| TECHNICAL REPORT DATA (Please read Instructions on the reverse before completing) | | |
|---|---|---|
| 1. REPORT NO. EPA/600/8-89/086 | 2. | 3. RECIPIENT'S ACCESSION NO PB90-142381/AS |
| 4. TITLE AND SUBTITLE Updated Health Effects Assessment for Benzene | | 5. REPORT DATE |
| | | 6. PERFORMING ORGANIZATION CODE |
| 7. AUTHOR(S) | | 8. PERFORMING ORGANIZATION REPORT NO. |
| 9. PERFORMING ORGANIZATION NAME AND ADDRESS | | 10. PROGRAM ELEMENT NO. |
| | | 11. CONTRACT/GRANT NO. |
| 12. SPONSORING AGENCY NAME AND ADDRESS Environmental Criteria and Assessment Office Office of Research and Development U.S. Environmental Protection Agency Cincinnati, OH 45268 | | 13. TYPE OF REPORT AND PERIOD COVERED |
| | | 14. SPONSORING AGENCY CODE EPA/600/22 |
| 15 SUPPLEMENTARY NOTES | | |

16. ABSTRACT

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. 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. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. 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, $RfD_S$ or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD 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. For compounds for which there is sufficient evidence of carcinogenicity, $q_1^*$s have been computed, if appropriate, based on oral and inhalation data if available.

| 17. KEY WORDS AND DOCUMENT ANALYSIS | | |
|---|---|---|
| a. DESCRIPTORS | b. IDENTIFIERS/OPEN ENDED TERMS | c. COSATI Field/Group |
| | | |
| 18. DISTRIBUTION STATEMENT Public | 19. SECURITY CLASS (This Report) Unclassified | 21. NO. OF PAGES |
| | 20. SECURITY CLASS (This page) Unclassified | 22. PRICE |

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

EPA/600/8-89/086
August, 1989

# HEALTH EFFECTS ASSESSMENT FOR BENZENE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
CINCINNATI, OH 45268

## DISCLAIMER

This document has been reviewed in accordance with the U.S. Environmental Protection Agency's peer and administrative review policies and approved for publication. 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 TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to March, 1987. 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. 1979. Carcinogen Assessment Group's Final Report on Population Risk to Ambient Benzene Exposures. Prepared by the Office of Health and Environmental Assessment, Carcinogen Assessment Group, Washington, DC, for the Office of Air Quality Planning and Standards, Research Triangle Park, NC. EPA-450/5-80-004. NTIS PB82-227372.

U.S. EPA. 1980a. Ambient Water Quality Criteria Document for Benzene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH, for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-018. NTIS PB 81-117293.

U.S. EPA. 1983a. Reportable Quantity for Benzene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH, 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 Office of Health and Environmental Assessment, Carcinogen Assessment Group, Washington, DC for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1985a. Drinking Water Criteria Document for Benzene. Prepared by the Office of Drinking Water, Washington, DC. Final Draft (on Public Comment). NTIS PB86-118122.

U.S. EPA. 1985b. Interim Quantitative Cancer Unit Risk Estimates Due to Inhalation of Benzene. Prepared by the Office of Health and Environmental Assessment, Carcinogen Assessment Group, Washington, DC, for the Office of Air Quality Planning and Standards, Research Triangle Park, NC. Internal Report.

The intent in these assessments is to suggest acceptable exposure levels for noncarcinogens and risk cancer potency estimates for carcinogens whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope, which tended to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard or risk associated with exposure 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, $RfD_S$ (formerly AIS) or subchronic reference dose, 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 that 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 $RfD_S$ 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. These values are developed for both inhalation ($RfD_{SI}$) and oral ($RfD_{SO}$) exposures.

The RfD (formerly AIC) is similar in concept and addresses chronic exposure. 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 (1980b) for a discussion of this concept]. The RfD is route-specific and estimates acceptable exposure for either oral ($RfD_O$) or inhalation ($RfD_I$) exposure with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for identifying reportable quantities and the methodology for their development is explained in U.S. EPA (1984).

For compounds for which there is sufficient evidence of carcinogenicity, $RfD_S$ and RfD values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. (1980b). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. For carcinogens, $q_1^*$s have been computed, if appropriate, 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 slope for inhaled benzene of $2.9 \times 10^{-2}$ $(mg/kg/day)^{-1}$ may be estimated using data from several epidemiological investigations. Animal data concerning the carcinogenicity of inhaled benzene are corroborative.

Data regarding cancer incidence in humans following oral exposure to benzene were not located. Animal studies clearly associate oral exposure to benzene with increased incidences of several types of cancer. A carcinogenic slope of $2.9 \times 10^{-2}$ $(mg/kg/day)^{-1}$ was estimated for oral exposure to benzene. This value was obtained by route extrapolation using the inhalation occupational data.

TABLE OF CONTENTS

TABLE OF CONTENTS (cont.)

## LIST OF TABLES

## LIST OF ABBREVIATIONS

| | |
|---|---|
| ADI | Acceptable daily intake |
| bw | Body weight |
| CAS | Chemical Abstract Service |
| CS | Composite score |
| NOEL | No-observed-effect level |
| ppm | Parts per million |
| RfD | Reference dose |
| $RfD_I$ | Inhalation reference dose |
| $RfD_O$ | Oral reference dose |
| $RfD_S$ | Subchronic reference dose |
| $RfD_{SI}$ | Subchronic inhalation reference dose |
| $RfD_{SO}$ | Subchronic oral reference dose |
| 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. 71-43-2) are given below:

| | |
|---|---|
| Chemical class: | monocyclic aromatic hydrocarbon |
| Molecular weight: | 78.12 |
| 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: | 135 (recommended value) (Hansch and Leo, 1985)<br>132 (Banerjee et al., 1980) |
| Bioconcentration factor: | 12.6 (Mackay, 1982) |
| Soil sorption coefficient ($K_{OC}$): | ~26.7 (Vowles and Mantoura, 1987) |
| Half-lives in Air: | ~6 days (Atkinson, 1985) |
| Water: | 3-23 days (Lay et al., 1985; Wakeham et al., 1983) |
| Surface soil: | 0.3-1.6 days (Jury et al., 1984) |

In water, the dominant fate determining processes for benzene are predicted to be volatilization and biodegradation. In an aquatic modeling study, it was estimated that 32% of benzene in water is lost by biodegradation, 66% loss occurs by volatilization and 2% remains in water (Mackay et al., 1985). The overall half-life (from all loss processes) of benzene in a marine ecosystem during winter, spring and summer and in a pond during fall was found to be 13, 23, 3.1 and 5 days, respectively (Lay et al., 1985; Wakeham et al., 1983).

