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Interoffice Communication

To Darrell Riffe, Laurie Mauerman, Sid Pitts
From Tom Grumbles
Date November 23, 1983
Subject CONFERENCE ON BENZENE HEALTH EFFECTS

For your information, enclosed are summary documents concerning a recent conference on the health effects of benzene. Several significant points are raised by the information presented at this meeting.

1. Data from recently completed animal studies involving inhalation and ingestion studies indicate that benzene is a "multi-site" tumor causing agent. The effects of benzene had been known to occur in the blood forming organs, but hard tissue tumors had not been seen until recently.
2. The evidence now available will probably be sufficient to meet the Supreme Court mandate to OSHA for demonstrating unacceptable risk at exposures below 10 ppm. A 1.0 ppm standard can probably be defended by OSHA.

Based on this new information, some revisions in our Benzene Education Program texts will be necessary when the programs are next updated.


Thomas G. Grumbles

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Enclosure

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Interoffice Communication

NOV 22 '83

To Distribution

From W. D. Broddle, Ph.D., Medical, Ponca City

Date November 9, 1983

Subject TRIP REPORT/INTERNATIONAL CONFERENCE ON BENZENE
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The above conference was held in New York City and was an intensive two-day review of health-related research on benzene. It was more than "coincidental" that recently a regulatory timetable has been published by OSHA wherein a new workplace standard will be published in November (1983), public hearings in February (1984) and a final rule by June (1984).

The conference was attended by approximately 80 people and included many well-known scientists who are actively involved with benzene research (see Attachment). Participants represented European organizations, EPA, NOISH, OSHA, unions, public interest groups (NRDC, etc.), API, CMA, CIIT and many oil or chemical corporations.

A summary of highlights follows:

- I. Selikoff, Mt. Sinai Hospital
Benzene represents a potential health hazard that must be assessed in terms of toxicology, epidemiology, regulations, politics, social and economic parameters.
- N. Nelson, New York University
Health effects of benzene have been known for many years (1897, first human deaths; 1910-13, benzene's initial effect of decreasing white blood cells, WBCs, is used to treat leukemia; 1918, search for benzene substitute; 1938, first reported case of benzene-related leukemia).
- B. Goldstein, EPA
New animal carcinogenesis data shows benzene (≥ 100 ppm) causes hematological and non-hematological solid tissue tumors. The OSHA workplace standard, PEL, of 10 ppm must be lowered. Benzene in gasoline ($\leq 2\%$, U.S.A.; $\leq 5\%$, Europe) should be lowered (remember that API studies with gasoline showed a carcinogenic response in the kidney); since the transportation and storage of gasoline creates the potential for polluting aquifers, a gasoline/drinking water carcinogenic study in animals should be instigated (API has placed this on low priority).
- M. Aksoy, Turkey
Dr. Aksoy is a hematologist who has published many studies involving Turkish shoeworkers since they use benzene-containing solvents. His work in the 1970s showed slight elevations of acute myelocytic leukemia, AML, but recent data also show slight increases of multiple myeloma and lung cancer.

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These studies are compromised due to several uncontrolled variables, such as mixed solvent exposure, cigarette smoking, and inadequate data for non-exposed populations. (Several participants raised the question of whether genetic testing would predict or demonstrate benzene toxicity since benzene is quite toxic to the immune system and genetic material.)

- M. Berlin, Sweden

Benzene exposures or content:

Cigarettes, 60-100 mcg/cigarette (40-100 ppm in smoke)

Gasoline, 1-5%

Urban air, 1 ppb

Strawberries and several other common foods, 1-100 ppm

Petroleum Operations: 3-10 ppm (transportation operations)
0.05-0.5 ppm (service station attendants)

Studies in humans show two detoxification half-lives ($t_{1/2}$) for benzene; one is 1-2 hours and the longer one is 24-48 hours (remember, it takes 6-7 half-lives to reach zero, i.e. total detoxification). Chemical workers had a breath concentration for benzene of 13 parts per billion (ppb) but this decreased to 7 ppb during a 6-week vacation. This decrease is less than anticipated and may indicate that benzene is only slowly removed from fatty tissues such as bone marrow, adipose tissue, etc. Another study showed a doubling of chromosomal aberrations in gasoline tank-truck drivers.

Even though cancer is commonly viewed as a non-threshold response (the "one-molecule, one cancer" theory), if benzene causes cancer by an initial process that is non-genotoxic (immunotoxic, tissue destruction, etc.), then the cancer response may have a threshold exposure that is non-carcinogenic due to tissue repair mechanisms.

