EXPERIMENTAL AND EPIDEMIOLOGICAL EVALUATION OF CARCINOGENIC RISK FROM EXPOSURE TO BENZENE

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- Kraybill

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The scientific literature reports on a series of studies on the evaluation of the carcinogenicity of benzene using the rodent as the experimental animal. All these *in vivo* studies pertain to mice and the application of benzene was by subcutaneous administration or topical application (skin painting). In most cases the benzene was administered in sesame oil or olive oil; however, in some experiments a variety of chemicals were dissolved in benzene prior to skin application. The mouse strains used were AKR, DBA_2, C3H, C57BL/6, Swiss mice, C57BL/6N and some albino mice. Hundreds of mice were involved in all of these experiments with benzene with no significant difference in tumor incidence over controls. One weakness in the experiments was failure to examine for all possible tumor sites. Despite these reported studies there is a view that benzene has not been adequately tested. This implies further work on other species and routes of administration with proper dose response studies (see Appendix A for details on all studies).

In the *in vitro* studies, benzene was inactive in the dominant lethal assay and host-mediated assay using bacterial systems (*S. typhimurium* TA 1950, TA 100, and TA98). Also, using *S. typhimurium*/liver microsome assay (metabolic activation), the response was negative. In addition, the test based on Chinese hamster lung fibroblast cells failed to show any induced chromosome damage. However, in a series of experiments with other animal cells, benzene did induce chromosome breaks, chromatid and isochromatid breaks and gaps in bone marrow cells, and chromatid gaps in rat leukocytes. The most significant finding was chromosome aberrations in blood cells of industrial workers exposed to benzene (details in Appendix A).

A series of epidemiological studies, starting in 1928, have been recorded. All of these earlier case reports provided little certainty that benzene, although used in various manufacturing processes, was the only etiologic agent in attempting to derive causal relationships between solvent exposure and leukemia. Thus, one could not clearly ascribe cases of myeloblastic leukemia or chronic myeloid leukemia to single exposure to benzene. Even as late as 1976, a committee of the National Research Council felt that there was not a remarkably high incidence of leukemia in workers from benzene exposure. The uncertainties again predominated because epidemiologists were not sure as to the history of potential exposures to other chemical agents (details in Appendix A).

There was a general consensus that benzene exposure was associated with blood dyscrasias and that heavy exposure could be associated with aplastic anemia. There is speculation by some occupational physicians that reportable anemias, which were compensable, may have progressed to leukemias in time. As mentioned above, other agents could produce aplastic anemias that could have progressed to leukemias. Thus, some inferential evidence could provide a basis that aplastic anemias correlated with benzene exposure could exacerbate ultimately to a leukemogenic state (details, Appendix A).

Some investigators considered the possibility that benzene could be a cocarcinogen and that if leukemias were produced they probably only occurred in highly susceptible members of the population. At best benzene, under high exposure conditions, could only be considered a suspect leukemogen.

The recent studies on pliofilm (rubber hydrochloride) workers, where benzene is apparently the singular solvent and exposure for these workers for many years, seems to have tipped the balance insofar as implication of benzene exposure in causality of cancer (leukemia) and related blood dyscrasias. The five-fold excessive risk of total leukemia and ten-fold excess of myelomonocytic leukemias seems most impressive (Appendix A).

What is not clear is whether the earlier exposures were high, at least beyond the range of more recent controlled exposures and the current standard of 10 ppm. Such earlier higher exposures could have set the stage for induction of cancers which have appeared in the era of lower exposures.

It is not within our purview as a non-regulatory agency to critique the current process of standard setting for carcinogens, including in this instance, benzene. In cases of low level exposure, that is in environmental exposures for the general population for chemical carcinogens in water, air and food, one has the advantage of definitive toxicological data and a derived risk factor from dose-response relationships (animals) to compute tolerances. To our knowledge no such risk factor (at least for benzene as a water contaminant) prevails for benzene (Appendix A).

