

BENZENE—THE CURRENT CONTROVERSY

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Since its original isolation from London town gas and the recognition of its excellent solvent properties in the first quarter of the 19th century, benzene has developed into a major chemical building block^(1,2). Over eleven billion pounds were produced in the U.S. in 1976⁽⁴⁾ and similar amounts were manufactured in Europe and Japan. A brief summary of the metabolism, toxic effects and regulatory history in the U.S. will be presented together with some comments on the present OSHA Permanent Standard,

Metabolism

After inhalation of benzene by a mammal, about 40% is eliminated unchanged in expired air. The liver converts the remainder to benzene oxide. Subsequently, some of the benzene oxide converts to phenol by spontaneous rearrangement, some goes through benzene glycol formation to catechol and trans-trans muconic acid and a third portion reacts with glutathione to produce phenylmercapturic acid.

The phenol undergoes conjugation to form phenylsulfates and phenylglucuronides or goes through hydroquinol to conjugation and elimination. Most catechol is conjugated and eliminated, small amounts being oxidized to hydroxyhydroquinol⁽³⁾. (See Figure 1.)

Acute Toxicity

As shown in Figure 2, direct skin contact dilates blood vessels, reddens and irritates the skin and removes natural fat. If this sequence is repeated the skin dries, scales and cracks. In general however, normal skin does not absorb benzene rapidly.

Eye contact produces similar irritation and if benzene is not removed serious tissue injury occurs.

Mucous membranes (nose, mouth, throat, lungs, etc.) also are irritated easily by benzene and the lung may develop a chemical pneumonia.

Inhalation of high concentrations causes exhilaration, then depression with drowsiness, fatigue, dizziness, headache and nausea. Ultimately unconsciousness, convulsions and death may occur⁽¹⁾. (See Figure 3.)

Chronic Benzene Toxicity. (See Figure 4.)

Important as the acute effects are, much more attention has been directed recently to chronic lower level exposures. These have their primary impact on the blood-forming system, producing a decrease in various formed elements of the circulating blood. When all of the major elements are affected (red cells, white cells and platelets) the term "pancytopenia" is used. This change is often referred to as "aplastic or hypoplastic anemia". Because some cases of benzene pancytopenia have been reported to have hyperplastic or "overactive" marrow, it is probably better to use the term "aplastic anemia" as a subset of pancytopenia rather than as an equivalent. It should also be noted that single cell types may be affected to produce anemia, decreased white cells or a low platelet count(3).

The incidence of these manifestations is very difficult to determine, primarily because most of the literature reports refer to single or small groups of patients. In the few series where longitudinal studies of employees exposed to benzene has exceeded two years, most have shown a tendency to return toward normal when exposure to benzene ceased. Some patients however, did show a persistently lowered white count or platelet count when compared to a control group(3).

Clinical manifestations of benzene induced pancytopenia generally tend to be rather nonspecific and presumably related to anemia - easy fatigue, headache, malaise, dizziness, palpitation and dyspnea on exertion (see Figure 5). Since the development of anemia is usually gradual these may not be recognized until the hemoglobin has dropped below 10.0 grams.

Where low white blood count or low platelet count are prominent, the clinical findings may be more dramatic and specific. Infection is the outstanding feature of a low white count appearing when counts are in the range of 1000 - 1200 (N-4,200 to 10,000) and may lead to death. Platelet counts of 30,000 or less (N-140,000 to 440,000) may be manifested by petechiae, purpura or frank bleeding internally or externally.

Where severe pancytopenia or aplastic anemia develops as a result of benzene exposure, the outcome appears to be similar to that observed in cases of idiopathic aplastic anemia - about 50% will die even with the most modern methods of treatment(3). Where the changes are less severe and the individual is removed from further exposure to benzene, recovery is also the general rule.

One of the most controversial questions related to the hematopoietic effect of benzene exposure is whether it results

in leukemia. This idea is supported by the series of case reports of leukemia in individuals with a history of long and heavy exposure to benzene in France, Italy and Turkey and the higher incidence of benzene exposure in groups of acute leukemia patients. Good epidemiologic studies relating to the question are lacking however, and to date efforts to produce leukemia experimentally in animals have been unsuccessful.

Dr. B. Goldstein in the N.Y. University review sums up his conclusion on the leukemia question as follows: "In summary, occupational exposure to benzene appears causally related to acute myelogenous leukemia and its variants. The question of whether leukemogenesis occurs only after high dose benzene exposure leading to significant bone marrow damage, whether it can result from any degree of a cytopenic stem cell effect, or, less likely, is totally unrelated to the pancytopenic effect of benzene, remains unanswered"(3).