In surface layers of soil, the dominant removal process is expected to be volatilization. The volatilization half-lives for benzene in soil (1 and 10 cm deep) were estimated to be 0.3 and 1.6 days, respectively (Jury et al., 1984). Considering its reasonably high water solubility and reasonably low soil-water distribution coefficient (Vowles and Mantoura, 1987), benzene is expected to leach from subsurface 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. The overall half-life of benzene in groundwater was estimated to be 0.3-1.0 years (Zoeteman et al., 1981).

The dominant removal mechanism of atmospheric benzene is its reaction with photochemically generated hydroxyl radicals. The atmospheric half-life reported above is based on a reaction rate constant of $1.28 \times 10^{-12}$ $cm^3$/molecule-sec at 25°C (Atkinson, 1985) and an average hydroxyl radical concentration of $10^6$ molecules/$cm^3$. A half-life of 6 days in air suggests that benzene would be transported long distances in air from its sources of emission.

## 2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

### 2.1. ORAL

Sabourin et al. (1987) investigated the gastrointestinal absorption of benzene in F344/N and Sprague-Dawley rats and B6C3F1 mice. All test animals were 13-week-old males and were given single gavage (0.5-300 mg/kg) or intraperitoneal (0.5-150 mg/kg) doses of $^{14}$C-benzene in corn oil. Cumulative excretion of radioactivity was measured in expired air, urine and feces for 48 hours after treatment. Using a formula for determining gastrointestinal absorption that incorporates excretion data following oral and intraperitoneal treatment, gastrointestinal absorption was measured at >97% at all dose levels in both strains of rats and B6C3F1 mice.

### 2.2. INHALATION

Sabourin et al. (1987) exposed young adult male F344/N rats and B6C3F1 mice by nose only to $^{14}$C-benzene in air at 26-2600 µg/ℓ (26-2600 mg/m$^3$) for 6 hours. Respiratory volume was measured and the inhaled dosage of radiolabeled benzene was estimated. The proportion of inhaled $^{14}$C-benzene retained was estimated as the amount of radioactivity retained in the carcass at the end of the exposure period or as the amount of radioactivity excreted over a 56-hour postexposure period. Retention values decreased from 33 to 15% in rats and from 50 to 10% in mice as the exposure concentration was increased from 26 to 2600 µg/ℓ.

Data regarding the inhalation absorption of benzene by humans suggest an absorption factor of ~50%. Nomiyama and Nomiyama (1974) exposed three men and three women to benzene at 52-62 ppm (166-198 mg/m$^3$) for 4 hours and estimated respiratory retention. Respiratory uptake (the difference between the concentration of benzene in inhaled and exhaled air expressed as a percent of the concentration in inhaled air) was measured at 46.9% with little difference between men and women.

Srbova et al. (1950) exposed volunteers to 47-110 ppm (150-351 mg/m$^3$) benzene for up to 3 hours and estimated mean respiratory absorption (uptake) at 53.8%, using a method of estimation similar to that described by Nomiyama and Nomiyama (1974).

Hunter and Blair (1972) exposed human volunteers to 63-405 mg/m$^3$ benzene for various lengths of time and measured the concentrations of benzene in inhaled and exhaled air. Benzene retention, estimated from graphs of inhaled and exhaled concentrations, was ~44%. In an earlier experiment (Hunter, 1968), benzene retention was estimated at 55-60% using concentrations of 100-120 mg/m$^3$.

## 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 1, 10, 50 or 100 mg/kg by gavage 5 days/week for 187 days to study effects on the hematopoietic system. 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. No effect on the hematopoietic system was seen at the 1 mg/kg level, very slight leukopenia was observed at the 10 mg/kg level, and leukopenia and erythrocytopenia were noted at both the 50 and 100 mg/kg levels.

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 (48-2655 mg/m$^3$) for 5-13 weeks. Rats exposed to $\geq$61 ppm (195 mg/m$^3$), 5 hours/day, ~5 days/week over a period of 38-46 days developed significant leukopenia after 1-4 weeks of exposure. Rats exposed to benzene vapors at 47 ppm (150 mg/m$^3$), 7 hours/day for 180 days over a period of 245 days had slight or moderate leukopenia, which began at 7-8 weeks of exposure and persisted to the end of the study. Likewise, leukopenia was observed among rats exposed to 44 ppm (141 mg/m$^3$) benzene, 7 hours/day, 5 days/week for 8 weeks. Leukopenia was not observed in groups of rats exposed to benzene levels $\leq$31 ppm (99 mg/m$^3$), 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 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 rats were observed during extensive histopathological examination of control rats and those exposed to 15, 31 or 47 ppm benzene.

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 ≥88 ppm (≥281 mg/m³, for rats and guinea pigs) and ≥80 ppm (≥256 mg/m³, for rabbits), respectively, 7 hours/day, 5 days/week for 204-269 days. Leukopenia was seen in all three species at these exposure levels. In addition, rats exposed to ≥88 ppm benzene had increased spleen weights; guinea pigs exposed to ≥88 ppm had growth depression, 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. In the same study, rats exposed to benzene vapors at 2200 ppm (7030 mg/m³) had depressed growth and unspecified histopathologic changes in the spleen and bone marrow, in addition to the effects also seen at the lower exposure levels.

No hematologic effects were seen in rats, guinea pigs or dogs exposed to benzene vapors at a level of 17.6 ppm (56.2 mg/m³) continuously for up to 127 days (Jenkins et al., 1970).

