

Benzene

Environmental benzene is both natural and anthropogenic in origin. Many industries use benzene, and as a result it is in the top 20 in production volume for chemicals produced in the United States. Typically, benzene is used to make other chemicals such as styrene, cumene, and cyclohexane. In manufacturing, benzene is used to produce rubbers, lubricants, dyes, detergents, drugs, and pesticides. Volcanoes and forest fires contribute to the amount of benzene in the environment. Benzene is also found in cigarette smoke, crude oil, and gasoline.

1. Physico-Chemical Properties

Benzene is a colorless liquid that has a sweet odor and is highly flammable. Benzene is volatile and readily dissolves in water. The physical and chemical properties of benzene are summarized in Table-1. (Adapted from ATSDR 1997)

Table-1. The physical and chemical properties of benzene.

Property	Characteristic
Synonym(s)	Annulene, benzeen (Dutch), benzen (Polish), benzol, benzole; benzolo (Italian), coal naphtha, cyclohexatriene, fenzen (Czech), phene, phenyl hydride, pyrobenzol, pyrobenzole
Chemical formula	C ₆ H ₆
CAS No.	71-43-2
Molecular weight	78.11
Color	Clear, colorless liquid
Physical state	Rhombic prisms
Melting point	5.5 °C
Boiling point	80.1 °C
Density at 15 °C, g/cm ³	0.8787
Odor	Aromatic
Solubility: Water at 25 °C Organic solvents	w/w: 0.188% Alcohol, chloroform, ether, carbon disulfide, acetone, oils, carbon, tetrachloride, glacial acetic acid
Partition coefficients: Log K _{ow} Log K _{oc}	2.13 1.8-1.9
Vapor pressure at 20 °C	75 mm Hg

Property	Characteristic
Henry's law constant at 25 °C	5.5×10^{-3} atm·m ³ /mol
Autoignition temperature	498 °C
Flashpoint	-11 °C (closed cup)
Flammability limits in air	1.2% (lower limit); 7.8% (upper limit)
Conversion factors	1 ppm = 3.24 mg/m ³ at 20 °C and 1 atm pressure; 1 mg/m ³ = 0.31 ppm
Explosive limits	1.4% (lower limit); 8% (upper limit)

2. Environmental Fate

Benzene is very volatile and readily partitions into the atmosphere. Despite being only slightly soluble in water, minor amounts of benzene can be removed from the atmosphere through wet deposition. However, the majority of benzene that is wet deposited to soil or water will return to the air through volatilization. The most significant pathway for the degradation of atmospheric benzene is reaction with photochemically produced hydroxyl radicals. Reaction of benzene with ozone can also occur, but to a much lesser extent.

In water, the primary mechanism of benzene degradation is aerobic biodegradation. Photolysis of benzene can occur when benzene is dissolved in oxygen-saturated deionized water. Reaction with hydroxyl radicals can also occur but proceeds slower than it does in air. Biodegradation of benzene can occur in both surface and groundwater.

In soil, benzene can volatilize to the air, partition to surface water through runoff, and partition to groundwater through leaching. Generally, benzene is considered to be mobile in soil. Organic matter facilitates that adsorption of benzene to soil. Benzene can biodegrade in soil under both aerobic and anaerobic conditions.

Bioconcentration of benzene in aquatic organisms is thought to be insignificant. No evidence was located that suggests that biomagnification of benzene occurs along aquatic food chains.

3. Toxicokinetics

Absorption

Inhalation is thought to be the major route of exposure to benzene. Evidence suggests that benzene is rapidly absorbed by the lungs following inhalation exposure. Studies suggest that approximately one half of inhaled benzene is absorbed. Animal studies show that show that benzene is rapidly absorbed through the lungs.

Definitive data were not located that describe the absorption of benzene following oral exposure. However, evidence from accidental and intentional poisonings show that benzene is absorbed following ingestion. Furthermore, animal studies suggest that the gastrointestinal tract absorbs the vast majority of an administered dose of benzene.

Both *in vivo* and *in vitro* studies of human skin shown that benzene can be absorbed dermally. However, absorption of benzene through the skin is less substantial than through inhalation. Evidence shows that dermal absorption of liquid benzene is of concern but dermal absorption of benzene vapor is insignificant. Animal data that show that benzene is readily absorbed through the skin.