- C. Maltoni, Institute of Bologna/Italy

Lifetime oral or inhalation animal studies in Sprague Dawley rats (oral doses of 50, 250 and 500 mg/kg; inhalation of 200 ppm) showed a carcinogenic response in all test groups (skin, mammary and zymbal gland, stomach, liver angiosarcomas and oral cavity). More rodent studies are ongoing (Wistar rat and Swiss mice).

PLEASE NOTE: Lifetime oral rat studies (500 mg/kg/day) for ethyl benzene, toluene and xylene showed a carcinogenic response but only if analyzed as total tumors per test group. Remember that previous chronic rodent studies (CIIT, API) do not substantiate this carcinogenic effect of alkyl benzenes. However, I am sure Dr. Maltoni will continue studying the carcinogenic potential of alkyl benzenes. Also the EPA is presently outlining a research program that they feel industry should conduct on alkyl benzenes.

- J. Huff, National Toxicology Program

Lifetime rodent oral studies with benzene (rats at 50, 100 and 200 mg/kg; mice at 25, 50 and 100 mg/kg) showed a similar tumorigenic

response as Maltoni's data except that tumors also occurred in the lung, Harderian gland, endometrium and lymphatic leukemia.

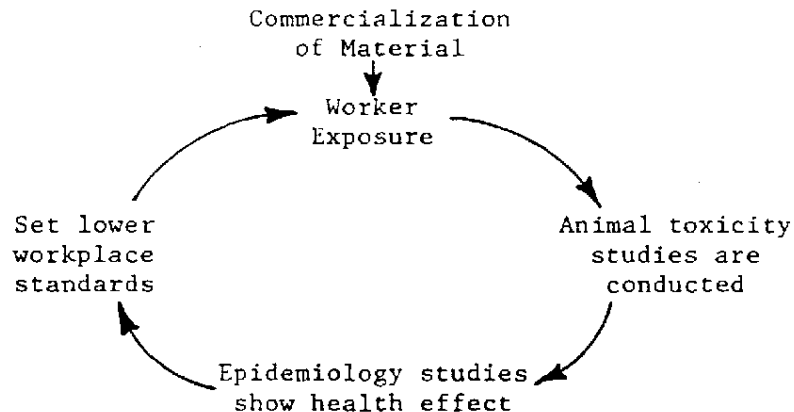
- R. Albert, New York University
Sprague Dawley rats and CD-1 or C-57 mice were exposed chronically to benzene on an intermittent basis (300 or 900 ppm/one of every three weeks or 1200 ppm for 10 weeks and no exposure thereafter). Each test group showed an increase of tumors in the zymbal gland and lung.
- E. Cronkite, Brookhaven National Laboratories and
C. Snyder, New York University
Studies with mice showed that benzene was toxic to white blood cells and the immune system at exposures as low as 10 ppm. In vitro studies show these effects at levels of 1-10 ppm.
- R. Snyder, Rutgers University
Studies with mice showed that benzene can alter its own cellular detoxification pathway.
- R. Irons, Chemical Industry Institute of Toxicology (U.S.A.)
Studies in mice revealed that benzene is detoxified to toxic metabolites like quinones, hydroquinones and perhaps ring-opened derivatives.
- A. Tunek, London
In vitro studies show that benzene toxicity is more dependent on time-weighted average exposures than to higher, intermittent exposures.
- G. Kalf, Jefferson Medical College
Benzene binds to and inhibits mitochondrial DNA activity.
- R. Tice, Brookhaven National Laboratories and
M. Gad-El-Karim, University of Texas
Studies with mice show that the earliest signs of benzene toxicity involve the bone marrow (cytotoxicity and chromosomal aberrations).
- H. Runion, Gulf Oil
Employee exposure data were given for the oil, chemical, steel and paint industries for 1978-83. Overall, 88% and 98% of the exposures were below 1 ppm and 10 ppm, respectfully. Note that petroleum transportation workers (barges, trucks, etc.) had higher exposures such that 95% of exposures were only below 5 ppm (total petroleum industry had 95% below 2.5 ppm).

The above data partially explains why the petroleum and chemical industries are not terribly against a benzene workplace standard of 1 ppm.

- L. Beliczky, United Rubber Workers Union
Skin exposure is prevalent in the rubber industry so air sampling does not reflect TOTAL BODY BURDEN of benzene.