Green et al. (1981) exposed a group of 11 or 12 male CD-1 mice to benzene vapors at a level of 302 ppm (965 mg/m³), 6 hours/day, 5 days/week for 26 weeks. Treatment-related effects included ~50% mortality by the end of the study, as well as marked lymphocytopenia, anemia and reduction of bone marrow and spleen cellularity and spleen weight.

In a more recent study (Ward et al., 1985), groups of 150 CD-1 mice/sex and 50 Sprague-Dawley rats/sex were exposed to benzene at 1, 10, 30 or 300 ppm (3, 32, 96 or 958 mg/m³), 6 hours/day, 5 days/week for ≤13 weeks.

Blood counts and clinical chemistry tests were performed on animals from all groups, complete histopathological examinations were performed on controls and 300 ppm group animals, and limited histopathological examinations were performed on 10 and 30 ppm group animals. At 300 ppm, rats had leukopenia and decreased bone marrow cellularity, and mice had leukopenia, anemia, testicular atrophy, decreased spermatogenesis, ovarian cysts and thymic atrophy. No significant effects were observed in either species at 10 or 30 ppm.

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. NTP (1986) administered benzene in corn oil by gavage to groups of 50 male and 50 female F344/N rats and equal numbers of B6C3F1 mice, 5 days/week for 103 weeks. Dosage levels were 0, 50, 100 and 200 mg/kg/day for male rats and 0, 25, 50 and 100 mg/kg/day for female rats and mice of both sexes. Significantly reduced survival was observed near the end of the study in high-dose male and middle- and high-dose female rats. All treated groups of male rats exhibited a statistically significant and dose-dependent lymphocytopenia throughout most of the study. A similar but less consistent trend was noted in female rats. Lymphoid depletion was observed in the spleens of all treated groups of rats; a dose-related lymphoid depletion was observed in the splenic follicles (both sexes of rats) and thymus (male rats). Hyperplasia of the adrenal occurred in low-dose rats of both sexes, hyperplasia of the Zymbal gland occurred in low-dose male and middle-dose female rats, and hyperkeratosis and acanthosis occurred in the forestomachs of high-dose male rats.

Male and female mice in the high-dose group had significantly reduced survival near termination of the study. Lymphocytopenia was evident in middle- and high-dose male mice for most of the study, but results in female mice were equivocal. Hyperplasia of the bone marrow occurred in all treated groups of mice and adrenal hyperplasia occurred in at least one sex at each exposure level. Hyperplasia and hyperkeratosis of the forestomach, hyperplasia of pulmonary alveolar epithelium, Zymbal gland, harderian gland and preputial gland, and epithelial hyperplasia and senile atrophy of the ovary were increased in incidence in some treated groups. These effects were attributed to treatment with benzene.

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 air containing 100 ppm (319 mg/m$^3$) benzene, 6 hours/day, 5 days/week for life (up to 505 days). There was no significant difference in median survival or rate of weight gain between treated and control mice. From the first week of exposure through the end of the experiment, marked increase in lymphocytopenia and slight, but statistically significant, anemia were reported for treated mice. Bone marrow hypoplasia was observed in 10/50 treated mice and in 1/50 controls. Similar but more severe effects on these parameters were reported in AKR mice in an earlier study conducted at a higher exposure level of 300 ppm benzene in the same laboratory (Snyder et al., 1978).

Snyder et al. (1980) also exposed groups of 40 male C57Bl/6J mice to filtered air or air containing 300 ppm (958 mg/m$^3$) benzene, 6 hours/day, 5 days/week for life (up to 488 days). A decreased survival rate was reported for treated mice, with a median survival of 41 weeks for the treated group and 75 weeks for the control group. Body weight gain of treated 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 mice relative to controls. Bone marrow hyperplasia was observed in 13/40 benzene-exposed 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 (958 mg/m$^3$) 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, 1980a; 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 (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, 1980a; 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, 1980a). According to NIOSH (1974), occupational exposures to benzene at 300-700 ppm (958-2236 mg/m$^3$) 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, 1980a; 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 mℓ/kg/day (790, 1320 or 2640 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 $\geq$0.5 mℓ/kg/day. 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, 1980a; 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).

Murray et al. (1979) exposed CF-1 mice and New Zealand rabbits to benzene vapors at a concentration of 500 ppm (1597 mg/m$^3$). 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. Mated females were exposed to 0 ppm (17 females), 10 ppm (32 mg/m$^3$, 18 females), 50 ppm (160 mg/m$^3$, 20 females) or 500 ppm (1597 mg/m$^3$, 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 through 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.

Keller and Snyder (1986) investigated the effects of maternal exposure to benzene on the development of the hematopoietic system in fetuses and offspring of Swiss-Webster mice. Mated mice were exposed to 0, 5, 10 or 20 ppm (0, 16, 32 or 64 mg/m$^3$), 6 hours/day on days 6-15 of gestation. A dose-related increase in fetal differentiated erythroid colony-forming cells (CFU-E) was observed at 5 and 10 ppm; a decrease in CFU-E was noted at 20 ppm. Some significant changes in CFU-E and GM-CFU-C were observed in 2-day-old neonates and 6-week-old adults following in utero exposure, but no pattern of response was discerned and the biological significance of the results is unclear.

### 3.4. TOXICANT INTERACTIONS

Benzene metabolism, and therefore benzene toxicity, may be altered by simultaneous exposure to some other solvents (e.g., xylene, toluene). These other aromatic solvents are oxidized by many of the same hepatic enzyme systems that metabolize benzene (Ikeda et al., 1972). Since benzene metabolites rather than the parent compound are suspected of inducing bone marrow toxicity, inhibition of benzene metabolism (hydroxylation) by toluene may increase the toxicity of benzene (Andrews et al., 1977; U.S. EPA, 1980a). This synergism might possibly explain the failure to induce leukemia in animals with exposure to benzene alone (NAS, 1976).

# 4. CARCINOGENICITY

## 4.1. HUMAN DATA

4.1.1. Oral. Pertinent data regarding the carcinogenicity of benzene by 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. These data are more completely reviewed 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) with an increased incidence of leukemia (Aksoy, 1977, 1980; Aksoy et al., 1971, 1972, 1974; 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, 1987; Wong et al., 1983). Only studies important in risk assessment are discussed in this section. The other epidemiology studies are reviewed in IARC (1982) and U.S. EPA (1978a, 1980a).

