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E. I. DU PONT DE NEMOURS & COMPANY
INCORPORATED
HASKELL LABORATORY FOR TOXICOLOGY
AND INDUSTRIAL MEDICINE
P.O. BOX 50, ELKTON ROAD
NEWARK, DELAWARE 19714

CENTRAL RESEARCH AND DEVELOPMENT DEPARTMENT

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CONFIDENTIAL

To: J. C. Olguin
ERD
N-11498-1

From: C. F. Reinhardt, M.D. CFR
CR&D Department
Haskell Laboratory

B. W. Culpepper, M.D. BWC
ER Department
N-11400

BENZENE
CAS REGISTRY NO. 71-43-2

Benzene is being reviewed* according to the August 1985 EQC "Guidelines for Control of Carcinogenic and Reproductive Risks Posed by Chemicals Made or Used within Du Pont."

General Toxicity

Benzene has slight acute oral toxicity with an LD50 in rats of 3339 mg/kg (11). Benzene is an irritant to the skin of rabbits, but there was no indication of absorption through the skin in acutely toxic amounts (29). Recent studies in the monkey indicate about 1% of an administered benzene dose is absorbed following multiple exposures (14). In the rabbit eye, benzene produced moderate conjunctival irritation and a very slight, transient corneal injury (29). By the acute inhalation route, benzene has very low toxicity with a 7-hour LC50 in mice of 10,000 ppm (26). In contrast to its very low acute inhalation toxicity, chronic exposure to benzene has a significant effect on the bone marrow leading, in some cases, to aplastic anemia and other hematopoietic changes. Depression of bone marrow function, resulting in leukopenia, was observed in rats exposed to 44 ppm of benzene, 7 hours a day, 4 days per week, for 5 weeks (6) and in mice exposed to 103 ppm of benzene, 6 hours per day, 5 days

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* Benzene was declared a suspected carcinogen requiring special control on December 17, 1976. Since 1976, a number of additional studies have been conducted. This letter provides an update.

per week for 26 weeks (8). Similar results were obtained in rats administered benzene by the oral (29) and subcutaneous (7) routes.

Carcinogenic Potential

Exposure of laboratory animals to benzene has been associated with tumors of several sites including the hematopoietic system and epidemiology studies have demonstrated a causal association of benzene exposure with leukemia.

In rats and mice, benzene produced increased incidences of tumors at several sites following administration by either the oral or inhalation route. In rats orally administered 50 or 250 mg/kg/day, 4 or 5 days a week, for 52 weeks, benzene was found to cause Zymbal gland carcinomas, mammary carcinomas, and leukemia in a dose-related manner (15). In another oral study in both rats and mice sponsored by NTP, benzene produced a significant increase in malignant tumors of the lung, ovary, mammary gland, lip, oral cavity, hematopoietic system, preputial gland, Zymbal gland, and Harderian gland. Doses ranged from 50 to 200 mg/kg (18). In mice exposed to 100 or 300 ppm of benzene for their lifetime, 2/40 exposed to 300 ppm developed myelogenous leukemia. No leukemia was observed in the control or 100 ppm groups (25).

Even though benzene was clearly carcinogenic in laboratory animals, the evidence in humans is considered more appropriate in estimating the risk of occupational benzene exposure.

Benzene has been associated with more than 100 occurrences of leukemia in humans since 1928. Recent epidemiological studies have demonstrated a causal association with leukemia. In a review of the epidemiology studies, API concluded that three studies best characterize the risk associated with benzene exposure (1).

In a NIOSH-sponsored study of 748 white male workers exposed to benzene at any time between 1940 and 1949 in two plants manufacturing synthetic rubber, a significant excess of leukemia deaths was observed (7 observed versus 1.25 expected). These leukemias were all of the myelogenous or monocytic type. Benzene exposure levels were estimated to be between 10 and 100 ppm with occasional high excursions to levels up to several hundred ppm. (9,22). This study has been updated to include 1196 white male workers with a least one ppm-day of cumulative exposure to benzene between January 1, 1940 and December 31, 1965. As in the initial study, leukemia deaths continued to be significantly increased (9 observed versus 2.7 expected) (23).

In a study of a Dow Chemical Co. manufacturing facility, two deaths from leukemia (0.8 expected) and one from aplastic anemia were reported among 594 benzene-exposed workers employed between 1940 and 1973. Another death was ascribed to myelogenous leukemia but listed incorrectly as due to pneumonia. These three

deaths from leukemia compared with 0.8 expected are considered to be statistically significant. Workers had relatively low benzene exposures, about 5 ppm (TWA), with a range of 0.1 to 35 ppm. However, benzene levels ranged up to a peak of 937 ppm (20). In an update of this study to include 956 workers exposed to benzene between 1940 and 1982, a total of 4 leukemias were observed versus 2.1 expected. However, all 4 leukemias were of the myelogenous type. The expected incidence of this type of leukemia is 0.9 and this excess was considered statistically significant (2).

In a CMA-sponsored study, a group of 4602 workers occupationally exposed to benzene for at least six months between 1946 and 1976 was followed through December 1977. Seven deaths from leukemia were noted versus 5.96 expected. This increase was not considered statistically significant. Additionally, none of the leukemias were of the type seen in the NIOSH and Dow studies (30).

The CMA study included two epidemiology studies that were done within Du Pont.