Distribution

Benzene is lipophilic and readily distribute into fatty tissue. Following inhalation exposure, distribution to the blood, brain, liver, kidney, stomach, and bile have all been observed. Benzene has also been found to cross the placenta into cord blood following inhalation exposure. Animal studies indicate that absorbed benzene is distributed throughout most of the body, but parent benzene is preferentially stored in fat. Other animal inhalation studies show benzene is distributed to lipid – rich tissue such as brain and fat, to well-perfused tissues such as the liver and kidney, and to the lung and spleen.

No studies were located that describe the distribution of benzene in humans following oral exposure. However, animal studies show that benzene is distributes into most tissues. No studies were located concerning the distribution of benzene following dermal exposure in humans. In animals, benzene is distributed to most areas of the body following dermal exposure, but is mainly distributed to the kidney and liver.

Metabolism

The metabolism of benzene is thought to be qualitatively the same for animals and humans. In fact, similar pathways of metabolism exist for both animals and humans. Metabolism in both systems involves cytochrome P-450 dependent mixed-function oxidase enzymes. Cytochrome P-450 is found throughout the body but is concentrated in the liver. As a result, benzene is predominantly metabolized in the liver. During the metabolism, both more and less toxic metabolites are formed. Of these metabolites, glucuronide and sulphate conjugates of phenol are found in the urine. Benzene dihydrodiol is also excreted as glucuronide and sulphate conjugates. Benzene's mechanism of toxicity is thought to be a result of the covalent binding of its metabolites to cellular macromolecules. These macromolecules include proteins and nucleic acids. Hydroquinone and muconic dialdehyde are thought to be responsible for hematological effects following exposure.

Excretion

Human and animal data show that following inhalation and oral exposure to benzene, the main route of excretion of unmetabolized benzene is exhalation and the main route of excretion of metabolized benzene is the urine. Only minor excretion of benzene occurs through the feces. Animal studies also suggest that

the proportion of benzene excreted by each route is dependent on the size of the dose. For example, at low oral dose the urine is the major route of excretion.

There is only limited information concerning the excretion of benzene following dermal exposure. However, urinary excretion of benzene is known to occur in humans following dermal exposure. In animals, the major route of excretion following dermal exposure is the urine, and phenol is the major urinary metabolite. Excretion also occurs through expired air following dermal exposure.

4. Human Health Effects

Death

Acute inhalation and oral exposure to benzene are known to cause death in humans. The cause of death from both inhalation and oral exposure is typically asphyxiation, respiratory arrest, central nervous system depression, or cardiac collapse. Benzene exposure can also be lethal in animals.

Gastrointestinal Effects

Ingestion of benzene is known to cause gastrointestinal effects in humans. These effects include congestive gastritis, intense toxic gastritis, and pyloric stenosis. Studies of animals show that following ingestion, hyperkeratosis, acanthosis, and hyperplasia in the forestomach can occur. These effects may also occur in humans.

Hematological Effects

Human and animal data show that exposure to benzene causes toxic effects in the hematological system. All blood cells including erythrocytes, leukocytes, and platelets are susceptible to these effects. Less severe toxicity is characterized by specific reductions in the count of individual blood elements (cytopenias). More severe toxicity is characterized by a reduction in the count of all three elements. A causal link has been established between the occurrence of aplastic anemia and benzene exposure. This anemia is characterized by severe damage to bone marrow and ineffective blood cell formation. Based on all available information, it is reasonable to conclude that adverse hematological effects might occur in humans following inhalation, oral, or dermal exposure since absorption through either of these routes leads to increased risk of damage to blood elements. Deficiencies in different types of blood cells can lead to such disorders as hemorrhagic conditions from a lack of platelets, susceptibility to infection from a lack of leukocytes, and increased cardiac output due to a lack of erythrocytes. It is generally thought that the hematotoxicity of benzene is connected to benzene metabolites rather than parent benzene.

Reproductive Effects

Profuse or scanty blood flow and dysmenorrhea have been observed in women occupationally exposed to benzene. These scanty menstruations are thought to be a result of ovarian atrophy resulting from

exposure to benzene. Studies of animals indicate that at high concentrations, inhalation of benzene vapors reduces the number of live fetuses as well as the incidence of pregnancy.

