March 31, 1987

820K87009

BENZENE

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

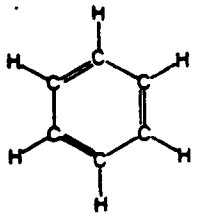
Health Advisories are developed for One-day, Ten-day, Longer-term (approximately 7 years, or 10% of an individual's lifetime) and Lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from such exposure. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

This Health Advisory is based on information presented in the Office of Drinking Water's Draft Health Effects Criteria Documents (CD) for Benzene (U.S. EPA, 1983b, 1985a). The HA and CD formats are similar for easy reference. Individuals desiring further information on the toxicological data base or rationale for risk characterization should consult the CDs. The CDs are available for review at each EPA Regional Office of Drinking Water counterpart (e.g., Water Supply Branch or Drinking Water Branch), or for a fee from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Rd., Springfield, VA 22161, PB # 86-118122/AS. The toll-free number is (800) 336-4700; in the Washington, D.C. area: (703) 487-4650.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 71-43-2

Structural Formula



Synonyms

- None

Uses

- Additive to gasoline to increase the octane.
- Chemical intermediate in the synthesis of compounds such as: styrene, synthetic rubber, phenol, alkylarnesulfonate detergent, nitrobenzene (aniline), and cyclohexane.

Properties (Von Gemert and Nettenbreijer, 1977; Windholz, 1983)

Chemical Formula	C_6H_6
Physical State	Volatile, colorless flammable liquid, aromatic hydrocarbon
Boiling Point	80.100°C
Freezing Point	5.53°C
Density at 25°C	0.8765 g/mL
Vapor Pressure at 26°C	100 mmHg
Water Solubility at 25°C	1.8 g/L
Odor Threshold, in air	4.9 mg/m^3 (characteristic odor)
Odor Threshold, in water	2.0 mg/L

Occurrence

- Benzene is produced at low levels in a number of biological processes and is a component of petroleum (U.S. EPA, 1983a).

- Benzene is produced in large amounts, e.g., 9 billion lbs in 1981 (U.S. ITC, 1984), and is used largely as a feedstock on the production of other chemicals. Small amounts of benzene have been used as a solvent; however, this use has been discontinued. Benzene also is produced indirectly in large volumes, such as during gasoline refining and other operations. The average benzene content of gasoline is less than 1% (Runion, 1975).

- Releases of benzene to the environment are largely to air due to its volatile nature, with smaller amounts to water and soil. Releases of benzene to water are mainly due to spills of gasoline and other petroleum products and from benzene's previous use as a solvent. Because of the widespread use of petroleum products, releases of benzene occur nationwide (Mara and Lee, 1978; OSHA, 1978).

- Benzene released to surface water rapidly volatilizes to the air.

- Benzene degrades rapidly in air with a half life of less than one day.

- Benzene released to the ground binds somewhat to soil and slowly migrates with ground water. Benzene is biodegraded poorly and is expected to be stable in ground water (Mara and Lee, 1978).

- Benzene occurs in drinking water, food, and air (U.S. EPA, 1983b).

- Benzene occurs in both ground water and surface public water supplies, with higher levels occurring in ground water supplies. Based upon Federal drinking water surveys, approximately 1.3% of all ground water systems are estimated to contain benzene at levels greater than 0.5 ug/L. The highest level reported in the surveys for ground water was 80 ug/L. Approximately 3% of all surface water system are estimated to be contaminated at levels higher than 0.5 ug/L. None of the systems are expected to contain levels higher than 5 ug/L.

- Benzene is found at ppb levels in a large number of foods as a naturally occurring compound (U.S. EPA, 1983b).

- Benzene is found in air in urban and suburban areas, generally at average levels of less than 10 ppb (U.S. EPA, 1983b), but at higher levels in certain metropolitan areas such as Los Angeles where Lonneman et al. (1968) measured an average benzene concentration of 15 ppb with a maximum of 57 ppb. Benzene has been reported to occur in indoor air at levels higher than those found outdoors. Based upon the available evidence, the major source of benzene exposure is believed to be from air.

