A. Hites and W.G. Thilly. 1979. Mutagenicity of soot and associated polycyclic aromatic hydrocarbons to Salmonella typhimurium. Cancer Res. 39: 4152-4159. (Cited in IARC, 1982)

Khan, H. and M.H. Khan. 1973. Cytogenetic studies following chronic exposure to benzene. (Ger.) Arch. Toxicol. 31: 39-49. (Cited in IARC, 1982)

Kissling, M. and B. Speck. 1971. Chromosome aberrations in experimental benzene intoxication. Helv. Med. Acta. 36: 59-66. (Cited in IARC, 1982)

Koizumi, A., Y. Dobashi, Y. Tachibana, K. Tsuda and H. Katsunuma. 1974. Cytokinetic and cytogenetic changes in cultured human leukocytes and HeLa cells induced by benzene. Ind. Health. 12: 23-29. (Cited in IARC, 1982)

Kuna, R.A. and R.W. Kapp, Jr. 1981. The embryotoxic/teratogenic potential of benzene vapor in rats. Toxicol. Appl. Pharmacol. 57(1): 1-7. (Cited in U.S. EPA, 1982)

Lange, A., R. Smolik, W. Zatonski and J. Szymanska. 1973. Serum immunoglobulin levels in workers exposed to benzene, toluene, and xylene. Int. Arch. Arbeitsmed. 31: 37-44. (Cited in U.S. EPA, 1980b, 1982)

Lebowitz, H., D. Brusick, D. Matheson, et al. 1979. Commonly used fuels and solvents evaluated in a battery of short-term bioassays (Abstract No. Eb-8). Environ. Mutagen. 1: 172-173. (Cited in IARC, 1982)

Ludwig, H. and A. Werthemann. 1962. Benzene myelopathy. (Ger.) Schweiz. Med. Wochenschr. 13: 378-384. (Cited in IARC, 1982)

Lyapkalo, A.A. 1973. Genetic activity of benzene and toluene. (Rus.) Gig. Tr. Prof. Zabol. 17: 24-28. (Cited in IARC, 1982)

Lyon, J.P. 1976. Mutagenicity studies with benzene (Abstract). Diss. Abstr. Int. B. 36: 5537. (Cited in IARC, 1982)

Mabey, W.R., J.H. Smith, R.J. Podoll, et al. 1981. Aquatic Fate Process Data for Organic Priority Pollutants. U.S. EPA, Monitoring and Data Support Division, Office of Water Regulations and Standards, Washington, DC. EPA 440/4-81-014.

MacKay, D. 1982. Correlation of bioconcentration factors. Environ. Sci. Technol. 16: 274-278.

Mallory, T.B., E.A. Gall and W.J. Brickley. 1939. Chronic exposure to benzene (benzol). III. The pathologic results. J. Ind. Hyg. Toxicol. 21: 355-377. (Cited in IARC, 1982)

Maltoni, C. and C. Scarnato. 1979. First experimental demonstration of the carcinogenic effects of benzene. Long-term bioassays on Sprague-Dawley rats by oral administration. Med. Lav. 70: 352-357. (Cited in U.S. EPA, 1983b)

McMichael, A.J., R. Spirtas, L.L. Kupper and J.F. Gamble. 1975. Solvent exposure and leukemia among rubber workers: An epidemiology study. J. Occup. Med. 17: 234-239. (Cited in IARC, 1982)

Meyne, J. and M.S. Legator. 1978. Cytogenetic analysis after an acute intraperitoneal exposure of mice to benzene. Mamm. Chromosomes Newsl. 19: 38. (Cited in IARC, 1982)

Meyne, J. and M.S. Legator. 1980. Sex-related differences in cytogenetic effects of benzene in the bone marrow of Swiss mice. Environ. Mutagen. 2: 43-50. (Cited in IARC, 1982)

Monson, R.R. and K.K. Nakano. 1976. Mortality among rubber workers. I. White male union employees in Akron, OH. Am. J. Epidemiol. 103: 284-296. (Cited in IARC, 1982)

Morimoto, K. 1976. Analysis of combined effects of benzene with radiation on chromosomes in cultured human leukocytes. Jap. J. Ind. Health. 18: 23-24. (Cited in IARC, 1982)

Morimoto, K. and S. Wolff. 1980. Increase of sister-chromatid exchanges and perturbations of cell division kinetics in human lymphocytes by benzene metabolites. Cancer Res. 40: 1189-1193. (Cited in IARC, 1982)

Murray, F.J., J.A. John, L.W. Rampy, R.A. Kuna and B.A. Schwetz. 1979. Embryotoxicity of inhaled benzene in mice and rabbits. Am. Ind. Hyg. Assoc. J. 40: 993-998.