- Dr. Greenberg, unknown affiliation

It is interesting how workplace standards for several potentially toxic industrial materials (asbestos, benzene, arsenic, etc.) have evolved:



- K. Miller, Oil, Chemical, and Atomic Workers Union (OCAW)

Animal, medical, and hematological review allows each worker to be his own control and allows for quicker detection of occupational health problems. This could help screen for benzene toxicity since leukemia may be preceded by aplastic anemia and pancytopenia.

OCAW is concerned over reports that benzene carcinogenesis may involve tissues other than the bone marrow or blood.

- R. Murray, England

Peak exposures to benzene may be more significant than a time-weighted average (see article by Van Raalte and Grasso). Also, no benzene-related diseases have been reported in England since 1952.

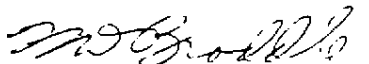
- D. Hoel, NIEHS

The risk of leukemogenic mortality in workers exposed to 10 ppm benzene for 45 years of employment ranged from 1-20%. This excess leukemia risk is calculated by using the very conservative One-Hit, Non-Threshold Probability Model. Risk would be better assessed if there were dose-response data in animals correlated with "delivered dose" at the site of toxicity (bone marrow, lung, etc.)

- P. Infante, OSHA

Multiple myelomas were elevated in epidemiology studies conducted by De Coufle et al. (Conoco benzene alkylation plant in Baltimore) and Thomas et al. (non-statistical increase in refinery workers). A recent press release by Shell Oil noted that epidemiology studies at five refineries showed an increase of leukemia in only the two refineries having a benzene unit.

- R. Yodaiken, OSHA
OSHA is drafting a new workplace standard for benzene and is contemplating the following:
 - ° If benzene is a respiratory carcinogen, should respirators be mandated? OSHA may require respirators depending on a risk/benefit analysis.
 - ° If benzene is a skin carcinogen, what special protection is needed?
 - ° To assess over-exposures, analysis of urinary phenols may be required.
- OSHA spokesman
OSHA is very aware that its regulations must consider all health-effect data, technologic and economic feasibility, the presence of a significant adverse health-effect and whether the regulation will significantly lower the adverse health-effect.
- J. Klotz, Natural Resources Defense Council
More controls are needed for benzene exposures in the workplace.
- T. Scovel, Texaco
Dr. Scovel questioned whether sufficient evidence is available to show that the 10 ppm workplace standard represents an unreasonable health hazard.
- B. Holmberg, Sweden
The Swedish government is comfortable with their 5 ppm benzene standard, which is based on chromosomal effects in humans.
- A. Upton, New York University
Dr. Upton summarized the presentations given at the conference but no surprises were evident, not even a conclusion concerning lowering the workplace standard.


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Senior Toxicologist

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Att.

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radiologist. In addition, plant physicians have undergone internal training in the early detection of lung abnormalities and the company's X-ray sales technical staff regularly visit all plant sites to evaluate and make sure that the best quality of film is being used.

In addition to 22 cases of malignancies, the Du Pont medical director reported that 200 employees were determined to have asbestosis and about 1,300 employees and pensioners, or slightly more than 1 percent, were found to have "evidence of asbestos related pleural thickening," but the majority were found to have "no illness or physical disability."

According to Culpepper, these results indicate that asbestos-related abnormalities "are more prevalent than we suspected four years ago," even considering the wide use of asbestos-containing insulation in chemical plants. On the other hand, he added, the results also show that "the vast majority" of the company's employees and pensioners do not have asbestos-related medical problems.

As another part of the asbestos screening program, the Du Pont medical director explained, all employees have seen a company-produced 25-minute film, "Caring About: Asbestos," which describes the problems involved in asbestos-related abnormalities, using Du Pont employees as well as medical experts such as Dr. Irving Selikoff of the Mt. Sinai Medical Center and Dr. Benjamin Felson of the University of Cincinnati College of Medicine.

Referral to Specialists

All those with asbestos-related abnormalities have been referred to pulmonary specialists at company expense for evaluation and consultation and are offered follow-up exams annually, "or at an interval prescribed by the specialist," to determine whether there is "any impairment that requires a change in work assignment," the medical director explained.

In those situations where work-related illness or impairment develops, Culpepper said that Du Pont "will accept responsibility for appropriate related medical costs, and will offer the employee or pensioner compensation based on our understanding of the workers' compensation laws in that jurisdiction," in addition to assisting in obtaining other community benefits. Further, he noted that the company's policy covers employees even "when we are not certain that the abnormality stems from exposure at a Du Pont site."