III. PHARMACOKINETICS

Absorption

- As a neutral, low molecular weight, lipid soluble material, benzene is readily absorbed via inhalation and ingestion. It is poorly absorbed through the intact skin (NIOSH, 1974).

- Administration of benzene to rats via inhalation or ingestion results in its rapid uptake and excretion, mainly via exhalation of unchanged benzene (Rikert et al., 1979; Parke and Williams, 1953). The exhalation of unchanged benzene has also been reported in dogs (Schrenk et al., 1941), rabbits (Parke and Williams, 1953) and mice (Andrews et al., 1977a).

- When humans are exposed to benzene in air, absorption via inhalation is approximately 50% (Nomiyama and Nomiyama, 1974 a,b).

Distribution

- Benzene is highly lipid soluble which accounts for its tendency to accumulate in fatty tissue (U.S. EPA, 1983b).

- In mice, benzene is stored in the bone marrow, liver and body fat (Snyder et al., 1978).

Metabolism

- The metabolic pathway for benzene has been thoroughly delineated in benzene background documents including U.S. EPA (1983b, 1985a). In humans, phenol sulfate is the major metabolite of benzene until 400 mg/L levels are reached in the urine. Beyond that level, glucuronide conjugates are also present in the urine (Sherwood, 1972).

Excretion

- The rate of elimination of benzene in humans is biphasic with initially about 16.2% eliminated unchanged via exhalation in 5 hours (Nomiyama and Nomiyama, 1974a,b). The remainder of the benzene is stored in the fatty tissues and is excreted much more slowly. Benzene has a half-life of 0.7 hours in rats (Rickert et al., 1979).

IV. HEALTH EFFECTS

Humans

- Acute exposure to high levels of benzene produces primarily central nervous system effects such as dizziness, giddiness, exhilaration, nausea, vomiting, headache, drowsiness, staggering, loss of balance, narcosis, coma and death. Exposure to 25,000 ppm in air is rapidly fatal (NAS, 1976). At nonlethal levels, mild central nervous system effects appear to be concentration-dependent and are rapidly reversible. Lower levels of benzene do not seem to elicit these effects no matter how long the exposure (U.S. EPA, 1983b).

- Benzene has been a known hematological poison since the 19th century when cases of aplastic anemia in workers fabricating bicycle tires were described by Santesson (1897).

- Benzene causes bone marrow toxicity resulting in a continuum of changes in the circulating formed blood elements ranging from a mild decrease in platelets to aplastic anemia, a rapidly fatal disease. The lowest level that produced changes in platelet counts in workers appears to be 10 ppm (Doskin 1971; Chang, 1972).

- Benzene causes acute myeloblastic leukemia, acute myelomonocytic leukemia and erythroleukemia (Rinsky et al., 1981). The exposure levels resulting in leukemia have not been determined.

- Epidemiologic studies show that exposure to benzene via inhalation at levels of 10 ppm or lower for approximately one year increases the risk of cancer by 560 fold and exposure for five or more years increases the risk by 2,100 fold (Rinsky et al., 1981).

- Immune system depression resulting from benzene exposure is a well known toxicological phenomenon. Susceptibility to tuberculosis (White and Gammon, 1914) and pneumonia (Winternitz and Hirschfelder, 1913) have been demonstrated to be increased in benzene-treated rabbits.

- Serum levels of IgG and IgA (immunoglobulins) were shown to be decreased in benzene workers (Lange et al., 1973; Smolick et al., 1973).

- These observations in conjunction with the well known ability of benzene to depress leukocytes which play a significant role in protection against infectious agents, may explain why individuals regularly exposed to benzene readily succumb to infection and the terminal event in severe benzene toxicity is often acute overwhelming infection.

