API TOXICOLOGICAL REVIEW

BENZENE

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This review was prepared at the Harvard School of Public Health, Boston, Mass., under the direction of Professor Philip Drinker. Anyone desiring to submit additional information or proposed changes for consideration prior to reissuance of this review is requested to send them to the American Petroleum Institute.

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API TOXICOLOGICAL REVIEW OF BENZENE

I. Substance

Benzene
Formula: C_6H_6

Structural formula: 

Molecular weight: 78.11
Synonyms: benzol
phene

II. Properties and Characteristics [1a, 2, 3]

Boiling point	= 80.1 C (176.2 F) at 760 mm.
Melting point	= 5.4 C to 5.5 C (41.7 F to 41.9 F).
Vapor pressure	= 74.6 mm of mercury at 20 C (68 F).
Liquid density	= 0.899 g per milliliter at 0 C (32 F).
Explosive limits	= 1.4 to 8 per cent.
Flash point	= 12 F (closed *cup*).
Refractive index	= 1.5016 at 20 C (68 F).
Specific gravity	= 0.8787 at 15C (59 F).
mg per liter	= 313 ppm; 1 ppm = 0.00319 mg per liter.

Benzene is a clear, colorless liquid with a characteristic pleasant odor at low concentrations and a disagreeable odor at higher concentrations. It forms a highly flammable and explosive mixture with air at concentrations ranging from 1.4 to 8.0 per cent benzene by volume. Pure benzene burns with a yellow, luminous, smoky flame and is a fire hazard unless proper care is taken in handling and storage.

Benzene is relatively insoluble in water (0.08 g in 100 ml of water at 22 C) but is readily miscible in all proportions with alcohol, ether, acetic acid, chloroform, carbon disulfide, carbon tetrachloride, and similar organic solvents. Commercial benzene is practically never pure and usually contains varying amounts of xylene, phenol, and toluene; commercial benzene also contains traces of carbon disulfide (0.2 to 1.0 per cent), thiophene (0.1 to 0.2 per cent), olefins, naphthalene, and similar substances.

Chemically, benzene is the simplest of the aromatic hydrocarbons. It is relatively stable but is capable of a variety of substitution reactions such as chlorination, nitration, sulfonation, and alkylation. Benzene is an excellent solvent for most organic substances.

• Figures refer to BIBLIOGRAPHY on p. 6.

III. Manufacture, Uses, and Possible Sources of Exposure

Benzene is usually manufactured from catalytically reformed light naphthas from which it is isolated by distillation or solvent extraction.

Benzene is used as a solvent in many applications. It is also used as a component of some motor fuels and as the raw material for the manufacture of a host of synthetic chemicals. Examples are: styrene, phenol, aniline, DDT, chlorobenzene, cumene, nitrobenzene, diphenyl, cyclohexane, adipic acid, and detergents.

Because of its volatility, benzene presents a vapor hazard. The vapor may arise from numerous handling operations, as well as from leaks and accidental spills. Skin contact is a possibility when handling or packaging.

IV. Toxicology

a. Acute Effects

Acute benzene poisoning generally results from the inhalation of relatively high concentrations of vapor. Exposure to air containing benzene in concentrations of 19,000 ppm to 20,000 ppm (61 to 65 mg per liter of air) may cause death within 5 to 10 min, whereas concentrations of 7,500 ppm (25 mg per liter) are dangerous to life in one-half to one hour.[4] Severe toxic effects may be caused by 1-hour exposure to concentrations of 1,500 ppm (4.8 mg per liter). Concentrations of 500 ppm (1.6 mg per liter) may lead to symptoms of illness when exposure continues for more than a short time.[5]

Inhalation of 50 ppm to 150 ppm (0.10 to 0.48 mg per liter) of benzene for 5 hours caused slight headache, weariness, and lassitude. The red-blood count decreased, the white-blood count was unchanged except for mild lymphocytosis, eosinopenia, and monocytopenia. The albumin-globulin ratio increased slightly at lower concentrations but decreased with higher concentrations. The urinary coproporphyrins were increased, whereas the urinary sulfate ratio was decreased.[6]

Skin contact will cause dehydration and defatting which may lead to dermatitis. Systemic intoxication by cutaneous absorption is unlikely.