NAS (National Academy of Sciences). 1976. Health effects of benzene: A review. Washington, DC. (Cited in U.S. EPA, 1980b)

Nawrot, P.S. and R.E. Staples. 1979. No title provided. Teratology. 19: 41. (Cited in U.S. EPA, 1980b, 1982)

NIOSH (National Institute for Occupational Safety and Health). 1974. Criteria for a Recommended Standard...Occupational Exposure to Benzene. U.S. DHEW, PHS, CDC, Cincinnati, OH. Publ. No. 74-137. (Cited in U.S. EPA, 1982)

NIOSH (National Institute for Occupational Safety and Health). 1980. Summary of NIOSH Recommendations for Occupational Health Standards, Rockville, MD. (Cited in IARC, 1982)

Nissen, N.I. and A. Soeborg Ohlsen. 1953. Erythromyelosis (morbus di Guglielmo). Review and report of a case in a benzene (benzol) worker. Acta Med. Scand. 145: 56-71. (Cited in IARC, 1982)

Nylander, P.O., H. Olofsson, B. Rasmuson and H. Svahlin. 1978. Mutagenic effects of petrol in Drosophila melanogaster. I. Effects of benzene and 1,2-dichloroethane. Mutat. Res. 57: 163-167. (Cited in IARC, 1982)

OSHA (Occupational Safety and Health Administration). 1980. Benzene. U.S. Code of Federal Regulations, Title 29, Parts 1910.19, 1910.1000, 1910.1028. (Cited in IARC, 1982)

Ott, M.G., J.C. Townsend, W.A. Fishbeck and R.A. Langner. 1978. Mortality among individuals occupationally exposed to benzene. Arch. Environ. Health. 33: 3-10. (Cited in U.S. EPA, 1980b)

Pagnotto, H.L. 1972. Written communication to NIOSH. (Cited in NIOSH, 1974; U.S. EPA, 1982)

Pagnotto, L.D., H.B. Elkins, H.G. Brugsch and E.J. Walkley. 1961. Industrial benzene exposure from petroleum naphtha. I. Rubber coating industry. Am. Ind. Hyg. Assoc. J. 22: 417-421. (Cited in NIOSH, 1974; U.S. EPA, 1980b, 1982)

Philip, P. and M. Krogh Jensen. 1970. Benzene induced chromosome abnormalities in rat bone marrow cells. Acta. Pathol. Microbiol. Scand. 78: 489-490. (Cited in IARC, 1982)

Picciano, D. 1979. Cytogenetic study of workers exposed to benzene. Environ. Res. 19: 33-38. (Cited in IARC, 1982)

Pollini, G. and G.P. Biscaldi. 1976. Persistence of karyotype alterations in lymphocytes 10 years after benzene poisoning. (Ital.) Med. Lav. 67 (Suppl. 5): 465-472. (Cited in IARC, 1982)

Pollini, G. and G.P. Biscaldi. 1977. Investigations of karyotype in the lymphocytes of subjects with benzene hemopathy twelve years after poisoning. (Ital.) Med. Lav. 68: 308-312. (Cited in IARC, 1982)

Pollini, G. and R. Colombi. 1964a. Damage to bone-marrow chromosomes in benzolic aplastic anaemia. (Ital.) Med. Lav. 55: 241-255. (Cited in IARC, 1982)

Pollini, G. and R. Colombi. 1964b. Chromosomal damage in lymphocytes during benzene haemopathy. (Ital.) Med. Lav. 55: 641-655. (Cited in IARC, 1982)

Pollini, G., E. Strosselli and R. Colombi. 1964. The relationship between chromosomal alterations in haemopoietic cells and the severity of benzene haemopathy. (Ital.) Med. Lav. 55: 735-751. (Cited in IARC, 1982)

Pollini, G., G.P. Biscaldi and G. Robustelli della Cuna. 1969. Chromosome changes in lymphocytes five years after benzene haemopathy. (Ital.) Med. Lav. 60: 743-758. (Cited in IARC, 1982)

Rinsky, R.A., R.J. Young and A.B. Smith. 1981. Leukemia in benzene workers. Am. J. Ind. Med. 2: 217-245. (Cited in IARC, 1982)

Rosenkranz, H.S. and Z. Leifer. 1980. Determining the DNA-modifying activity of chemicals using DNA-polymerase-deficient Escherichia coli. In: Chemical Mutagens. Principles and Methods for their Detection, Vol. 6, F.J. de Serres and A. Hollaender, Ed. Plenum Press, NY. p. 109-147. (Cited in IARC, 1982)

Rozman, C., S. Woessner and J. Saez-Serrania. 1968. Acute erythromyelosis after benzene poisoning. Acta Haematol. 40: 234-237. (Cited in IARC, 1982)

Rushton, L. and M. Alderson. 1980. The influence of occupation on health -- Some results from a study in the UK oil industry. Carcinogenesis. 1: 739-743. (Cited in IARC, 1982)

Rushton, L. and M.R. Alderson. 1981. A case-control study to investigate the association between exposure to benzene and deaths from leukemia in oil refinery workers. Br. J. Cancer. 43: 77-84. (Cited in IARC, 1982)

Savilahti, M. 1956. More than 100 cases of benzene poisoning in a shoe factory. Arch. Gewerbepathol. Gewerbehyg. 15: 147-157. (Ger.) (Cited in NIOSH, 1974; U.S. EPA, 1982)

Sellyei, M. and E. Kelemen. 1971. Chromosome study in a case of granulocytic leukemia with 'pelgerisation' 7 years after benzene pancytopenia. Eur. J. Cancer. 7: 83-85. (Cited in IARC, 1982)

Shahin, M.M. and F. Fournier. 1978. Suppression of mutation induction and failure to detect mutagenic activity with Athabasca tar sand fractions. Mutat. Res. 58: 29-34. (Cited in IARC, 1982)

Singh, H.B., L.J. Salas, A.J. Smith and H. Shigeishi. 1981. Measurements of some potentially hazardous organic chemicals in urban environments. Atmos. Environ. 15: 601-612.