- Benzene has caused chromosomal aberrations in exposed workers (Kissling and Speck, 1969; Tough et al., 1970; Forni et al., 1971).

Animals

Short-term Exposure

- Dogs exposed to benzene by inhalation at 600 to 1,000 ppm for 12 to 15 days developed leukopenia (reduction in the number of circulating leukocytes) (Hough and Freeman, 1944).

- Mice exposed to benzene by inhalation at 600 to 1,000 ppm developed fatal anemia within 12 to 15 days (Petrini, 1941).

- When exposed to benzene by inhalation at 80 to 85 ppm, rats (136 doses), guinea pigs (193 doses), rabbits (187 doses) and monkeys (187 doses) developed leukopenia (Wolf et al., 1956).

- Deichmann et al. (1963) conducted a series of experiments in which Sprague-Dawley rats (40/group) were exposed to benzene vapor for 5 hours per day, 4 days per week for 6 to 31 weeks. Average exposure concentrations ranged from 15 to 831 ppm. Rats exposed to benzene vapor at 61, 65 or 831 ppm developed severe leukopenia within 2 to 4

weeks. At 44 and 47 ppm, moderate leukopenia was observed, especially in females, in 5 to 8 weeks, and no leukopenia was observed when animals were exposed to 29 or 31 ppm for 4 months. Therefore, 31 ppm (96 mg/m^3) is identified as the NOAEL for this study.

Long-term Exposure

- Sprague-Dawley rats and both AKR/J and C57BL/6J mice were exposed to benzene by inhalation at concentrations of either 100 ppm or 300 ppm 6 hours per day, 5 days per week for life by Snyder et al. (1980). Both rats and mice exhibited lymphocytopenia, anemia and decreased survival time. In mice these effects were accompanied by granulocytosis and reticulocytosis. A later evaluation of the same study showed preliminary evidence of carcinogenicity, bone marrow hypoplasia, anemia and lymphocytopenia (Snyder et al., 1980).

Reproductive Effects

- There is no strong evidence that benzene produces teratogenic effects. It is a potent inhibitor of growth in utero (U.S. EPA, 1983b).

Mutagenicity

- Benzene was found not to be mutagenic in Drosophila melanogaster by Nylander et al. (1978). In this study, newly hatched larvae were exposed to media containing benzene at a concentration of 1% or 2%. Mutation, as measured by a shift in eye pigmentation, was not noted at either concentration.

- Benzene at 20 or 600 ug/plate was shown not to be mutagenic in Salmonella typhimurium when tested with or without metabolic activation in strains TA100, TA98, TA1535, TA1537 and TA1538. Levels up to 880 ug/plate with activation were not mutagenic in strains TA98 and TA1000 (Dean, 1978).

- Benzene oxide , the presumed initial metabolite of benzene, was mutagenic without activation in an Ames test using S. typhimurium (Pulkrabek et al., 1980).

- A marked increase in sister chromatid exchanges (SCE) was reported in DBA/2 mice exposed to benzene at 3100 ppm by inhalation for 4 hours (Tice et al., 1980).

Carcinogenicity

- Benzene has produced both solid tumors and leukemias in Sprague-Dawley rats (Maltoni and Scartano, 1979). Benzene dissolved in olive oil was administered by gavage to 13 week old Sprague-Dawley rats at doses of 50 or 250 mg/kg/day 4 to 5 days a week for 52 weeks. The animals were then allowed to live until spontaneous death. The high dose group consisted of 35 rats of each sex; the low dose and vehicle control goups consisted of 30 rats of each sex. After 20 weeks of exposure, the denominators were corrected (numbers of animals

surviving) to reflect compound-related deaths. The 250 mg/kg group then consisted of 33, males and 32 female rats; the 50 mg/kg and control groups consisted of 28 male and 30 female rats each. At the end of 144 weeks, 25% of the females had Zymbal gland tumors, 6.2% had skin carcinomas and and 12.1% had leukemias.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for One-day, Ten-day, Longer-term (approximately 7 years) and Lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (BW)}{(UF) \times (\_\_\_ L/day)} = \_\_\_ mg/L \ (\_\_\_ ug/L)$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect-Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100 or 1,000), in accordance with NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

