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API TOXICOLOGICAL REVIEW

BENZENE

SEPTEMBER 1948

Note: This review summarizes the best available information on the properties, characteristics, and toxicology of *benzene*. It offers suggestions and tentative recommendations pertaining to medical treatments, medical examinations, and precautionary measures for workers who are exposed to benzene. It was prepared at the Harvard School of Public Health, Boston, Mass., under the direction of Professor Philip Drinker. The review has been accepted for publication by the Medical Advisory Committee of the American Petroleum Institute. Anyone desiring to submit additional information or proposed changes for consideration prior to re-issuance of this review is requested to send them to the American Petroleum Institute.

This review was prepared by Marshall Clinton, M. D.

AMERICAN PETROLEUM INSTITUTE
DEPARTMENT OF SAFETY
50 WEST 50TH STREET
NEW YORK 20, N. Y.

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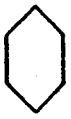
TOXICOLOGICAL REVIEW ON BENZENE

I. Substance

Benzene.
Formula: C_6H_6.
Structural formula:



Molecular weight=78.11.
Synonyms: benzol.
phene.

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

Boiling point =80.1 deg C (176.2 deg F).
Melting point =5.5 deg C (41.9 deg F).
Vapor pressure =74.6 mm of mercury at 20 deg C (68 deg F).
Liquid density =0.899 g per milliliter at 0 deg C (32 deg F).
Specific gravity =0.8787 at 15 deg C (59 deg F).
Refractive index=1.5016 at 20 deg C (68 deg F).
1 mg per liter =313 ppm; 100 ppm=0.319 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 inflammable and explosive mixture with air at concentrations ranging from 1.4 to 6.8 per cent benzene by volume. Pure benzene burns with a yellow, luminous, smoky flame.

Benzene is relatively insoluble in water (0.08 g in 100 ml water at 22 deg 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; also 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.

III. Probable Sources of Contact [4]

Benzene is used extensively in the petroleum industry. By far the greatest amounts of benzene are blended into motor gasolines. Some is used as a solvent in commercial processes such as the benzene-methyl ethyl-ketone dewaxing process, whereas minor amounts are used in pilot plants and laboratories for solvent or reagent purposes. Exposure to benzene is usually limited to vapor exposure, although skin contact may occur.

IV. Toxicology

1. Acute Effects

Acute benzene poisoning generally results from the inhalation of relatively high concentrations of the vapor. Exposure to air containing benzene in concentrations of 19,000 to 20,000 ppm (61 to 65 mg per liter of air) causes death within a few minutes, whereas concentrations of 7,500 ppm (25 mg per liter) are dangerous to life in ½ to 1 hour. The maximum concentration which can be tolerated for 1 hour without serious disturbances is estimated at from 3,000 to 4,700 ppm (10 to 15 mg per liter). Mild symptoms supervene following exposure to 1,500 to 3,000 ppm (5 to 10 mg per liter) for a period of several hours.[5] The drinking of benzene produces symptoms similar to those following inhalation of like amounts of the substance, plus local evidences of acute irritation of the mouth, throat, esophagus, and stomach.[1]

Acute exposure to benzene produces rapidly increasing symptoms of tightening of leg muscles, dizziness, excitation, and pallor, followed by flushing, weakness, headache, breathlessness, apprehension of death, and constriction in the chest. The pulse becomes rapid, and the color blue. Visual disturbances, tremors, and muscular weakness are encountered. The victim may lose consciousness and pass into coma, or may develop acute mania and delirium. Convulsions are fairly frequent. Death may occur almost at once or several hours to several days following exposure.[6]

Recovery from acute benzene poisoning requires from 1 to 4 weeks. Immediately after exposure there are temporary symptoms of chest and head pain, shortness of breath, giddiness, nausea, and loss of appetite. Evidences of unsteady gait, nervous irritability, and breathlessness may persist for 2 or 3 weeks, whereas cardiac distress and a peculiar yellow

[a] Figures refer to bibliography on p. 5.

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.[6]

The acute effects of benzene exposure result from its depressant action on the central nervous system. In addition to its general narcotic action, benzene apparently has a characteristic neuro-irritant effect, which accounts for the hypertonicity, excitement, and convulsions which are encountered. Benzene also sensitizes the heart muscle to the action of epinephrine, so that instant death due to ventricular fibrillation may occur. 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 import.[6]

Skin contact with benzene results in defatting of the skin, and leads to the development of erythema, dry scaling and, in some cases, the formation of vesicular papules. Prolonged exposure may produce lesions resembling first- or second-degree burns.