Drinking benzene causes acute symptoms with local evidence of acute irritation of the mouth, throat, and stomach. A tablespoonful or less of benzene when swallowed has been known to cause serious collapse. Subse-

quently, it may result in bronchitis or pneumonia which is probably caused by benzene entering the air passages.[7]

Acute exposure to benzene exerts a toxic action on the central nervous system. Benzene first behaves as a stimulant—in the early stages of acute poisoning, persons show excitement, euphoria, hilarity; then quite suddenly this changes to weariness, fatigue, and sleepiness, followed by coma and death.[1]

Acute exposure to benzene produces rapidly increasing symptoms of dizziness, excitation, and pallor, followed by flushing, weakness, headache, breathlessness, constriction in the chest, and fear of impending death. Visual disturbances, tremors, and muscular weakness are also encountered. The victim may lose consciousness and pass into coma or may develop acute mania and delirium. Convulsions occur frequently. Death may supervene almost at once or several hours to several days following exposure.[9]

Recovery from acute benzene poisoning requires from one to four weeks. Immediately after exposure then are temporary symptoms of chest and head pains, shortness of breath, giddiness, nausea, and loss of appetite. Evidence of unsteady gait, nervous irritability, and breathlessness may persist for two or three weeks, whereas cardiac distress and a peculiar yellow pallor to the skin may last for as long as a month. Recovery from acute poisoning is generally complete after this period, although evidences of chronic benzene poisoning may be encountered later.[9]

Benzene also sensitizes the heart muscle to the action of epinephrine, so that instant death may occur as a result of ventricular fibrillation.[1] Muscular activity increases the rate and severity of acute benzene poisoning. Persons dying of acute benzene poisoning generally show absence of clotting of the blood and widespread petechial hemorrhages in the brain, pleura, pericardium, urinary tract, intestinal tract, mucous membranes, and skin. There are no specific lesions of diagnostic importance.[9]

Local effects from acute exposure are seldom seven. Continued skin contact with benzene results in defatting of the skin and leads to erythema, dry scaling, and, in some cases, the formation of vesicular papules. Prolonged exposure may produce lesions resembling &st- or second-degree burns. It may cause considerable irritation of the eyes or mucous membranes of the nose and throat on contact.

Benzene poisoning by skin absorption has received scant attention in the literature. The possibility of percutaneous absorption of benzene has been studied in three uses. Immersion of the hands and forearms from 25 to 35 min showed no evidence of skin absorption.[10] Unquestionably, small amounts of benzene can be absorbed through the skin, but it is very doubtful that enough would be absorbed by this route to cause systemic poisoning.[7]

b. Chronic Effects

Chronic benzene poisoning results from repeated or continuous exposure to relatively low concentrations of benzene vapor. The level and degree of exposure necessary to produce poisoning vary widely. There are at least two well-authenticated cases of poisoning by repeated exposures to 75 ppm.[11]

The toxic action is exerted mainly on the hematopoietic system. It may take months or even years to show harmful effects. Symptoms may be present over long periods, i.e. headaches, dizziness, fatigue, anorexia, and dyspnea. They may be varied and vague and not obviously connected with benzene poisoning.

During the early stages of poisoning, Heinz bodies may be present in the red-blood cells and a neutropenia is often seen. At this stage the blood picture may return to normal after removal from contact with benzene.

As chronic poisoning progresses, nausea and vomiting, burning sensations of the eyes and throat, and hemorrhages from mucous membrana, tongue, and gums become manifest. Purpuric spots and ecchymoses may follow the slightest injury, and epistaxis may occur. Menorrhagia, metrorrhagia, and spontaneous abortion may develop in otherwise healthy women. Blood examination at this point may show leukopenia (below 4,000 white cells), neutropenia, and a severe anemia. Later the platelet count falls and thrombopenia is marked, The blood condition, at this stage, may have become irreversible. The clinical picture of a worker with chronic benzene poisoning at this stage is characteristic—he complains of headaches, giddiness, drowsiness, lassitude, loss of appetite, and nausea with occasional vomiting. He looks pale; is short of breath; has a rapid pulse, a low blood pressure, and a mildly elevated temperature. He may also have epistaxis, bleeding from the gums, a purpuric rash, or subconjunctival hemorrhages. The condition progresses slowly to acute leukopenia ending in fatal aplastic anemia.[1] Repeated small doses of benzene hv mouth can produce the same type of chronic poisoning.[7]

Repeated contact ot benzene with the skin will cause dehydration and delipidization predisposing to dermatitis.