Aksoy (1977) 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 (671-2078 $mg/m^3$). Of the 28,500 subjects studied, 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 75% of 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).

Rinsky et al. (1981) published a follow-up report to the Infante et al. (1977a,b) studies using the same cohort but with vital status data obtained for 98% of the workers compared with 75% in the Infante et al. (1977a,b) reports. Among 748 workers exposed to benzene for $\geq$1 day between 1940 and 1950, seven workers died of leukemia. Based on U.S. death rates standardized for age, sex and calender time period, 1.25 leukemia deaths were expected, resulting in a statistically significant SMR of 560 ($p<0.001$). The mean duration of exposure to benzene was brief; and 437 (58%) of the workers were exposed for <1 year. In workers exposed for $\geq$5 years, deaths from leukemia resulted in an SMR of 2100. Had four additional known cases been included (they were excluded for technical reasons), the SMR would have been 3780. The investigators estimated past exposure and concluded that, although generally TWA exposures fell within permissible limits in effect at the time of exposure, benzene concentration occasionally rose to several hundred ppm in some areas of the plant.

Rinsky et al. (1987) have published an update of risk assessment of a cohort of 1165 rubber workers, as reported by Infante et al. (1977a,b) and Rinsky et al. (1981). In order to reduce the uncertainties posed by estimates of group exposures, individual work histories were compiled and cumulative exposures were estimated for each employee in the cohort based on the available past industrial hygiene measurements. Standardized mortality ratios were determined for leukemia by four cumulative exposure categories (i.e., <40, 40-200, 200-400 and >400 ppm • years) and a marked, progressive increase in standardized mortality ratios was observed with

increasing cumulative dose. There was no apparent pattern for nine leukemia deaths with regard to latency, which ranged from under 5 years to more than 30 years.

Ott et al. (1978) used a retrospective cohort analysis to examine the mortality of 594 individuals occupationally exposed to benzene in chemical manufacture during 1940-1973. Three deaths attributable to leukemia (two acute myelogenous leukemia and one myeloblastic leukemia) were reported among the 594 workers compared with 0.8 case of expected leukemia deaths (excluding lymphocytic or monocytic cell types), based on incidence data from the third National Cancer Survey (SMR=375). The difference between observed and expected incidence 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 (32 mg/m$^3$).

Wong et al. (1983) examined the mortality data of 7676 workers employed for $\geq$6 months in the period January 1, 1946 to December 31, 1975 in seven chemical plants in which exposure to benzene occurred. A total of 4602 workers were exposed to benzene. The exposed group was divided into two categories; those exposed continuously (exposed at least 3 days/week) vs. those exposed intermittently. Air concentrations and TWA exposures to benzene were estimated. The remaining 3074 workers constituted an internal control group. Vital statistics were compiled through December 31, 1977; 1036 of the 7676 workers had died and death certificates were obtained for 1013 (97.8%). SMRs were calculated for several causes of death using data from the United States population for comparison. SMRs were slightly but not statistically significantly >100 for lymphatic and hematopoietic cancer, and within the general category of hematopoietic cancer, specifically for leukemia, non-Hodgkins lymphoma and non-Hodgkins lymphopoietic cancer when

compared with the general population. However, the relative risk of death from lymphatic and hematopoietic cancer was significantly increased with a dose-response relationship between excess cancer risk and cumulative dose when compared with data from internal controls. The investigators noted that deaths from hematopoietic cancers were unusually low in the control cohort.

Only a small proportion of exposed individuals actually develop leukemia and it has been suggested that there is a sensitive subpopulation, possibly with some metabolic idiosyncrasy that allows the formation of reactive metabolites at a specific cellular target. Blattner et al. (1976) described a family involving a father and four of five siblings with chronic lymphocyctic leukemia. They all had been employed in the dry cleaning business since the 1940s, a period during which benzene was widely used.

## 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.

More recent evidence for the carcinogenicity of benzene to orally-exposed animals was provided by the 2-year NTP (1986) gavage study using rats and mice. Details of the protocol and tumor incidences are presented in Tables 4-2 (rats) and 4-3 (mice). In rats, benzene administration was associated with Zymbal gland carcinomas and squamous cell papillomas and

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<br>mammary gland | carcinoma<br>carcinoma | 0/30 (NA)<br>3/30 |
| F | 50 mg/kg 4-5 times/week | 52 | lifespan | NR | olive oil | Zymbal gland<br>mammary gland | carcinoma<br>carcinoma | 2/30 (NS)[b]<br>4/30 |
| F | 250 mg/kg 4-5 times/week | 52 | lifespan | NR | olive oil | Zymbal gland<br>mammary gland | carcinoma<br>carcinoma | 8/35 ($p<0.05$)[b]<br>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 Neoplastic Lesions in F344/N Rats Administered Benzene by Gavage[a]

| Lesion | Males (mg/kg)[b] | | | | Females (mg/kg)[b] | | | |
|---|---|---|---|---|---|---|---|---|
| | 0[c] | 50 | 100 | 200 | 0[c] | 25 | 50 | 100 |
| Zymbal gland<br>Carcinoma | 2/32[d] | 6/46 | 10/42[e] | 17/42[d] | 0/45[d] | 5/40[e] | 5/44[e] | 14/46[d] |
| Oral Cavity<br>Squamous cell papilloma or carcinoma | 1/50[d] | 9/50[f] | 16/50[d] | 19/50[d] | 1/50[f] | 5/50 | 12/50[d] | 9/50[f] |
| Skin<br>Squamous cell papilloma or carcinoma | 0/50[g] | 7/50[f] | 4/50 | 11/50 | NR | NR | NR | NR |

[a]Source: NTP, 1986

[b]Groups of 50 rats/sex/dose were administered benzene in corn oil by gavage, 5 days/week for 103 weeks and killed at ~104 weeks.