The production of systemic benzene poisoning by skin absorption has received scant attention in the literature, and definitive information on this subject is not available. Skin absorption is difficult to distinguish, as inhalation of benzene vapor would accompany it and confuse the picture, unless a mask was worn. However, reputable authorities have stated verbally that skin absorption is extensive, and should be avoided.

2. 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 apparently vary widely. There are at least two well authenticated cases of poisoning by repeated exposures of only 75 ppm;[7] yet many chemists repeatedly expose themselves to far higher concentrations over periods of many years with no apparent ill effects.

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 occurs within a few minutes after the exposure is terminated. Higher concentrations of benzene are obtained in tissues with a greater fat content, and saturation and elimination are more gradual.[8]

Most of the benzene absorbed by the body is metabolized to a variety of substances, the principal one of which is phenol. Minor amounts of pyrocatechol, hydroquinone, muconic acid, and similar substances are also produced.[8] Whether the toxicity of benzene is due to one of these metabolites or to unaltered benzene is not known. These substances are all eliminated in the urine after combination with sulfate and glycuronic acid.

Practically all of the chronic effects of exposure are a result of the influence of benzene or its oxidation products on the blood-forming system. A variety of reactions may be encountered, and 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. There is no single change in the blood or blood-forming organs which is universally present in benzene poisoning.[9]

The bone marrow where blood is formed may be hypoplastic, fairly normal in appearance, or hyperplastic. Abnormal forms or young cells may abound, and reasonably well documented instances of the development of leukemia as a result of chronic benzene exposure have been cited. It is generally believed that various individuals differ in their bone-marrow response to benzene—some showing no essential change; some showing decreased cellularity; and others increased cellularity, and even evidences of malignant changes. Cases with symptoms fairly soon after exposure usually have fewer cells in the bone 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.[10, 11]

The findings on microscopic examination of the blood are as variable as the bone-marrow response. 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 can 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. Examination of the blood for evidences of benzene poisoning should never be limited to a single determination such as a red- or white-cell count, but should consist of a complete study of the red, white, and platelet fractions. Progressive changes are of more significance than the absolute alteration.

Benzene is eliminated from the body in part via the lungs and in part via the kidneys. The ratio of renal to lung excretion is not known. That portion excreted in the urine is in combination with sulfate or with glucuronic acid. The combination of benzene with sulfate alters the organic-inorganic sulfate ratio, so that an estimation of the ratio of organic to inorganic sulfate may provide a useful guide to the degree of absorption of benzene by the body.[13, 14]

There is speculation in the literature on the occurrence of latent bone-marrow injury due to benzene without any immediate alteration in blood findings, followed by the development of obvious blood changes years later, under the stress of intercurrent illnesses or the general wear and tear of everyday life.[11] Conclusive proof is lacking, but the occurrence of delayed toxic effects appears likely.

The wide individual variation in susceptibility to benzene has already been mentioned. Certain factors have been noted to influence this to a limited degree. Overweight individuals are more commonly affected,[15] but no difference in susceptibility has been noted between young men and women.[11, 16] A low-protein high-fat diet is said to promote the disease,[8] whereas the presence of lung disease, heart disease, and liver or kidney damage are believed to predispose to the condition.[16] Pregnant women may be more prone to benzene poisoning than others.[5]

3. Safe Limits

The American Standards Association[17] and most states[18] have set an arbitrary limit of 100 ppm as the maximum permissible benzene concentration for workers exposed to this substance during an 8-hour day. Massachusetts and Oregon have set limits of 75 ppm, whereas New York considers 50 ppm as the highest permissible level. Inasmuch as the body develops no tolerance to benzene, and as there is a wide variation in individual susceptibility, it is generally considered that the only absolutely safe concentration for benzene is zero.[11] The inadequacy of a limit of 100 ppm is indicated by well authenticated reports of at least 2 cases of benzene poisoning following exposure to only 75 ppm.[7] A limit of 50 ppm or less is strongly recommended, particularly where exposures are recurrent. Skin contact should be avoided.

V. Treatment of Benzene Poisoning[1, 19]

Acute poisoning by benzene should be considered as an acute emergency. The victim must be removed from the contaminated atmosphere at once, and kept at *complete* rest subsequently. Care must be taken that the rescuers are not also overcome by the fumes. Frequently, rescuers who exert themselves will subsequently die, whereas the inactive victim recovers. Artificial respiration should be administered if natural breathing has been interrupted, and oxygen may be administered, as well, if it is available. The use of adrenin should be avoided because of the danger of inducing ventricular fibrillation. There are poorly substantiated reports of benefit from the intravenous injection of lecithin, but such measures should be considered with skepticism at present.[20] Inasmuch as benzene is excreted rapidly, no specific measures to promote its removal from the body are necessary.