Insufficient data are available to calculate a One-day HA for benzene. Similarly, the National Academy of Sciences (1982) has stated that there are insufficient data to determine a one-day SNARL. The Ten-day HA (0.235 mg/L or 235 ug/L) is considered to be adequately protective for a one-day exposure as well.

Ten-day Health Advisory

The calculation of the Ten-day HA is based on the study of Deichman, et al. (1963) who exposed Sprague-Dawley rats to benzene by inhalation 6 hours per day, 4 days per week, at a broad range of concentrations and monitored their hematology weekly. By the second week of treatment, there was definite hematological impairment, including severe leukopenia, at the 61, 65 and 831 ppm exposure concentration and moderate leukopenia, especially in females, at the 44 and 47 ppm exposure concentrations. Leukopenia was not observed, however, at 29 or 31 ppm.

Using the NOAEL of 31 ppm (96 mg/m^3), the Ten-day HA is calculated as follows:

Step 1: Determination of the Total Absorbed Dose (TAD)

$$TAD = \frac{(96\ mg/m^3)\ (6\ m^3)\ (0.5)\ (4)}{(70\ kg)\qquad\qquad (7)} = 2.35\ mg/kg/day$$

where:

96 mg/m^3 = 31 ppm exposure; NOAEL for leukopenia in rats.

6 m^3 = volume of air inhaled during 6 hours of exposure; based upon equivalent lung to whole body ratios for adult humans and rats (Olson and Gehring, 1976).

0.5 = pulmonary absorption factor for benzene (Nomiyama and Nomiyama, 1974a,b).

4/7 = conversion of total weekly dose to equivalent daily dose.

Step 2: Determination of the Ten-day Health Advisory

$$\text{Ten-day HA} = \frac{(2.35\ mg/kg/day)(10\ kg)}{(100)\ (1\ L/day)} = 0.235\ mg/L\ (235\ ug/L)$$

where:

2.35 mg/kg/day = TAD.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Longer-term Health Advisories

Longer-term Health Advisories have not been calculated because of the carcinogenic potency of benzene.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body

weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

A Lifetime Health Advisory has not been calculated because of the carcinogenic potency of benzene.

Evaluation of Carcinogenic Potential

- Benzene is a known human carcinogen.
- U.S. EPA (1985a) has estimated that excess upper-bound lifetime cancer risks of 10^{-4}, 10^{-5} and 10^{-6} correspond to benzene in drinking water at concentrations of 70, 7 and 0.7 ug/L, respectively.
- IARC (1982) has classified benzene as a Group 1: Human carcinogen.
- Applying the criteria in the EPA guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), benzene may be classified as a Group A: human carcinogen. This category is for substances for which there is sufficient evidence from epidemiologic studies to support the causal association between exposure to the agents and cancer.

VI. OTHER CRITERIA, STANDARDS AND GUIDANCE

- The National Academy of Sciences has not calculated SNARLS or ADIs for benzene (NAS, 1982).
- The current OSHA recommendation for a 10-hour time-weighted average (TWA) exposure to benzene in air is 3.2 ug/L (1 ppm) and is a lowest feasible level in the work place. This level would allow a daily dose of 16 mg.

VII. ANALYTICAL METHODS

- Analysis of benzene is by a purge-and-trap gas chromatographic procedure used for the determination of volatile aromatic and unsaturated organic compounds in water (U.S. EPA, 1985b). This method includes the bubbling of an inert gas through the sample and trapping benzene on an adsorbent material which is then heated to drive off benzene onto a gas chromatographic column. The gas chromatograph is temperature-programmed to separate the resulting analytes which are then detected by the photoionization detector. This method is applicable to the measurement of benzene over a concentration range of 0.02 to 1500 ug/L. Confirmatory analysis is by mass spectrometry (U.S. EPA, 1985c), which has a detection limit of 0.2 ug/L for benzene.