Smolik, R., et al. 1973. Serum complement level in workers exposed to benzene, toluene, and xylene. Inc. Arch. Arbeitsmed. 31: 243. (Cited in U.S. EPA, 1980b, 1982)

Snyder, C.A., B.D. Goldstein, A. Sellakumar, et al. 1978. Hematotoxicity of inhaled benzene to Sprague-Dawley rats and AKR mice at 300 ppm. J. Toxicol. Environ. Health. 4: 605-618. (Cited in Snyder et al., 1980; U.S. EPA, 1982)

Snyder, C.A., B.D. Goldstein, A.R. Sellakumar, I. Bromberg, S. Laskin and R.E. Albert. 1980. The inhalation toxicology of benzene: Incidence of hematopoietic neoplasms and hematotoxicity in AKR/J and C57Bl/6J mice. Toxicol. Appl. Pharmacol. 54(2): 323-331. (Cited in U.S. EPA, 1982, 1983b)

Tabershaw, I.R. and S.H. Lamm. 1977. Benzene and leukemia. Lancet. ii: 867 868. (Cited in IARC, 1982)

Tareeff, E.M., N.M. Kontchalovskaya and L.A. Zorina. 1963. Benzene leukemias. Acta Unio. Int. Cancru. 19: 751-755. (Cited in IARC, 1982)

Thorpe, J.J. 1974. Epidemiologic survey of leukemia in persons potentially exposed to benzene. J. Occup. Med. 16: 375-382. (Cited in IARC, 1982)

Tough, I.M. and W.M. Court Brown. 1965. Chromosome aberrations and exposure to ambient benzene. Lancet. i: 684. (Cited in IARC, 1982)

Tough, I.M., P.G. Smith, W.M. Court Brown and D.G. Harnden. 1970. Chromosome studies on workers exposed to atmospheric benzene. The possible influence of age. Eur. J. Cancer. 6: 49-55. (Cited in IARC, 1982)

Tyroler, H.A., D. Andjelkovic, R. Harris, W. Lednar, A. McMichael and M. Symons. 1976. Chronic diseases in the rubber industry. Environ. Health Perspect. 17: 13-20. (Cited in IARC, 1982)

U.S. EPA. 1978a. Assessment of Health Effects of Benzene Germane to Low-Level Exposure. Office of Health and Ecological Effects, U.S. EPA, Washington, DC. EPA 600/1-78-061.

U.S. EPA. 1978b. Estimation of Population Cancer Risk from Ambient Benzene Exposure. Prepared by the Carcinogen Assessment Group, OHEA, Washington, DC. Internal draft. (Cited in U.S. EPA, 1980b)

U.S. EPA. 1980a. Guidelines and Methodology Used in the Preparation of Health Effects Assessment Chapters of the Consent Decree Water Quality Criteria. Federal Register. 45: 79347-79357.

U.S. EPA. 1980b. Ambient Water Quality Criteria for Benzene. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 440/5-80-018. NTIS PB 81-117293.

U.S. EPA. 1982. Reportable Quantity for Benzene. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1983a. Methodology and Guidelines for Reportable Quantity Determinations Based on Chronic Toxicity Data. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1983b. Review of Toxicologic Data in Support of Evaluation for Carcinogenic Potential of Benzene. Prepared by the Carcinogen Assessment Group, OHEA, Washington, DC for the Office of Solid Waste and Emergency Response, Washington, DC.

Van den Berghe, H., A. Louwagie, A. Broeckaert-Van Orshoven, G. David and R. Verwilghen. 1979. Chromosome anaylsis in two unusual malignant blood disorders presumably induced by benzene. Blood. 53: 558-566. (Cited in IARC, 1982)

Vigliani, E.C. 1976. Leukemia associated with benzene exposure. Ann. NY Acad. Sci. 271: 143-151. (Cited in IARC, 1982)

Vigliani, E.C. and G. Saita. 1964. Benzene and leukemia. N. Engl. J. Med. 271: 872-876. (Cited in NIOSH, 1974; U.S. EPA, 1982)

Wolf, M.A., V.K. Rowe, D.D. McCollister, R.L. Hollingsworth and F. Oyen. 1956. Toxicological studies of certain alkylated benzenes and benzene. Arch. Ind. Health. 14: 387-398. (Cited in U.S. EPA, 1982)