Culpepper said that the company generally has not purchased asbestos-containing insulation since the 1970s and is replacing the asbestos it has with non-asbestos insulation when other repairs are necessary. In the few sites where asbestos-containing products are used, there are strict controls, and plant employees follow written procedures, including routinely monitoring exposure levels, using protective equipment and clothing, and having regular medical examinations.

Determining Pulmonary Disability

Judging the degree of pulmonary disability resulting from asbestos exposure has been a problem for Du Pont which has been further complicated by the varying criteria established by state workers' compensation laws. Culpepper explained that in some cases the company relies on X-ray abnormalities and pulmonary function changes and has found the American Medical Association's criteria for disability "frequently useful," except in assessing lesser degrees of disability. The British Medical Research Council's criteria "are even less suitable," he added, since they were developed primarily for emphysema and chronic bronchitis.

In an effort to overcome this continuing problem, the company medical director reported, Du Pont has contracted with Selikoff to help develop a system "for a quantitative, reproducible, analytical method for the evaluation of pulmonary disability."

Culpepper told BNA that the project has been in the works for about a year and that the company hopes to get something definitive this year so that it can "begin setting some real boundaries for medical determination of pulmonary disability for asbestosis."

Since Du Pont knows little about the risk of developing disabling conditions from asbestos-related abnormalities, Culpepper said that the company also is beginning an epidemiologic study of all employees and pensioners with asbestos-related abnormalities. He anticipated that the data would be helpful "to quantitate the risk of future malignancies, impaired lung function, or other diseases," as well as in assessing "the relative contributions of cigarette smoking and asbestos exposure to pulmonary disease and impaired lung function."

Benzene

BENZENE CALLED MULTI-POTENTIAL CARCINOGEN, BUT DOSE-RESPONSE RELATIONSHIP SEEN UNCLEAR

NEW YORK — (By a BNA Staff Correspondent) — Although the dose-response relationship between exposure to benzene and the occurrence of leukemia is still unclear, it is certain that benzene is an indirect-acting, multi-potential carcinogen, Arthur Upton, of New York University, concluded in summing up the results of an international conference on the substance.

The conference, sponsored by the Collegium Ramazzini, focused on recent experimental observations regarding carcinogenicity, blood dyscrasias, and toxicology associated with benzene.

Results presented by scientists attending the conference indicated that benzene produces leukemia and many other cancers in laboratory animals and there is "cause to believe that it produces the same results in humans, although this is not yet proven," according to Upton. The following conclusions also were drawn by Upton:

- Variations in the duration and extent of exposure may be responsible for production of the different types of cancer found in the laboratory animals.

- Age and sex of the exposed animals affect their physical responses to benzene exposure.

- A risk assessment modeled to an exposure dose is still difficult at this point.

Upton emphasized the need to determine the metabolic derivative or active principal in benzene that causes leukemia. He also stressed the need for better empirical data and additional animal research to determine the effects of intermittent peak exposures as opposed to time-weighted averages.

Most conference speakers agreed that determination of a dose/time relationship for benzene, or the impact of intermittent exposure vs. constant exposure in the development of leukemia, is crucial.

Health Effects of Benzene Exposure

Muzaffer Aksoy of Medical School, Istanbul, Turkey, asserted that leukemia develops through both genetic factors and environmental factors, citing familial studies indicating that some people are genetically more susceptible to leukemia.

Chromosomal changes were found in humans exposed to benzene, according to M. Berlin, University of Lund, Sweden. It is unclear, however, whether there is a connection between chromosomal changes and the carcinogenic effect of benzene.

C. Maltoni, of the Institute of Oncology, Bologna, Italy, presented research showing that benzene produces different types of cancers in different organs, produces cancer whether administered by inhalation or ingestion, and produces solid tumors in multiple sites with different exposure methods. He emphasized the need for more systematic investigation of the effects of benzene, additional experimental inhalation studies, and further experimental studies oriented toward primary prevention. On the basis of his research, Maltoni also hypothesized that toluene and xylene may be carcinogens.

Actual Industrial Exposures

An overview of benzene exposure in American industry from 1978 to 1983, presented by H.E. Runion of the Gulf Oil Corporation, indicated that on a national basis 87.6 percent of all industrial exposures to benzene were below 1 ppm and that 98.4 percent were below 10 ppm. Runion noted that some variability between industries occurred as expected, with the highest exposures seen in those operations involving the bulk transfer of benzene and in benzol plant operations.