VIII. TREATMENT TECHNOLOGIES

- Treatment technologies which will remove benzene from water include granular activated carbon (GAC) adsorption, air stripping and boiling.

- Dobbs and Cohen (1980) developed adsorption isotherms for several organic chemicals including benzene. It was reported that Filtrasorb® 300 carbon columns exhibited adsorptive capacities of 0.007 mg, 0.03 mg, 1 mg and 40 mg benzene/g carbon (Beaudet et al., undated, Bilello and Beaudet, 1981).

- Air stripping is an effective, simple and relatively inexpensive process for removing benzene and other organics from water. Benzene is amenable to air stripping on the basis of its Henry's Law Constant of 240 atm at 20°C (Kavanaugh and Trussel, 1980). Cummins (1985) reported that benzene could be removed from water contaminated by a gasoline spill by packed column air stripping. In this field study, 24' x 2' columns packed with plastic saddles were used to treat water containing 190 ug/L benzene and other contaminants. Removal efficiencies of 70 to 100% were obtained using air-to-water ratios of 8.1:1 to 87:1. At air-to-water ratios of 17:1 or greater, efficiencies were 97% or better. Use of this process, however, transfers the contaminant directly to the air stream. When considering the use of air stripping as a treatment process, it is suggested that careful consideration be given to the overall environmental consequences and various hazards associated with release of this chemical into the air.

- Boiling also is effective in eliminating benzene from water. Studies have shown that 10 minutes of vigorous boiling will remove 99% of the benzene (Love et al., 1983).

IX. REFERENCES

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. Pharmacol. 26:293-300.

Beaudet, B.A., E.M. Keller, L.J. Bilello and R.J. Turner. Undated. Removal of specific organic contaminants from industrial wastewaters by granular activated carbon adsorption. Incomplete citation.

Bilello, L.J., and B.A. Beaudet. 1981. Evaluation of activated carbon by the dynamic mini-column adsorption technique. Incomplete citation.

Chang, I.W. 1972. Study on the threshold limit value of benzene and early diagnosis of benzene poisoning. J. Cath. Med. Coll. 23:429.

Cummins, M.D. 1985. Field evaluation of packed column air stripping. U.S. EPA.

Dean. B.J. 1978. Genetic toxicology of benzene, toluene, xylenes and phenols. Mut. Res. 47:75.

Deichmann, W.B., W.E. MacDonald and E. Bernal. 1963. The hemopoietic tissue toxicity of benzene vapors. Toxicol. Appl. Pharmacol. 5:201-224.

Dobbs, R.J., and J.M. Cohen. 1980. Carbon isotherms for toxic organics. U.S. EPA.

Doskin, T.A. 1971. Effect of age on the reaction to a combination of hydrocarbons. Hygiene and Sanitation. 36:379.

Forni, A., E. Pacifico and A. Limonta. 1971. Chromosome studies in workers exposed to benzene or toluene or both. Arch. Environ. Health. 22:373-354.

Gemert Von, L.J., and A.H. Nettenbreijer. 1977. Compilation of odor threshold values in air and water. National Institute for Water Supply, Voorburg, Netherlands.

Gerarde, H.W. 1960. Toxicology and biochemistry of aromatic hydrocarbons. Elsevier Publishing Company., N.Y.

Hough, H., and S. Freeman. 1944. Relative toxicity of commercial benzene and a mixture of benzene, toluene and xylene. Fed. Proc. 3:20.

IARC. 1982. International Agency for Research on Cancer. IARC monographs, some industrial chemicals and dyestuffs. 29, 83.