History of the Environmental Control of Eenzene in the U.S.
(See Figure 6.)

The Pre-1976 Experience

In the U.S. the recognition in the early 1920's that benzene exposure produced pancytopenia led to sore states imposing limitations of 100 ppm exposure for an 8-hour day. In a few states this was reduced to 50 ppm and then 35 ppm by the early 1940's. During the war years a Federal "war-time standard" raised the limit to 100 ppm with additional excursions permitted for limited periods. By 1946 the first ACGIH TLV of 100 ppm was established and soon became not only a country wide standard but also a world wide guideline.

Over the next 13 years the level was lowered to 50 ppm (1947) and then to 35 ppm (1948). In 1957 the TWA was reduced to 25 ppm. In 1963 the 25 ppm level was made a ceiling value. Until March 13, 1978 the standard was based on an ANSI recommendation adopted in 1969 which established the level for benzene at 10 ppm on an 8-hour daily Time Weighted Average (TWA) and a 25 ppm 15 min. ceiling. This became an official OSHA standard in October 1972. This was again recommended when the 1974 NIOSH criteria document was published(4). This had however, an "action level" proviso which required certain biological monitoring if the employee was exposed to more than half the TWA (or more than 5 ppm).

Environmental monitoring was mandated within six months of the promulgation of the standard and subsequently based on the number of workers. If the TWA was exceeded, sampling was to be repeated every 15 days until two consecutive surveys demonstrated normal values.

Although there was some concern about the extent of the laboratory investigation at time of preplacement examination and the decision to relate environmental monitoring to the number of workers, the 1974 standard was generally accepted by those who had practical experience in industry.

The Post-1976 Experience

On August 25, 1976 NIOSH issued a revised recommendation for an occupational exposure standard for benzene lowering the level to 1 ppm as determined by a 2-hour air sample collected at one liter per minute⁽⁵⁾. The bases for this change were several epidemiologic studies on rubber workers in the Akron, Ohio, area and a number of case reports from France, Italy and Turkey. Although it was admitted that in many instances the exposure levels were unknown or, if known, were high (several hundred ppm) NIOSH took the position that that data established benzene as a carcinogen and this justified setting the exposure level at the lowest detectable level.

On April 29, 1977 OSHA issued an Emergency Temporary Standard⁽⁶⁾ which followed the NIOSH recommendations of August 1976 but cited as its justification for the "imminent danger" category the work of Infante et al. This study became available to OSHA from the NIOSH Division of Surveillance, Hazard Evaluations and Field Studies in early 1977 but was not published in Lancet until July 9, 1977⁽⁷⁾. The authors reported that seven cases of acute or chronic myelogenous or monocytic leukemia occurred in 748 workers in a pliofilm operation in Akron and St. Mary's, Ohio, during the period January 1, 1940 and June 30, 1949 - an incidence 10 times normal. Moreover, it was alleged that the exposure levels of benzene were below the limits recommended at the time of their measurement, the implication being that these levels were the lowest reported to date.

The ETS was promptly blocked by court action on the part of the API and a number of petroleum companies. On May 27, 1977 OSHA issued a proposed permanent standard which in essence repeated the regulations of the ETS⁽⁸⁾.

The standard did propose exemptions for the handling of gasoline from bulk terminals out to the consumer and situations where a Liquid stream contained 1% or less of benzene (the latter exemption would probably for one ppm only ~0 then would drop to 0.1%).

During late July and August 1977 administrative hearings were held at which the supporters and opponents of the proposed permanent standard presented their arguments.

The basic position of NIOSH and OSHA presented, at the hearings may be summarized as follows (see Figures 7 and 8):

1. The evidence from many case reports and several epidemiologic studies confirms the fact that benzene is a leukemogen (or a cancer producing substance for the hematopoietic system).
2. It is impossible to prove that a safe level of exposure exists for any leukemogen (carcinogen), hence, exposures must be reduced to the lowest measurable level.
3. The practical realities of establishing an environmental and medical control program for the thousands of people involved in handling gasoline dictate that for the moment at least these individuals should be exempted from control.