[c]Vehicle control

[d]$p<0.001$ in Cochrane-Armitage trend test (reported with vehicle control incidence) or Fisher Exact test (reported with dosed group incidence).

[e]$p\leq0.05$ in Cochrane-Armitage trend test (reported with vehicle control incidence) or Fisher Exact test (reported with dosed group incidence).

[f]$p\leq0.01$ in Cochrane-Armitage trend test (reported with vehicle control incidence) or Fisher Exact test (reported with dosed group incidence).

[g]p Value not reported

NR = Not reported

TABLE 4-3

Incidences of Neoplastic Lesions in B6C3F1 Mice Administered Benzene by Gavage[a]

| Lesion | Males (mg/kg)[b] | | | | Females (mg/kg)[b] | | | |
|---|---|---|---|---|---|---|---|---|
| | 0 | 25 | 50 | 100 | 0 | 25 | 50 | 100 |
| Zymbal gland | | | | | | | | |
| Carcinoma | 0/43[c] | 1/34 | 4/40[d] | 21/39[c] | 0/43[d] | 0/32 | 1/37 | 3/31 |
| Hematopoietic system | | | | | | | | |
| Malignant lymphoma | 4/49[e] | 9/48 | 9/50 | 15/49[e] | 15/49[e] | 24/45[d] | 24/50 | 20/49 |
| Lung | | | | | | | | |
| A/B adenoma | 6/49[d] | 6/48 | 8/50 | 12/49 | 4/49[d] | 2/42 | 5/50 | 9/49 |
| A/B carcinoma | 5/49[d] | 11/48 | 12/40 | 14/49[d] | 0/49[d] | 3/42 | 6/50[d] | 6/49[d] |
| A/B adenoma or carcinoma | 10/49[d] | 16/48 | 19/50[d] | 21/49[d] | 4/49[e] | 5/42 | 10/50 | 13/49[d] |
| Liver | | | | | | | | |
| Adenoma | 7/49 | 11/48 | 6/50 | 3/47 | 1/49 | 8/44[e] | 5/50 | 4/49 |
| Adenoma or carcinoma | 15/49 | 17/48 | 22/50 | 11/47 | 4/49 | 12/44[d] | 13/50[d] | 7/49 |
| Harderian gland | | | | | | | | |
| Adenoma | 0/49[e] | 9/46[c] | 13/49[c] | 11/48[c] | 5/48 | 6/44 | 10/50 | 6/47 |
| Adenoma or carcinoma | 1/49[c] | 10/46[e] | 13/49[c] | 14/48[c] | 5/48 | 6/44 | 10/50 | 10/47 |
| Preputial gland | | | | | | | | |
| Carcinomas | 0/21[c] | 5/28 | 19/29[c] | 31/35[c] | NA | NA | NA | NA |

TABLE 4-3 (cont.)

| Lesion | Males (mg/kg)[b] | | | | Females (mg/kg)[b] | | | |
|---|---|---|---|---|---|---|---|---|
| | 0 | 25 | 50 | 100 | 0 | 25 | 50 | 100 |
| Ovary | | | | | | | | |
| Granulosa cell tumor | | | | | 1/47[d] | 1/44 | 6/49 | 7/48[d] |
| Benign mixed tumor | NA | NA | NA | NA | 0/49[d] | 1/44 | 12/49[c] | 7/48[e] |
| Mammary gland | | | | | | | | |
| Carcinoma | | | | | 0/49[c] | 2/45 | 5/50[d] | 10/49[c] |
| Carcinosarcoma | NA | NA | NA | NA | 0/49[e] | 0/45 | 1/50 | 4/49 |

[a]Source: NTP, 1986

[b]Mice were administered 0 (vehicle control), 25 (low dose), 50 (mid dose) or 100 (high dose) mg/kg/day in corn oil by gavage on 5 days/week for 103 weeks and were killed at ~104 weeks.

[c]$p<0.001$ in Cochrane-Armitage trend test (reported with vehicle control incidence) or Fisher Exact test (reported with dosed group incidence).

[d]$p\leq0.05$ in Cochrane-Armitage trend test (reported with vehicle control incidence) or Fisher Exact test (reported with dosed group incidence).

[e]$p\leq0.01$ in Cochrane-Armitage trend test (reported with vehicle control incidence) or Fisher Exact test (reported with dosed group incidence).

A/B = Alveolar/bronchiolar; NA = not applicable

carcinomas of the oral cavity and of the skin. In mice, benzene administration was associated with malignant lymphoma, particularly in males, and tumors of the Zymbal gland, lung, harderian gland, preputial gland, ovary, mammary gland and possibly the liver.

4.2.2. Inhalation. A statistically significant increase in hematopoietic neoplasms was reported for male C57Bl/6J mice (n=40) exposed by inhalation to 300 ppm (958 mg/m$^3$) benzene, 6 hours/day, 5 days/week for 488 days (Snyder et al., 1980). These tumor incidences are summarized in Table 4-4. In the same study, there was no increase in tumors in 50 male AKR/J mice exposed to 100 ppm (319 mg/m$^3$) benzene under the same exposure schedule (see Table 4-4). Snyder et al. (1980) also failed to find a statistically significant increased incidence of 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. Leukemia was observed in 1/40 male Sprague-Dawley rats exposed to benzene vapors at a level of 100 ppm, 6 hours/day, 5 days/week for life (Snyder et al., 1980). Because leukemia is seldom observed in CD-1 mice and Sprague-Dawley rats, the authors concluded that benzene exposure may have been responsible for these cancers.

A major continuing study (Cronkite et al. 1984, 1985; Cronkite, 1986) provides a basis on which a reproducible model can be built. In this study C57Bl/6 BNL and CBA/Ca mice were exposed to 0, 10, 25, 100, 300 or 400 ppm (0, 32, 80, 319, 958 and 1276 mg/m$^3$), 6 hours/day, 5 days/week for 16 weeks followed by lifetime observation. This exposure regimen was selected because the authors thought it most closely paralleled likely human exposure. Human epidemiological studies in the literature reported that

TABLE 4-4

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 |
|---|---|---|---|---|---|---|---|---|---|
| C57Bl | M | 0.0 ppm | NA | lifespan | NA | NA | hematopoietic | all tumors | 2/40[b] |
| C57Bl | M | 300 ppm 6 hours/day, 5 days/week | 488 | lifespan | NR | vapor | hematopoietic | all tumors | 8/40[b] |
| 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

occupationally-exposed persons were exposed for ~15% of their lifespan and 16 weeks represent ~15% of the lifespan for mice. The C57Bl/6 and CBA/Ca mouse strains were chosen for this study because of their low spontaneous rates of acute myeloblastic leukemia, the disease most frequently associated with benzene exposure in humans.