Benzene is relatively insoluble in body fluids and tissues. Therefore, only small amounts are absorbed by the body. Equilibrium between blood and air is approached within a few minutes after exposure is begun, and practically complete elimination of benzene from the

blood accurs withii a few minutes after exposure is terminated. Higher concentrations of benzene are obtained in tissues with a greater fat content, and saturation and elimination are more gradual.[12]

Human subjects inhaled benzene in concentrations of 340 micrograms per liter of air for 5 hours. Between 33 and 65 per cent of the inhaled benzene was retained (385 mg). During the desaturation period 3.8 to 27.8 per cent of retained benzene was excreted through the lungs and 0.1 to 0.2 per cent in the urine and other body excreta. Of the absorbed benzene, 9.7 to 42 per cent was excreted in the urine as phenol, 0 to 5.4 per cent as pyrocatechol, and 0.1 to 3.3 per cent as hydroquinone. Excretion of phenol and pyrocatechol was highest during the first 24 hours and complete in 48 hours, whereas hydroquinone took more than 48 hours. Excretion of organic sulfates in urine of exposed subjects was increased. The opinion was expressed that benzene affects the metabolism of proteins, the metabolites of which are excreted in urine as ethereal sulfates.[13]

Benzene is Unique in its myelotoxicity. It has been shown that the introduction of an alkyl group into the aromatic ring results in a loss of its myelotoxic property. This difference may be a result of the difference in the metabolic pathway. Benzene is metabolized to phenols and quinones which inhibit cell production. The *in vivo* metabolites of alkyl benzenes are alcohols and carboxylic acids resulting from side chain oxidations. These compounds have a low-order toxicity and are devoid of specific cell destructive effects.[14]

A variety of reactions may be encountered as the result of the chronic effect of benzene poisoning. There is little correlation between the degree and duration of exposure and the severity or nature of the findings in the blood on microscopic examination.[15] They may consist of a reduction in red-cell, white-cell, or platelet levels—in any two of these or in all three. These changes may develop gradually or suddenly. The blood usually shows a moderate reduction in red cells (below 3.5 million), white cells (below 4,500), and platelets. Blood examinations for evidence of benzene poisoning should consist of a complete study of red, white, and platelet reactions. Progressive changes are more significant than the absolute levels.

In anemia caused by benzene, it has been shown that there is a constant increase in serum iron (average increase, 213 micrograms) which is associated with a reduction of transferrin (average reduction, 225 micrograms). The iron saturation of transferrin is above normal and is matched by iron saturation of the tissue. The cause of the disturbance of iron metabolism in benzene poisoning is the failure of the marrow to utilize iron as well as increased intake of iron supplied parenterally by transfusion.[16]

There is some evidence that chronic benzene poisoning produces a blood-clotting defect which is caused by functional and morphological as well as a quantitative alteration of the platelets.[17] The marrow cells exhibit a decrease in peroxidase in benzene poisoning. Because benzene inhibits granulocyte maturation, it may act on peroxidase metabolites, or the peroxidase may be used up in detoxifying benzene.[18]

The bone marrow may be hypoplastic, fairly normal, or hyperplastic in appearance. Abnormal forms or young cells may abound, and leukemia as a result of chronic benzene exposure has been reported. Various individuals differ in their bone marrow response to benzene—cases with symptoms fairly soon after exposure usually have fewer cells in the marrow, whereas cases developing later are more apt to have an increased number of cells in the marrow. It is believed that this represents an early weeding out of those who develop hypoplastic changes, rather than a gradual shift from one type of response to the other.[19, 20]

In a long-term follow-up of chronic benzene poisoning 4,538 cases were studied from 2 to 12 years after cessation of work involving exposure. There has been only one fatal case, six cases involving bone marrow changes, and one case of lowered resistance to infection.[21] The others were practically well but show varying degrees of neutropenia.

Benzene is eliminated from the body via the lungs and the kidneys. In one study C—14 labeled benzene was given orally to rabbits. In 2 days 45 per cent of the dose was eliminated in the expired air (43 per cent as unchanged benzene and 1.5 per cent as carbon dioxide), and 35 per cent was eliminated as metabolites in urine (23 per cent as phenol, 4.8 per cent as quinol, 2.2 per cent as catechol, 0.3 per cent as hydroxyquinol, 0.5 per cent as L-phenylmercapturic acid, and 1.3 per cent as *trans*-, trans-muconic acid). Five per cent of the administered radioactivity was found in the tissues occurring mainly as metabolites.[22]