The opponents of the proposed permanent standard offered the following arguments:

1. Benzene has not been proven to be a primary carcinogen although it may be a promoter or co-carcinogen at levels well above the present standard. This is supported by the epidemiological studies of Thorpe (Exxon affiliates in Europe, 1961-70) (9), Lloyd (Incidence of Leukemia in Coke Oven Workers) (10) and Joyner (Shell Oil Company employees) (11). The Infante study when subjected to close review also tends to support this concept - the actual exposure levels averaged over 100 ppm with excursions that probably reached the 1,000 ppm mark on numerous occasions.
2. The concept that there is no threshold for a carcinogen is fallacious.
3. The OSHA proposal does not identify the benefits, consider reasonable regulatory alternatives or adequately assess the economic impact as required by law.

4. The exemptions proposed under the new permanent standard are arbitrary and illogical: arbitrary because they cut off service stations and terminals where exposures are as high as in bulk plants or many producing areas; illogical because they are based on the percentage of benzene in liquids rather than on ppm of benzene vapor in air.

That the argument was in vain was demonstrated when the final version of the permanent standard dated January 31, 1978 was issued on February 10, 1978. Although notice was taken of the testimony presented at the hearings in the long background section, the standard still mandated:

1. A level of 1.0 ppm in air over an 8-hour period.
2. A 5 ppm ceiling for any 15-minute period.
3. An 0.5 ppm action level for monitoring and medical surveillance.

Time does not permit a more detailed discussion of the monitoring or medical requirements, the various aspects of regulatory reporting, protective equipment, training, labeling or record keeping. For many companies in the API, compliance will be possible but costly, for others it will pose significant problems. The basic reasons for our continued opposition to this standard however, are not economic:

1. Control of benzene exposure to the lowest feasible level because it is a carcinogen is unscientific because it denies the concept of a threshold and a dose-response relationship. To accept this point is to legitimize the generic standard for carcinogens.
2. The diversion of scarce medical, technical and management resources cannot be justified on the basis of the theoretical gains for society as a whole.

The issue is now joined in the courts so the last chapter is still to be written. An optimist might hope that something akin to the scientifically defensible conclusions of the International Workshop on Benzene held in Paris in November 1976 will emerge, namely:

"The Workshop discussed but could not agree on whether there was a concentration below which there would be no leukemogenic effect clearly attributable to benzene. Despite this inability to exclude the possible induction of leukemia at benzene exposures below 10 ppm it

was agreed that such a case would be a rare occurrence.

"Benzene exposure should be controlled to be as low as possible but in no case should the Time Weighted Average exceed 10 ppm for an 8-hour day and a 40-hour week. The average should be based on a single work day. The ceiling value should not exceed 25 ppm based on a 10-15 minute sampling period." (12)

Time and the courts will decide if such optimism is justified.

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- (1) Gerarde, H.W. Toxicology and Biochemistry of the Aromatic Hydrocarbons .
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- (4) Criteria Documents - Recommendations for a Benzene Standard. 1974. NIOSH.
- (5) Revised Recommendation for an Occupational Exposure Standard for Benzene. 1976. NIOSH.
- (6) Emergency Temporary Standard for Benzene. 29 April 1977. OSHA.
- (7) Infante, P.F. et al. Leukemia in Benzene Workers. Lancet, July 9, 1977; pp. 76-78.
- (8) Proposed Permanent Standard for Benzene. 27 May 1977. CSHA.
- (9) Thorpe, J.J. Epidemiologic Survey Of Leukemia in Persons Potentially Exposed to Benzene. J.O.M. 16; 375-382; 1974.
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- (11) Joyner, R. Report on Mortality from Leukemia, Shell Oil Company. Testimony at OSHA Hearing, 1 August 1977.
- (12) International Workshop on Toxicology of Benzene. p. 7, Permanent Commission and International Association on Occupational Health. Paris, France, 9-11 November, 1976.

3/3/78.

To be given at the Division of Refining Meeting at Toronto on May 11, 1978.

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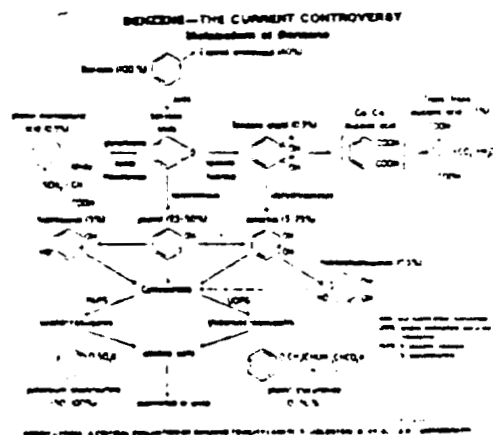


Figure 1. Metabolism of Benzene.