Preliminary results associate benzene with leukemia in both strains of mice at concentrations ≥25 ppm. An elevated incidence of leukemia was associated with CBA/Ca mice exposed by the same schedule to ≥100 ppm (319 mg/m$^3$). No dose-related effect information is available for evaluation at this point.

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). A preliminary study suggests that benzene oxide, a postulated intermediate metabolite of benzene, might be mutagenic in S. typhimurium (IARC, 1982). 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 on mammalian chromosomes in vitro, but accumulated data seem to suggest that benzene metabolites may be 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 in mouse micronucleus assays following treatment

with benzene (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) have also been reported.

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; Sarto et al., 1984)).

### 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 Infante et al. (1977a,b), Rinsky et al. (1981, 1987) and Ott et al. (1978) provide sufficient direct human evidence for the carcinogenicity of benzene.

Animal bioassays, which demonstrate increased incidence of many tumor types in orally-exposed rats and mice (Maltoni and Scarnato, 1979; NTP, 1986) and suggest increased incidence of hematopoietic tumors in mice exposed by inhalation (Snyder et al., 1980; Cronkite et al., 1984, 1985; Cronkite, 1986), may be considered corroborative data that are supportive of a carcinogenic role for benzene. Applying the criteria for weight of evidence adopted by the U.S. EPA (1986a), benzene is appropriately designated a Group A human carcinogen.

# 5. REGULATORY STANDARDS AND CRITERIA

Regulations and recommended guidelines reported by 15 countries for limiting occupational exposure to benzene are summarized in Table 5-1. The current ACGIH (1986) TWA-TLV for benzene is 10 ppm (30 mg/m$^3$).

The U.S. EPA (1980a) has estimated ambient water concentrations of 0.066, 0.66 and 6.6 µg/ℓ associated with excess cancer risks of $10^{-7}$, $10^{-6}$ and $10^{-5}$, respectively. These estimates are based on an earlier CAG analysis (U.S. EPA, 1978b), which used the epidemiology studies performed by Infante et al. (1977a,b), Aksoy (1977) and Ott et al. (1978).

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 |
| | 1987 | 3.2 | 1 | TWA | regulation |
| | | 1.5 | 5 | STEL | 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 | | Interpretation | Status |
|---|---|---|---|---|---|
| | | ($mg/m^3$) | (ppm) | | |
| USSR | 1980 | 5 | NR | ceiling[b] | regulation |
| Yugoslavia | 1971 | 50 | 15 | ceiling[b] | regulation |

[a]Sources: ACGIH, 1983; ILO, 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. SUBCHRONIC REFERENCE DOSE ($RfD_S$)

Benzene is a known carcinogen for which data are sufficient for estimating carcinogenic potency. Therefore, it is inappropriate to calculate an oral or inhalation $RfD_S$ for benzene.

## 6.2. REFERENCE DOSE (RfD)

Benzene is a known carcinogen for which data are sufficient for estimating carcinogenic potency. Therefore, it is inappropriate to calculate an oral or inhalation RfD for benzene.

## 6.3. CARCINOGENIC POTENCY ($q_1$* or UNIT RISK SLOPE)

6.3.1. Oral. Oral cancer data include a 52-week gavage study using rats by Maltoni and Scarnato (1979) and a 103-week gavage study using rats and mice sponsored by the NTP (1986). Benzene was clearly carcinogenic in rats and in mice in these studies. Benzene is an EPA Group A carcinogen, which means that human data are sufficient to support a causal association between exposure and cancer. Therefore, it is more appropriate to base estimation of carcinogenic potency on human rather than animal data.

U.S. EPA (1978b) derived a slope factor of 0.024074 $(ppm)^{-1}$ for inhalation exposure to benzene based on the epidemiology studies by Aksoy (1977), Infante et al. (1977a,b) and Ott et al. (1978). In estimating excess cancer risk associated with benzene in ambient water, U.S. EPA (1980a) chose the inhalation unit risk slope developed by CAG (U.S. EPA, 1978b) over an estimate of carcinogenic potency derived from the first positive oral rat study (Maltoni and Scarnato, 1979). The reasoning for this decision is that it is more appropriate to base risk assessment on human rather than animal data, even if route-to-route extrapolation is involved, when sufficient human data are available.

In a later CAG assessment (U.S. EPA, 1985b), an inhalation unit risk slope of $2.60 \times 10^{-2}$ $(ppm)^{-1}$ was developed from the epidemiological data of Rinsky et al. (1981), Wong et al. (1983) and Ott et al. (1978). This estimate was considered as "single best judgment unit risk estimate" by CAG (U.S. EPA, 1986b). U.S. EPA (1986b) stated that this slope factor was equivalent to $2.8 \times 10^{-2}$ $(mg/kg/day)^{-1}$. A slope factor for oral exposure was calculated to be $5.6 \times 10^{-2}$ $(mg/kg/day)^{-1}$, by dividing the inhalation unit risk slope with absorption factor for inhalation (0.5).

In a recent CRAVE meeting (March 1, 1988), the oral slope factor for benzene has been verified to be $2.9 \times 10^{-2}$ $(mg/kg/day)^{-1}$ based on the occupational data that served as the basis of the slope estimate for inhalation exposure (Aksoy, 1977; Ott et al., 1978; Rinsky et al., 1981). The unit risk for oral exposure was calculated to be $8.3 \times 10^{-7}$ $(\mu g/\ell)^{-1}$ (U.S. EPA, 1988). It should be noted that the more recent study of Rinsky et al. (1987) has not been reviewed by the U.S. EPA and, therefore, results from this study have not been integrated into the quantitative assessment that has been verified by the CRAVE work group.