Kavanaugh, M.C., and R.R. Trussel. 1980. Design of aeration towers to strip volatile contaminants from drinking water. JAWWA. Dec.

Kissling, M., and B. Speck. 1969. Chromosome aberrations in experimental benzene intoxication. Helv. Med. Acta 36:59.

Lange, A.R., Smolick, W. Zatonski and J. Syzmanska. 1973. Serum immunoglobulin levels in workers exposed to benzene, toluene and xylene. Int. Arch. Arbeitsmed. 31:248.

Lonneman, W.A., T.A. Bellar and A.P. Altshuller. 1968. Aromatic hydrocarbons in the atmosphere of the Los Angeles basin. Environ. Sci. Technol. 2(11):1017.

Love, O.T., R.J. Miltnen, R.G. Eilers and Fronk-Leist. 1983. Treatment of volatile organic compounds in drinking water. U.S. EPA, MERL, Cincinnati, OH 45268. EPA-600/8-83-019.

Maltoni, C., and C. Scartano. 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.

Mara, S.J., and S.S. Lee. 1978. Assessment of human exposures to atmospheric benzene. U.S. Environmental Protection Agency, Research Triangle Park, NC. EPA-450/3-78-031.

NAS. 1976. National Academy of Sciences. Health effects of benzene: A review. Committee on Toxicology, Assembly of Life Sciences, National Research Council. Wash. D.C.

NAS. 1982. National Academy of Sciences. Drinking Water and Health. Volume 4. National Academy Press, Washington, D.C..

NIOSH. 1974. National Institute of Occupational Safety and Health. Criteria for a recommended standard . . . occupational exposure to benzene. U.S. DHEW, Washington, DC. PB246 700.

Nomiyama, K., and H. Nomiyama. 1974a. Respiratory retention uptake and excretion of organic solvents in man. Benzene, toluene, n-hexane, trichloroethylene, acetone, ethyl acetate, and ethyl alcohol. Int. Arch. Arbeitsmed. 32:75-83.

Nomiyama, K., and H. Nomiyama. 1974b. Respiratory elimination of organic solvents in man. Benzene, toluene, n-hexane, trichloroethylene, acetone, ethyl acetate, and ethyl alcohol. Int. Arch. Arbeitsmed. 32:85-91.

Nylander, P., H. Olaffsson, B. Rasmuson and H. Svahlin. 1978. Mutagenic effects of petrol in Drosphila melanogaster. I. Effects of benzene and 1,2-dicloroethane. Mut. Res. 57:163.

OSHA. 1978. Occupational Safety and Health Administration. Final environmental impact statement. Benzene. U.S. Dept. of Labor, Washington, DC.

Parke, D.V., and R.T. Williams. 1953. Studies in detoxication. The metabolism of benzene containing ^{14}C benzene. Biochem. J. 54:231-238.

Petrini, M. 1941. Investigations on acute and subacute poisoning by benzene. Rass. Med. Ind. 12:435-476. (In Italian)

Pulkrabek, P., T. Kinoshita and A.M. Jeffery. 1980. Benzene oxide: In vitro mutagenic and toxic effects. Proc. 16th Ann. Meeting Amer. Soc. Clin. Oncol. 21:107.

Rinsky, R.A., R.J. Young, A and B. Smith. 1981. Leukemia in benzene workers. Amer. J. Ind. Med. 2:217-245.

Rickert, D.E., T.S. Baker, J.S. Bus, C.S. Barrow and R.D. Irons. 1979. Benzene disposition in the rat after exposure by inhalation. Toxicol. Appl. Pharmacol. 49:417-423.

Runion, H.E. 1975. Benzene in gasoline. Am. Indust. Hyg. Assn. J. 36:338-350.

Santesson, C.G. 1897. Uber chronische vergiftung mit steinkohlentheerbenzin; vir todesfalle. Arch. Hyg. Berl. 31:336.