In a group of 863 men who had been exposed to benzene since 1945, three cases of leukemia were observed versus 0.6 expected. This increase was considered statistically significant. These leukemias (one chronic myeloid leukemia, one acute lymphatic leukemia, and one unspecified lymphatic leukemia) were also different from those seen in the NIOSH and Dow studies. Benzene exposure levels during the study period were unknown. However, these men spent relatively short periods in benzene areas (0.3 to 2.0 years) and worked in jobs that were considered to have little potential for benzene exposure. In 1975, benzene exposures ranged from 1 to 3 ppm (19).

In a group of 1250 men who had been exposed to benzene since 1946, one case of leukemia (type was not specified) was observed versus 1.3 expected. Benzene exposure levels were not known. In an update of this study through 1978, two deaths from leukemia were observed versus 1.4 expected. This increase is not statistically significant (21).

Each of these studies has some limitations with the following highlighted by API:

- Benzene levels are not well established, and higher levels than estimated probably existed.
- Workers were most likely exposed to other chemicals and these workers may have had other jobs involving benzene exposure.
- Significant dermal exposure was not considered.

In API's review of these data, the NIOSH-sponsored study was considered the most appropriate for quantitative risk assessment. These data were analyzed by several risk assessment models with varying conclusions. API chose to have the data assessed by a model that used linear logistic regression, the same method used in the latest update by NIOSH (23), but with modifications to the case-control analysis (3). Based on this assessment, 0.6 excess leukemia deaths were estimated at 1 ppm and 8 deaths at 10 ppm (1,3).

Genotoxic Potential

Benzene is not mutagenic in Salmonella typhimurium when tested by the standard plate assay (24), the host-mediated assay in mice (13), or the forward-mutation assay (10). However, benzene does cause structural and numerical chromosome aberrations in humans occupationally exposed to benzene (12). Chromosomal aberrations (16), SCEs (27), and micronuclei (16) were also observed in mice exposed to benzene. Additionally, a number of other in vivo studies have shown benzene to have positive effects on other genotoxic endpoints including, sperm-head abnormalities, inhibition of DNA and RNA synthesis, DNA binding, and interference with cell cycle progression (18).

Developmental Toxicity

Benzene has been studied for its developmental toxicity in rats, mice, and rabbits by inhalation, oral gavage, and subcutaneous injection. Because exposure to benzene is usually by inhalation, studies by this route will be considered.

Mice and rabbits were exposed for 7 hours a day on days 6 through 15 (mice) or days 6 through 18 (rabbits) of gestation to 500 ppm of benzene. Growth retardation and increased skeletal variants were observed but no malformations in the fetuses and no effect on the incidence of pregnancy, average number of live fetuses, or resorptions per litter were noted (17).

No teratogenic effects were observed in offspring of rats exposed 6 hours a day on days 6 through 15 of gestation to 1, 10, 40, or 100 ppm of benzene. A slight fetotoxic effect (reduced mean fetal body weights) was noted in the 100 ppm group (4,5).

Reproductive Toxicity

Male and female mice were exposed 6 hours a day, 5 days a week, for 13 weeks to 1, 10, 30, or 300 ppm of benzene. Histopathological changes were observed in the ovaries (bilateral cysts) and testes (atrophy/degeneration, decrease in spermatozoa, moderate increase in abnormal sperm forms) of mice exposed to 300 ppm of benzene (28).

Testicular changes were also seen in rabbits and guinea pigs exposed 7 to 8 hours a day, 5 days a week, for up to 6 months. The guinea pigs showed a slight increase in average testicular weight when exposed to 88 ppm of benzene. Rabbits showed slight histopathological changes (degeneration of the germinal epithelium) when exposed to 80 ppm of benzene (29).

AEL Review

These data were reviewed by the Haskell Laboratory AEL Committee on February 10 and May 11, 1988. Based on analysis of the results of epidemiology studies, less than one excess leukemia death would be expected at an exposure level of 1 ppm of benzene and 8 excess deaths would be expected at 10 ppm. However, because the actual benzene exposures of the workers in these studies have most likely been underestimated, the actual risk may be lower. The Committee recommended AELs of 1 ppm (8- and 12-hour TWA) and 5 ppm (15-minute TWA).

Summary

Benzene is carcinogenic in laboratory animals and leukemogenic in humans. Based on analysis of epidemiology studies, AELs of 1 ppm (8- and 12-hour TWA) and 5 ppm (15-minute TWA) were recommended by the Haskell AEL Committee.

Because benzene is carcinogenic in more than one species of laboratory animal exposed by more than one route of administration and is also leukemogenic in humans, we conclude that benzene should be considered a carcinogen according to the guidelines for carcinogenic hazard designations, and will be categorized as a capital C. Benzene is not a developmental hazard at levels not producing other signs of toxicity and this will be signified by (D 1988). The hazard for reproductive toxicity can not be definitively determined based on the available data; however, ovarian and testicular effects have only been observed in laboratory animals exposed to benzene concentrations well above those that produce other toxic effects.

Note: Because of its Du Pont and OSHA status, benzene already requires an annual employee communication update. Therefore, issuance of this updated hazard determination letter would not require any additional communication to employees at U.S. sites, assuming the new AEL of 1 ppm (8- and 12-hour TWA), 5 ppm (15-minute TWA) has been communicated. However, the new AEL should be communicated, where appropriate, to employees at Du Pont sites outside the U.S. Those receiving copies of this letter, if they have an interest, should coordinate any actions they plan to take with J. C. Olguin, the representative of the Petrochemicals Department.

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