6.3.2. Inhalation. The U.S. EPA (1980a) 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 (1977), in which a significantly increased incidence of leukemia was observed for workers exposed to benzene principally by inhalation. Using these epidemiology studies, 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 slope factor of $7.52 \times 10^{-3}$ $(mg/m^3)^{-1}$. Assuming an inhalation rate of 20 $m^3$/day for a 70 kg man, the unit risk also may be expressed as $3.76 \times 10^{-4}$ $(mg/day)^{-1}$ or $2.6 \times 10^{-2}$ $(mg/kg/day)^{-1}$.

In a later evaluation by CAG (U.S. EPA, 1985b), an inhalation slope factor of $2.60 \times 10^{-2}$ $(ppm)^{-1}$ was developed from the epidemiological data of Rinsky et al. (1981), Wong et al. (1983) and Ott et al. (1978) (see Section 6.3.1.). This slope factor transforms to $2.8 \times 10^{-2}$ $(mg/kg/day)^{-1}$ as determined by U.S. EPA (1986b). The inhalation carcinogenic slope factor for benzene was verified by the CRAVE work group of EPA on March 1, 1988 to be $2.9 \times 10^{-2}$ $(mg/kg/day)^{-1}$, based on the occupational results obtained by Rinsky et al. (1981), Ott et al. (1978) and Aksoy (1977). The corresponding inhalation unit risk is calculated to be $8.3 \times 10^{-6}$ $(\mu g/m^3)^{-1}$ (U.S. EPA, 1988).

## 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.

ACGIH (American Conference of Governmental Industrial Hygienists). 1986. Threshold Limit Values and Biological Exposure Indices for 1986-1987. Cincinnati, OH. p. 10.

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, 1980a)

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 hematopoietic toxicity of $^{3}$H-benzene. Biochem. J. Pharmacol. 26: 293-300. (Cited in U.S. EPA, 1980a)

Atkinson, R. 1985. Kinetics and mechanisms of the gas-phase reactions of hydroxyl radical with organic compounds under atmospheric conditions. Chem. Rev. 85: 69-201.

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.

Blattner, W.A., W. Strober, A.V. Muchmore, R.M. Blaese, S. Broder and J.F. Fraumen. 1976. Familial chronic lymphocytic leukemia. Ann. Int. Med. 84: 554-557.

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. J. Med. Lyon. 50: 757-759. (Fre.) (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.

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)

Cronkite, E.P. 1986. Benzene hematotoxicity and leukemogenesis. Blood Cells. 12: 129-137.

Cronkite, E.P., J.E. Bullis, T. Inoue and R.T. Drew. 1984. Benzene inhalation produces leukemia in mice. Toxicol. Appl. Pharmacol. 75: 358-361.

Cronkite, E.P., R.T. Drew, T. Inoue and J.E. Bullis. 1985. Benzene hematotoxicity and leukemogenesis. Am. J. Ind. Med. 7: 447-456.

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, 1983a)

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. J. Med. Lyon. 9: 227-233. (Fre.) (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. Gig. Sanit. 1: 32-34. (Rus.) (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)

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. Bull. Inst. Natl. Sante Rech. Med. 22: 421-441. (Fre.) (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, 1983a)

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, 1983a)

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)

Hansch, C. and A.J. Leo. 1985. Medchem Project. Issue No. 26. Pomona College, Claremont, CA.

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, 1983a)

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

Hartwich, G., G. Schwanitz and J. Becker. 1969. Chromosomal aberrations in a leukaemia due to benzene. Dtsch. Med. Wochenschr. 94: 1228-1229. (Ger.) (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. Munkavedelem. 23: 50-51. (Hung.) (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)

Hunter, C.G. 1968. Solvents with reference to studies on the pharmacodynamics of benzene. Proc. Roy. Soc. Med. 61: 913-915.

Hunter, C.G. and D. Blair. 1972. Benzene: Pharmacokinetic studies in man. Ann. Occup. Hyg. 15: 193-199.

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, 1980a)

ILO (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)

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, 1980a)

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, 1980a)

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, 1980a)

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, 1980a, 1983a)

Jury, W.A., W.F. Spencer and W.J. Farmer. 1984. Behavior assessment model for trace organics in soil. III. Application of screening model. J. Environ. Qual. 13(4): 573-579.

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)

Keller, K.A. and C.A. Snyder. 1986. Mice exposed in utero to low concentrations of benzene exhibit enduring changes in their colony forming hematopoietic cells. Toxicology. 42(2-3): 171-181.

Khan, H. and M.H. Khan. 1973. Cytogenetic studies following chronic exposure to benzene. Arch. Toxicol. 31: 39-49. (Ger.) (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, 1983a)

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, 1980a, 1983a)

Lay, J.P., W. Schauerte, L. Peichl, W. Klein and F. Korte. 1985. Influence of benzene on the phytoplankton and on Daphnia pulex in compartments of an experimental pond. Ecotoxicol. Environ. Saf. 10(20): 218-227.

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. Schweiz. Med. Wochenschr. 13: 378-384. (Ger.) (Cited in IARC, 1982)

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

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

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

Mackay, D., S. Paterson, B. Cheung and W.B. Neely. 1985. evaluating the environmental behavior of chemicals with a Level III fugacity model. Chemosphere. 14(3-4): 335-374.

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. Mann. 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, 1980a)

Nawrot, P.S. and R.E. Staples. 1979. No title provided. Teratology. 19: 41. (Cited in U.S. EPA, 1980a, 1983a)

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, 1983a)

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)

Nomiyama, K. and H. Nomiyama. 1974. Respiratory retention, uptake and excretion of organic solvents in man. Int. Arch. Arbeitsmed. 32: 75-83.

NTP (National Toxicology Program). 1986. Toxicology and carcinogenesis studies of benzene in F344/N rats and B6C3F1 mice (gavage studies). U.S. DHHS, PHS NIH. Publ. No. 86-2545. NTP TR 289.