Chronic benzene poisoning is extremely refractory to treatment. Practically all therapeutic measures attempted have failed, although transfusions are at least temporarily useful in combatting severe anemia.[21] The administration of fairly large doses of ascorbic acid (100 mg per day) may be of value and should be carried out.[22] It is most important, however, that the condition be diagnosed early and the individual withdrawn from all contact with the affecting agent for the rest of his life.

VI. Examinations

The pre-employment examination should include a detailed history, physical examination, chest X-ray, and complete blood count. All workers with organic disease of the heart, lungs, liver, or kidneys should be eliminated, as should those with any history of previous benzene intoxication or any evidence of abnormality of the blood or blood-clotting mechanism.[15, 16]

Periodic re-examinations should be carried out regularly, their frequency being determined by the severity of the exposure. Individuals exposed to concentrations approaching the accepted "safe" limits should be examined at monthly intervals at least.[19, 23] The examination should include a brief interval history and physical inspection, together with a complete blood study, including white and differential counts and an estimation of the platelet levels. The ratio of inorganic to total urinary sulfates should be determined in order to detect the presence of excessive absorption and excretion of benzene.[13, 14] Any change in the blood picture or the presence of an inorganic total sulfate ratio of less than 50 per cent is cause for withdrawal of the worker from any further exposure. Due to the delayed character of benzene poisoning, it would be well to continue periodic blood counts for several months after exposure has ceased.

VII. Precautionary Measures

The safety measures necessary for the prevention of benzene poisoning are primarily those designed to prevent the inhalation of benzene vapor. Ventilation, either by dilution or local exhaust, should be so designed as to prevent toxic concentrations of the vapors from reaching the breathing zone of the workers. All apparatus and piping should be inspected regularly and systematically for the presence of leaks. Workers who must be exposed to benzene vapor should be rotated in order to reduce their exposure time to a minimum. When excessive concentrations are unavoidably encountered in operations, such as the cleaning of tank cars, vats, or storage tanks, air masks should be employed.[24]

The concentration of benzene vapor on equipment previously exposed to the liquid should be reduced by cleaning with steam, if possible, or by cooling. Apparatus to be cleaned in benzene should be cold, in order to reduce evaporation, and stopcocks or joints should be smeared with glycerin which, being insoluble in benzene, keeps them airtight.[23]

Skin contact and possible dermatitis from benzene should be avoided entirely if possible; but, if the hands must contact the solvent, then neoprene gloves or protective creams should be used.

The prophylactic administration of 100 mg of ascorbic acid (vitamin "C") daily to individuals unavoidably exposed to benzene vapor might well be of value, although it would be difficult to prove its effectiveness or to justify its cost.

The concentration of benzene vapor in the air should be checked regularly in situations where excessive exposures are apt to be encountered. This can be done by a variety of methods, among the best of which are the butanone method,[2] in which benzene is nitrated to form *m*dinitrobenzene, which is subsequently estimated colorimetrically with the aid of butanone; the *m*dinitrobenzene reduction method,[2] in which *m*dinitrobenzene formed from benzene is separated from nitrating acids by steam distillation, reduced by an excess of standard titanous chloride solution, and the excess titanous chloride back-titrated with a standard ferric-alum solution; the use of the benzol indicator, which depends on an indirect measurement of the heat produced by oxidation of benzol; and, finally, the colorimetric determination of benzene by oxidation with hydrogen peroxide in the presence of a ferrous sulfate solution.[2] More recently, an absorptiometric method has been introduced in England which is said to be more specific than other methods.[25] In this procedure benzene, xylene, and toluene vapors are absorbed in a bead bubbler charged with a nitration mixture, diluted, and neutralized. The nitro derivatives are extracted with butanone, and the yellow color imparted to the butanone by the nitro derivatives of toluene and xylene is measured. The mixture is then made alkaline, and color development allowed to proceed. The solution is then acidified, with disappearance of the blue-green color due to xylene and toluene but persistence of the color due to benzene. This color is then measured.

The individual method chosen must depend on circumstances. The *m*dinitrobenzene reduction method and the absorptiometric method are accurate but rather cumbersome. The butanone and oxidation in presence of hydrogen-peroxide and iron-salts methods are simpler and more rapid, but are less accurate. The use of the benzol indicator is probably the simplest, but the presence of other hydrocarbons will interfere seriously, as they are also oxidized.

VIII. Bibliography

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vents," *Industrial Health Research Board Report No. 80* (London) (1937).
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