How much benzene causes cancer?

The question is controversial. Industry is thus threatened with over-reaction to the substance's potential carcinogenicity. Here's a rundown on benzene's background as a toxic material and where it is leading the refiner

John J. Thorpe, Exxon Corp., New York

FOR MANY COMPANIES, compliance with the new U.S. permanent standard for benzene exposure* will be possible but costly. For others, it will pose major problems. But the basic reason for industry's opposition to this standard is *not* economic. The reason is twofold:

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 legitimatize 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.

Courts will decide. 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.*[1]

* U.S. permanent benzene standard (February 1978)
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 and the courts will decide if such optimism is justified. In the meantime, it is well to know as much as possible about benzene's metabolism, toxic effects, regulatory history in the U.S. and the new standard's contents, as a guideline for the controversy's likely outcome.

Metabolism. After inhalation of benzene by a mammal, about 40 percent 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. 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.[2]

Acute toxicity. As shown in Table 1, 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. If benzene is not removed serious tissue injury occurs.

Mucous membranes (nose, mouth, throat, lungs, etc.)

TABLE 1—Acute benzene toxicity

Skin Vasodilatation Erythema Irritation Drying	**Mucusmembranes & lungs** Irritation Vasodilatation Pulmonary edema Hemorrhage Tissue necrosis	
Eye Itching Lacrimation Irritation	**C.N.S.** Exhilaration Drowsiness Fatigue Dizziness Headache Nausea	Tachycardia Dyspnea Unconsciousness Convulsions Tremor Death

TABLE 2—Effects of benzene vapor on man

Air concentration		Duration of exposure (minutes)	Effects
p.p.m.	mg/l		
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).
Credit—from: Gerarde, H. W., Toxicology and Biochemistry of Aromatic Hydrocarbons

also are irritated easily by benzene. The lung may develop a chemical pneumonia.

Inhalation of high concentrations causes exhilaration, then depression with drowsiness, fatique, dizziness, headache and nausea. Ultimately unconsciousness, convulsions and death may occur (see Table 2).

Chronic benzene toxicity. Important as the acute effects are, much more attention has been directed recently to chronic lower level exposures (see Table 3). 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. Also, single cell types may be affected to produce anemia, decreased white cells or a low platelet count.[2]

The incidence of these manifestations is very difficult to determine. Most of the literature reports refer to single or small groups of patients. In the few series where longitudinal studies of employes 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.[2]

Anemia. Clinical manifestations of benzene induced pancytopenia generally tend to be rather non-specific. They are presumably related to anemia—easy fatique, headache, malaise, dizziness, palpitation and dyspnea on exertion (see Table 4). 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 1,000 - 1,200 (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 cause 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 percent will die even with the most modern methods of treatment.[2] Where the changes are less severe and the individual is removed from further exposure to benzene, recovery is also the general rule.

Cause lukemia? 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. To date, efforts to produce leukemia experimentally in animals have been unsuccessful.

TABLE 3—Chronic toxicity—hematopoietic effects

PANCYTOPENIA Anemia Granulocytopenia Thrombocytopenia	Hypoplastic Marrow (Aplastic Anemia) Hyperplastic Marrow
UNICELLULAR CYTOPENIAS Anemia or Granulocytopenia or Thrombocytopenia	

TABLE 4—Clinical signs of hematotoxicity

2° To Anemia	2° To Granulocytopenia	2° To Thrombocytopenia
Easy Fatigue Headache Malaise Dizziness Palpitation External Dyspnea	Fever Infection Death	Petechiae Purpura Hemorrhage (internal or external)

TABLE 5—Evolution of benzene standard

1920s	100 ppm for 8-hour day Massachusetts and a few other states
1930s	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)

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 casually 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."[2]

Benzene regulations. History of the environmental control of benzene in the U.S. helps show how we got where we are, and gives some clues to the outcome (see Table 5).

In the U.S., the recognition in the early 1920s that benzene exposure produced pancytopenia led to some 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 1940s. 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

HOW MUCH BENZENE CAUSES CANCER?

ppm 15 min. ceiling. This became an official OSHA standard in October 1972.

Standard reiterated. The above 1972 standard was again recommended when the 1974 NIOSH criteria document was published.[3] This had, however, an "action level" proviso which required certain biological monitoring if the employe 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 Aug. 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.[4] 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. It was admitted that in many instances the exposure levels were unknown or, if known, were high (several hundred ppm). But 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[5] which followed the NIOSH recommendations of August 1976 but cited as its justification for the "imminent danger" category to 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.[6]

Leukemia in Akron. The above authors reported that seven cases of acute or chronic mylogenous or monocytic leukemia occurred in 748 workers in a pliofilm operation in Akron and St. Mary's, Ohio, during the period Jan. 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 was that these levels were the lowest reported to date.

The ETS was promptly blocked via court action by

OSHA's position. The basic position of NIOSH and OSHA presented at the hearings are as follows:

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, exposure 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.

Opponents' position. 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),[8] Lloyd (Incidence of Leukemia in Coke Oven Workers)[9] and Joyner (Shell Oil Co. employes).[10] 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.

Keep informed. That the argument was in vain was demonstrated when the final version of the permanent standard dated Jan. 31, 1978, was issued on Feb. 10, 1978.

Space 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. It suffices to say that we in the industry will have to watch developments in these and other areas to stay "on top" of benzene control developments.

(Adapted from a paper presented at the Midyear Refining Meeting of API, Toronto, May 8-11, 1978).