Developmental Effects

A strong link has not been established between exposure to benzene and developmental effects in humans. In animals, exposure to benzene through inhalation has been shown to cause harmful effects on the developing fetus. Such symptoms include low birth weight, delayed bone formation, and bone marrow damage.

Dermal/Ocular Effects

Exposure to high doses of benzene either through contact with the air or by contact with the skin can result in dermal effects in both animals and humans. These effects include erythema, edema, frank burns, and necrosis. Occupational studies show that exposure to benzene in air can cause ocular effects such as moderate conjunctival irritation and transient corneal damage.

Immunological Effects

Exposure to benzene is known to cause immunological effects following inhalation exposure for intermediate to chronic durations. In animals such effects have been observed following inhalation and oral exposure over acute, intermediate, and chronic durations. These effects include both humoral (antibody) and cellular (leukocyte) response damage. Occupational studies show that intermediate to chronic exposure to benzene induces a reduction in the levels of circulating leukocytes in the body. Similar effects have been observed in animals following exposure to benzene.

Genotoxic Effects

Studies show that benzene and/or its metabolites are genotoxic in humans. The targets of genotoxicity appear to be peripheral lymphocytes and bone marrow cells. Occupational studies, epidemiological studies of humans, animal studies, and *in vitro* cell cultures show that benzene is genotoxic by being clastogenic (capable of breaking DNA in a manner observable at the chromosome level). Both structural and numerical chromosome aberrations have been observed in bone marrow cells following exposure to benzene. *In vitro* studies strongly suggest that the genotoxicity of benzene is related primarily to its metabolites. It is thought that each metabolite has the possibility of causing a different genotoxic effect.

Cancer

Benzene is known to cause damage to the hematopoietic system including pancytopenia with subsequent manifestation of acute myelogenous leukemia (AML). In AML, there is a reduced production of normal erythrocytes, granulocytes, and platelets, which can in turn lead to death by anemia, infection, or hemorrhage. With this, there is the appearance in the peripheral blood cells morphologically indistinguishable from myeloblasts. Both case reports and epidemiological studies have provided a causal

relationship between benzene exposure and AML. Those suffering from MDS (disorders of stem cells characterized by maturation defects) may die of infection or hemorrhage (due to platelet/clotting abnormalities) or they may develop acute leukemia. Based on the available information, it appears that benzene can cause cancer in humans following inhalation or oral exposure.

USEPA (1998) classified benzene as Category A (*a known human carcinogen*). WHO (1998) classified benzene as Group I (*carcinogenic to humans*).

5. Potency

Oral-Cancer

USEPA (1998) developed an *Oral Slope Factor* $2.9E-2$ per (mg/kg)/day and a *Drinking Water Unit Risk* of $8.3E-7$ per ($\mu\text{g/L}$) for benzene. These were based on studies by Rinsky et al. (1981), Ott et al. (1978), and Wong et al. (1983) that examined the incidence of leukemia after occupational inhalation exposure to benzene. For the purposes of extrapolation from inhalation to oral estimates, respiration rate of $20 \text{ m}^3/\text{day}$ was assumed. The slope factor is a geometric mean of four maximum likelihood estimates based on the data of Rinsky et al., Ott et al., and Wong et al.

Inhalation-Cancer

USEPA (1998) developed an *Air Unit Risk* in a range of $2.2E-6$ to $7.8E-6$ for an increase in the lifetime risk of an individual who is exposed for a lifetime to $1 \mu\text{g}/\text{m}^3$ of benzene in air. This was based on studies by Rinsky et al. (1981, 1987), Paustenbach et al. (1993), Crump and Allen (1984), Crump (1992,1994), and USEPA (1998) that examined the risk of leukemia in humans at different concentrations of benzene. The estimate is based on a low-dose linear extrapolation utilizing maximum likelihood estimates.

WHO (1995) developed an *Air Quality Guideline* for benzene of $6E-6 (\mu\text{g}/\text{m}^3)^{-1}$. Estimates of the excess lifetime risk of leukemia at an air concentration of $1 \text{ ug}/\text{cm}^3$ ranged between $4.4E-6$ and $7.5E-6$. To produce a guideline, WHO used the dose-response assessment by Crump (1994).

6. References

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