Certain factors have been noted which influence individual variation in susceptibility to benzene. Overweight individuals are more commonly affected,[23] and a low-protein, high-fat, low-Vitamin C diet is said to promote the disease. The presence of heart or lung disease and liver or kidney damage are believed to predispose to the condition.[24] Pregnant women may be more susceptible to benzene poisoning.[4] Pathological changes in ovaries, testes, thyroid, and pituitary are attributed to benzene; and changes in women workers leading to sterility are emphasized.[25]

e. Recommended Limit of Atmospheric Exposure

The generally recognized maximum acceptable concentration for benzene vapor is 25 ppm by volume in air (0.08 mg per liter of air) for an 8-hour daily exposure. In Germany the [illegible] permissible concentration to which workers may be exposed is 313 ppm by volume in air (0.1 mg per liter of air).[24] The Massachusetts laws have established 25 ppm as a maximum benzene concentration.[27]

V. Treatment

Acute benzene poisoning should be considered an acute emergency. Remove the victim from further exposure at once and call a physician immediately. The patient should be kept warm and quiet in the recumbent position. If breathing has stopped, artificial respiration should be started at once. Oxygen should be administered by a qualified person as long as necessary to maintain the normal color of skin and mucous membranes. This may prevent the development of severe pulmonary edema. Stimulants will rarely be necessary when adequate oxygenation is maintained.[1]

Care should be taken that rescuers are not also overcome by vapors.

Chronic benzene poisoning is extremely refractory to treatment. It is most important that the condition be diagnosed early and the individual withdrawn from further contact with the hydrocarbon. Blood transfusions are temporarily useful in combating severe anemia.

VI. Examination

The pre-employment examination should include a detailed history, physical examination, chest X-ray, and complete blood count. Workers with organic disease of the heart, lungs, liver, or kidneys should be eliminated, as should those with a history of previous benzene intoxication or evidence of an abnormality of the blood or blood-clotting mechanisms.[22, 24]

Periodic re-examinations should be carried out regularly, the frequency being determined on the basis of the probable degree of exposure. The examination should include a brief interval history and physical examination, together with a complete blood study. The presence of any of the blood changes described require re-examination at least twice at intervals of one week and a thorough study of the working conditions. Unless there is noticeable improvement on re-examination, the worker should be withdrawn from further exposure. The following changes call for re-examination: white-blood count less than 4,000, red-blood count less than 4,000,000, hemoglobin less than 12 g per 100 ml (80 per cent), blood platelets less than 100,000 per cu mm, differential count less than 50 per cent polymorphonuclear leukocytes, and more than a very few immature blood cells. The urine sulfate test may be used, not as a diagnostic test, but as a measure of the degree of the current benzene exposure. It does not measure the degree of benzene poisoning nor the blood changes present.[1]

VII. Precautionary Measures

The safety measures necessary for the prevention of benzene poisoning are primarily those designed to prevent the inhalation of benzene vapor. Proper ventilation, local exhaust, and closed systems should be used to maintain a concentration below the maximum acceptable concentration of 25 ppm by volume in air. All apparatus and piping should be inspected regularly and systematically for leakage. When excessive concentrations are unavoidably encountered in operations such as the cleaning of tank cars, vats, or storage tanks, air masks and protective clothing should be employed.[28] Employees should be fully instructed regarding health hazards which may be present in the handling of benzene and should immediately report any unusual symptoms or illness. Clothing wet with benzene should be removed promptly.

If the hands are likely to have contact with benzene, impervious gloves or protective creams should be used. Proper ventilation, routine plant inspection, control of benzene air concentration, and periodic medical examinations are of the utmost importance.[28]

The concentration of benzene vapor in the air should be checked regularly in locations where the possibility of excessive exposure may be encountered. This may be done by a variety of procedures among which are the butanone method,[2] the m-dinitrobenzene reduction method,[2] an absorptiometric method, and a photocolorimetric determination. The latter method involves the nitration of benzene with Stepanov mixture which forms m-dinitrobenzene. This gives a color reaction with acetone in alkaline solutions. Under similar conditions toluene gives a faint violet color. Based on these photocolorimetric methods small quantities of benzene and toluene can be determined in air.[29] More recently a silica gel adsorption method has been reported.[30] Accurate quantitative study of atmospheric benzene as low as 0.003 mg per ml (0.9 ppm) may be determined by adsorption on activated silica gel and elution with absolute alcohol. The benzene content is then determined spectrophotometrically according to *ASTM Designation D 1017: Method*

of *Test for Benzene and Toluene by Ultraviolet Spectrophotometry*. The range of measurement is 0.003 mg to 1.28 mg per liter. The mean yield was approximately 93 per cent.

There are a number of instruments on the market which measure hydrocarbon air contamination. The presence of more than one hydrocarbon vapor, however, produces erratic results.

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