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Acute Benzene Toxicity

<u>SKIN</u>		<u>MUCOUS MEMBRANES • LUNGS</u>	
Vasodilatation		Irritation	
Erythema		Vasodilatation	
Irritation		Pulmonary edema	
Drying		Hemorrhage	
		Tissue necrosis	
<u>EYE</u>		<u>C.N.S.</u>	
Itching		Exhilaration	Tachycardia
Lacrimation		Drowsiness	Dyspnea
Irritation		Fatigue	Unconsciousness
		Dizziness	Convulsions
		Headache	Tremor
		Nausea	Death

Figure 2. Acute Benzene Toxicity.

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EFFECTS OF BENZENE VAPOR ON MAN

<i>Air concentration p.p.m.</i>	<i>mg/l</i>	<i>Duration of exposure (minutes)</i>	<i>Effects</i>
20,000-19,000	65-61	5-10	Fatal
7,500	25	30	Dangerous to life
3,000	9.6	30	Endurable
1,500	4.8	60	Serious symptoms
500	1.6	60	Symptoms of illness
150-50	0.48-0.16	300	Headache, lassitude, weariness
25 (MAC)*	0.08	480	None

* MAC - Maximum allowable concentration (Threshold limit).

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OF AROMATIC HYDROCARBONS.

Figure 3. Effects of Benzene Vapor on Man.

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Chronic Toxicity—Hematopoietic Effects

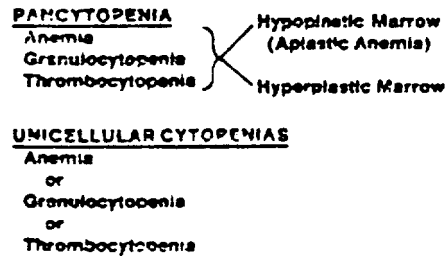


Figure 4. Chronic Toxicity - Hematopoietic Effects.

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Clinical Signs of Hematotoxicity

<u>2° TO</u> <u>ANEMIA</u>	<u>2° TO</u> <u>GRANULOCYTOFENIA</u>	<u>2° TO</u> <u>THROMBOCYTOPENIA</u>
Easy Fatigue	Fever	Petechiae
Headache	Infection	Purpura
Malaise	Death	Hemorrhage (internal or external)
Dizziness		
Palpitation		
External Dyspnea		

Figure 5. Clinical Signs of Hematotoxicity.

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Evolution of Benzene Standard

1920's	100 ppm for 8-hour day	Massachusetts and a few other states
1930's	50 ppm for 8-hour day	(State Standard)
1940	35 ppm for 8-hour day	(State Standard)
1942-45	100 ppm for 8-hour day	Federal "War-time Standard"
1946	100 ppm	ACGIH-TLV
1947	50 ppm	ACGIH-TLV
1948	35 ppm	ACGIH-TLV
1957	25 ppm	TWA-ACGIH-TLV
1963	25 ppm ceiling value	—ACGIH-TLV
1969	10 ppm TWA with 25 ppm ceiling	—ANSI
1972	10 ppm TWA with 25 ppm ceiling	—OSHA
1974	10 ppm TWA with 25 ppm ceiling with 5 ppm action level	—NIOSH
1976	1 ppm with 5 ppm excursion	—NIOSH (proposed)
1977	1 ppm with 5 ppm excursion	—OSHA (proposed)

Figure 6. Evolution of Benzene Standard.

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Opposing Positions on 1977 Proposed Standard

NIOSH—OSHA	INDUSTRY
1. Benzene is a Leukemogen Case reports Rubber workers studies Infante study	1. Benzene is not a primary carcinogen. It may be a promoter or co-carcinogen. No cases below 40 ppm Epidemiology studies of Thorpe, Lloyd and Joyner
2. There is no safe level for leukemogen. (carcinogen)	2. The "no threshold" concept for carcinogens is fallacious. a. A number of factors can prevent cancer induction or delay it. e.g. Metabolic block, DNA repair, immune response, etc. b. Do relationship to latent period. c. Demonstration of co-carcinogenic or promoter mechanisms.

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Opposing Positions on 1977 Proposed Standard (Cont'd.)

3. Practical considerations justify exemption of gasoline handlers.	3. The proposed exemptions are illogical and arbitrary.
4. The economic consequences are bearable.	4. The proposal does not identify the benefits or assess the economic impact.

Figures 7 and 8 Opposing Positions on 1977
Proposed Standard.

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