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)

OSHA (Occupational Safety and Health Administration). 1987. Occupational Exposure to Benzene. Final Rule. Federal Register. 52: 34560-34578.

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, 1980a)

Pagnotto, H.L. 1972. Written communication to NIOSH. (Cited in NIOSH, 1974; U.S. EPA, 1983a)

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, 1980a, 1983a)

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. Med. Lav. 67 (Suppl. 5): 465-472. (Ital.) (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. Med. Lav. 68: 308-312. (Ital.) (Cited in IARC, 1982)

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

Pollini, G. and R. Colombi. 1964b. Chromosomal damage in lymphocytes during benzene haemopathy. Med. Lav. 55: 641-655. (Ital.) (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. Med. Lav. 55: 735-751. (Ital.) (Cited in IARC, 1982)

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

Rinsky, R.A., A.B. Smith, R. Hornung, et al. 1987. Benzene and leukemia: An epidemiologic risk assessment. N. Engl. J. Med. 316: 1044-1050.

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)

Sabourin, P.J., B.T. Chen, G. Lucier, L.S. Birnbaum, E. Fisher and R.F. Henderson. 1987. Effect of dose on the absorption and excretion of [$^{14}$C] benzene administered orally or by inhalation in rats and mice. Toxicol. Appl. Pharmacol. 87: 325-336.

Sarto, F., I. Cominato, A.M. Pinton, et al. 1984. A cytogenic study on workers exposed to low concentrations of benzene. Carcinogenesis. 5(6): 827-832.

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, 1983a)

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)

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, 1980a, 1983a)

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, 1983a)

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, 1983a,b)

Srbova, J., J. Teisinger and S. Skramovsky. 1950. Absorption and elimination of inhaled benzene in man. Arch. Ind. Hyg. Occup. Med. 2(1): 1-8.

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. 1: 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, 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, 1980a)

U.S. EPA. 1979. Carcinogen Assessment Group's Final Report on Population Risk to Ambient Benzene Exposures. Prepared by Office of Health and Environmental Assessment, Carcinogen Assessment Group, Washington, DC for the Office of Air Quality Planning and Standards, Research Triangle Park, NC. EPA 450/5-80-004. NTIS PB82-227372.

U.S. EPA. 1980a. Ambient Water Quality Criteria for Benzene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-018. NTIS PB 81-117293.

U.S. EPA. 1980b. Guidelines and Methodology Used in the Preparation of Health Effects Assessment Chapters of the Consent Decree Water Criteria Documents. Federal Register. 45(231): 79347-79357.

U.S. EPA. 1983a. Reportable Quantity for Benzene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH 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 Office of Health and Environmental Assessment, Carcinogen Assessment Group, Washington, DC for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1984. Methodology and Guidelines for Ranking Chemicals Based on Chronic Toxicity Data. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1985a. Drinking Water Criteria Document for Benzene. Prepared by the Office of Drinking Water, Washington, DC. Final Draft (on Public Comment). NTIS PB86-118112.

U.S. EPA. 1985b. Interim Quantitative Cancer Unit Risk Estimates Due to Inhalation of Benzene. Prepared by the Office of Health and Environmental Assessment, Carcinogen Assessment Group, Washington, DC for the Office of Air Quality Planning and Standards, Research Triangle Park, NC. Internal Report.

U.S. EPA. 1986a. Guidelines for Carcinogen Risk Assessment. Federal Register. 51(185): 33992-34003.

U.S. EPA. 1986b. Evaluation of the Potential Carcinogenicity of Benzene. Prepared by the Office of Health and Environmental Assessment, Carcinogen Assessment Group, Washington, DC, for the Office of Solid Waste and Emergency Response, Washington, DC. Review Draft.

U.S. EPA. 1988. Integrated Risk Information System (IRIS). Carcinogenicity Assessment for Lifetime Exposure to Benzene. Online. (Verification date 03/01/88.) Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

Van den Berghe, H., A. Louwagie, A. Broeckaert-Van Orshoven, G. David and R. Verwilghen. 1979. Chromosome analysis 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, 1983a)

Vowles, P.D. and R.F.C. Mantoura. 1987. Sediment-water partition coefficients and HPLC retention factors of aromatic hydrocarbons. Chemosphere. 16: 109-116.

Wakeham, S.G., A.C. Davis and J.L. Karas. 1983. Mesocosm experiment to determine the fate and persistence of volatile organic compounds in coastal seawater. Environ. Sci. Technol. 17: 611-617.

Ward, C.O., R.A. Kuna, N.K. Snyder, R.D. Alsaker, W.B. Coate and P.H. Craig. 1985. Subchronic inhalation toxicity of benzene in rats and mice. Am. J. Ind. Med. 7(5-6): 457-473.

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, 1983a)

Wong, O., R.W. Morgan, M.D. Whorton. 1983. Comments on the NIOSH study of leukemia in benzene workers. Technical report submitted to Gulf Canada, Ltd., by Environmental Health Associates. (Cited in U.S. EPA, 1985b, 1986b)

Zoeteman, B.C.J., E. Degreef and F.J.J. Brinkman. 1981. Persistence of organic contaminants in ground water, lessons from soil pollution incidents in the Netherlands. Sci. Total Environ. 21: 187-202.

## APPENDIX

### Summary Table for Benzene

| | Species | Experimental Dose/Exposure | Effect | Carcinogenic Slope or Unit Risk | Reference |
|---|---|---|---|---|---|
| Inhalation | | | | | |
| Carcinogenic Potency | humans | occupational | leukemia | $8.3 \times 10^{-6}$† $(\mu g/m^3)^{-1}$ | Rinsky et al., 1981; Ott et al., 1978; Wong et al., 1983; U.S. EPA, 1987 |
| Oral | | | | | |
| Carcinogenic Potency | humans | occupational | leukemia | $2.9 \times 10^{-2}$ $(mg/kg/day)^{-1}$ | Rinsky et al., 1981; Ott et al., 1978; Wong et al., 1983; U.S. EPA, 1987 |

†Calculated from a carcinogenic slope of $2.9 \times 10^{-2}$ $(mg/kg/day)^{-1}$