Schrenk, H.H., W.P. Yant, S.J. Pearce, F.A. Patty and R.R. Sayers. 1941. Absorption, distribution and elimination of benzene by body tissues and fluids of dogs exposed to benzene vapor. J. Ind. Hyg. Toxicol. 23:20-34.

Sherwood, R.J. 1972. Benzene: The interpretation of monitoring results. Ann. Occup. Hyg. 15:409-421.

Smolick, R., K.Grzybek-Hryncewica, A. Lange and W. Zatonski. 1973. Serum complement level in workers exposed to benzene, toluene and xylene. Int. Arch. Arbeitmed. 31:243.

Snyder, R., E.W. Lee and J.J. Kocsis. 1978. Binding of labeled benzene metabolites to mouse liver and bone marrow. Res. Commun. Chem. Pathol. Pharmacol. 20:191-194.

Snyder, C.A., B.D. Goldstein and A.R. Sellakumar. 1980. Hematotoxicity of inhaled benzene to Sprague-Dawley rats and AKR mice at 300 ppm. J. Toxicol. Environ. Health. 4:605-618.

Tice, R.R., D.L. Costa and R.T. Drew. 1980. Cytogenetic effects of inhaled benzene in murine bone marrow: Induction of sister chromatid exchanges, chromosomal aberrations, and cellular proliferation inhibition in DBA/2 mice. Proc. Natl. Acad. Sci. USA 77:21483152B.

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. Europ. J. Cancer 6:49-55.

U.S. EPA. 1979. U.S. Environmental Protection Agency. Water related environmental fate of 129 priority pollutants. Office of Water Planning and Standards, EPA-440/4-79-029, December 1979.

U.S. EPA. 1983a. U.S. Environmental Protection Agency. Benzene occurrence in drinking water, food, and air. Office of Drinking Water. Washington, DC.

U.S. EPA. 1983b. U.S Environmental Protection Agency. Benzene draft criteria document. Office of Drinking Water. Washington, DC.

U.S. EPA. 1984a. U.S. Environmental Protection Agency. Intermedia priority pollutants guidance documents. Office of Toxic Substances. Washington, DC.

U.S. EPA. 1984b. U.S. Environmental Protection Agency. National primary drinking water regulations; Volatile synthetic organic chemicals; Proposed rulemaking. Fed. Reg. 49(114):24330-24355. June 12.

U.S. EPA. 1985a. U.S. Environmental Protection Agency. Proposed RMCL background document for Benzene for the Office of Drinking Water, Criteria and Standards Division. Washington, DC.

U.S. EPA. 1985b. U.S. Environmental Protection Agency. Method 503.1. Volatile aromatic and unsaturated organic compounds in water by purge and trap gas chromatography. Environmental Monitoring and Support Laboratory, Cincinnati, Ohio. June 1985.

U.S. EPA. 1985c. U.S. Environmental Protection Agency. Method 524.1. Volatile organic compounds in water by purge and trap gas chromatography/ mass spectrometry. Environmental Monitoring and Support Laboratory, Cincinnati, Ohio. June 1985.

U.S. EPA. 1986. U.S. Environmental Protection Agency. Guidelines for carcinogenic risk assessment. Fed. Reg. 51(185):33992-34003. September 24.

U.S. ITC. 1984. U.S. International Trade Commission. Synthetic organic chemicals. United States production, 1983. U.S. ITC Publication 1422. Washington, D.C.

White, W.C., and A.M. Gammon. 1914. The influence of benzol inhalation on experimental pulmonary tuberculosis in rabbits. Trans. Assoc. Amer. Phys. 29:332-337.

Windholz, M. 1983. The Merck Index. 10th Edition. Merck and Co., Inc. Rahway, NJ.

Winternitz, M.C., and A.D. Hirschfelder. 1913. Studies on experimental pneumonia in rabbits: Parts I-III. J. Exptl. Med. 17:664.

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. 14:387-389.