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

Date November 9, 1983

Subject TRIP REPORT/INTERNATIONAL CONFERENCE ON BENZENE NOVEMBER 3-4

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 "coincidential" 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 ($\geq$ 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 myloma 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 ($t_{\frac{1}{2}}$) 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.

note the widely known benzene can being studied in carcinogenic potential

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 mitochrondrial DNA activity.

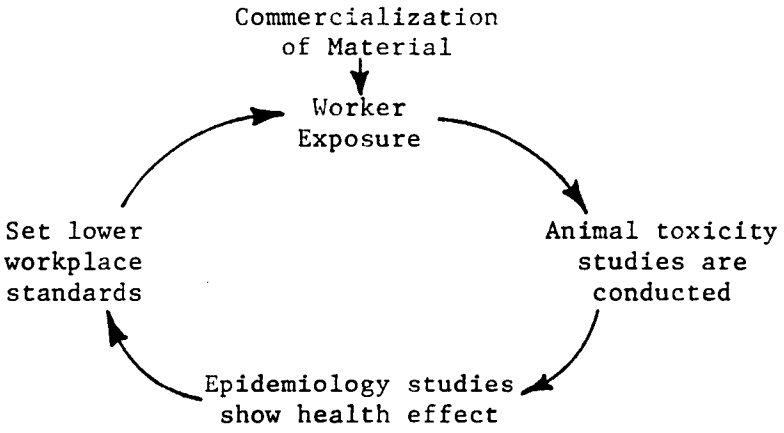
- R. Tice, Brookhaven National Laboratories and
M. Gad-El-Karim, University of Texas
Studies with mice show that the earliest signs of benzene toxicity involve the bone marrow (cytotoxicity and chromosomal aberrations).

- 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, HIEHS
  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 feasibilty, 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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