U.S. industry operates well below the present Occupational Safety and Health Administration standard of 10 ppm, he asserted. Runion suggested that these data may have some relevancy to the absence of reported benzene-induced leukemias among workers having initial exposure since 1977.

Louis Beliczky, industrial hygiene director for the United Rubber Workers, urged that benzene be eliminated from industrial solvents altogether since it is present only as an impurity. Citing URW study results, he also noted a decrease in benzene exposure in the workplace, from a 1.3 ppm average exposure in 1977 to a 0.2 ppm average exposure in 1983.

Peter Infante, director of the OSHA Office of Carcinogen Identification and Classification, estimated that a working lifetime exposure of 45 years to benzene at 10 ppm would result in a leukemia risk ranging from approximately 44 to 152 excess leukemia deaths per 1,000 exposed workers. A working lifetime exposure to benzene at 1 ppm would result in a leukemia risk ranging from five to 16 excess leukemia deaths per 1,000 exposed workers, he stated.

At different lengths of exposure, the risk associated with 10 ppm was consistently 10 times greater than the risk at 1 ppm. Infante explained that this order of magnitude difference in risk was expected because the risk estimates were based on the one-hit model, and the one-hit model has been shown to be essentially linear at low doses.

Deficiencies in Proposed Rule

Ken Miller, of the Oil, Chemical and Atomic Workers Union, asserted that the proposed OSHA benzene standard is deficient in several areas. He criticized the absence of a provision for following previously exposed workers once they have retired or changed jobs. In addition, there is no provision requiring personal sampling for benzene-exposed workers so there is no method for determining actual individual exposures, he said. Miller suggested that requiring maintenance of a cumulative exposure log for each employee could remedy these problems.

"Prospective surveillance is sorely lacking," Miller maintained. Studies of the effects of benzene exposure on human reproduction and studies to determine whether there is a

correlation between chromosomal aberrations and leukemic response are needed, he said.

Retrospective surveillance and cohort mortality studies also are needed to determine the effects of benzene and to detect excess risks for various other conditions, Miller stated.

OSHA realizes that its benzene standard will be challenged in nearly its entirety and is striving to propose a feasible regulation that can be achieved, according to Ralph Yodaiken, director of OSHA's Office of Occupational Medicine.

Yodaiken raised difficult questions regarding the regulation of benzene in the workplace, including: Is a complete blood count a good indicator of the incidence of leukemia? If so, how often should it be done? What is the upper limit of normal for a white blood count? Should OSHA mandate gloves and hoods for handling benzene if it can be absorbed through the skin? Should respirators be required? Should breath analysis be part of a medical surveillance program? Should phenols in urine be measured as part of medical surveillance?

J. Klotz, of the Natural Resources Defense Council, supported strict application of state-of-the-art technology to controlling benzene. She stated that the federal government must be urged to consider the long-run protection of the public, halt the discharge of hazardous chemicals into the environment, and "err on the side of safety."

Litigation

ADDITIONAL TWO WEEKS FOR PLAN GRANTED TO MANVILLE; MULTI-LATERAL TALKS ORDERED

NEW YORK — (By a BNA Staff Correspondent) — Manville Corporation Nov. 7 was granted an additional, conditional two-week extension for submitting a reorganization plan to a federal bankruptcy judge for the Southern District of New York.

The extension granted by Judge Burton Lifland in *In Re Johns-Manville Corporation* (Nos. 82-B-11656 — 11676) requires that discussions between Manville and claimants seeking compensation for asbestos-related injuries be broadened by Nov. 14 to include other concerned parties.

In requesting an additional extension of the deadline for submitting a plan, Manville attorney Michael Crammes stated that his client needed additional time to respond to proposals made by the litigants group at a meeting Nov. 4. Based on this response, the two groups will decide whether further meetings to arrive at an acceptable reorganization plan would be fruitful, Crammes said.

Crammes did not discuss the substance of the proposals.

Objection to a further extension was voiced by Arthur S. Olick, an attorney representing an unofficial committee of companies which are co-defendants with Manville in a number of asbestos compensation cases. Manville and its claimants have had 14 months to develop a reorganization plan, a grant of time that is "manifestly excessive," Olick argued.

The credibility of the court is at stake, Olick further contended, because Lifland's first grant of extension was a "pre-emptory" grant that precluded any further extensions. However, Olick noted, two additional extensions have been granted since then.

The matter should be brought to a "speedy conclusion," the lawyer asserted, because Manville is protected from its creditors while its co-defendants are languishing.