Of interest is the fact that benzene is ubiquitous; it occurs naturally in many foods, is formed in processed foods, and is present in air and water. A calculation from such sources to the general population reveals a total potential inadvertent exposure that approaches the exposure level of the new standard set at 1 ppm or 3.2 milligrams of benzene per cubic meter of air. Thus, if cancer risk is envisioned at low levels of exposure to benzene for certain occupations, then one has for consideration the inadvertent low level ubiquitous exposure to benzene by the general population which could require some perspective on all comparative risks and their significance in the interpretative and assessment process.

- while methodology reported has resulted in a positive determination of statistical significance, the study is negative by a different statistical approach. (An evaluation of alternate statistical methods will follow in a separate communication.)

I would point out that the possible increase in fetal resorptions at low dosages reported in the present study is not in accord with investigations conducted at the NYU Institute of Environmental Medicine. Here, dams were exposed by inhalation to benzene at 2,200, 300 and 100 ppm and no evidence of fetal resorption was found at any of the three dose levels, although skeletal deformities (missing sternebra) were found in the groups exposed to 2,200 and 300 ppm. (Greene, J.A., Laskin, S. and Leong, B.K.J.: Embryo and fetotoxicity of inhaled benzene in rats, presented at AIHA Conference, May 25, 1977).

Previous reports of teratogenicity and/or fetal resorption in rodents (Gofmekler, V.A. Effect in embryonic development of benzene and formaldehyde in inhalation treatments. Hyg. Sanit. 33:327-332, 1968. Watanabe, G-I, Yoshida, S., The teratogenic effect of benzene in pregnant mice. Act. Med. Biol. 19(4): 285-291, 1970.) involved different experimental conditions (exposure prior to impregnation or exposure by injection) from the protocols currently in use. These reports were cited in Laskin, S. and Goldstein, B.D.: Benzene toxicity, a critical evaluation. J. Tox. & Env. Health, Supplement 2, Dec. 1977, a pre-publication copy of which was made available to the Administrator of EPA, as well as to NIOSH, OSHA, NIEHS and other organizations in June, 1977, by this office.

Additional studies which are underway may serve to clarify some of the areas in question which are cited above; we shall advise you of further findings when available.

TOXIC SUBSTANCES CONTROL ACT

"Notification of (Possible) Substantial Risk Under Section 8(e)"

Chemical Substances Covered in this Notice: - Benzene

Summary of Adverse Effects and Description of Nature and Extent of Risk Involved

A Teratology Study in Rats exposed to benzene was conducted by Litton Bionetics, Inc., under sponsorship by the API Medicine and Biological Science Department. The report summary follows:

> "Pregnant female rats were exposed to air-borne benzene concentrations of 10 and 40 ppm during Days 6 through 15 of gestation. No effect, (behavior, appearance, body weight gain) was observed in the dams. No teratogenic effect was evident in the fetuses, however, there was an increase in the frequency of resorption of the fetuses from dams exposed to both 10 and 40 ppm of benzene."

The occurrence of fetal resorption is reported as an "adverse effect" under Section 8(e) of the Act since it possibly represents a reproductive disorder. However, the significance of this finding with respect to human exposure is unknown, and whether or not it represents "substantial risk" is in question for the following reasons:

- there was no observed decrease in the number of viable pups per litter in the benzene-exposed as compared to the control group,
- there were no observed nonviable fetuses in the benzene-exposed animals at the time of sacrifice of the dams,
- there were no exposure-related malformations in pups (no evidence of teratogenicity),
- the statistical significance of the apparently increased number of fetal resorptions in the exposed animals may be questioned, because
  - the laboratory's historical control data (not provided in the report) showed more early resorptions per number of live fetuses than were found in the controls of this study; thus, the limited number of controls tends to exaggerate differences between the control and test groups of the present study,

p.16, no. 5: Change "GF" to "FG"; "1970" to "1960"

p. 20, line 3: Add parenthesis: "(and thus only 6.8% of the cases)"

p. 20, line 24: Change "10-20ppm" to "100 ppm"; Following "100 ppm, add "or benzene-related hematologies below 10 to 20 ppm,"...

Errata Sheet for

Review of the Carcinogen Assessment

Group's Report on

POPULATION RISK TO AMBIENT BENZENE EXPOSURE

and the EPA External Review Draft on

BENZENE HEALTH EFFECTS ASSESSMENT

by

Tabershaw Occupational Medicine Associates

p. i, line 11: guess to guess

p. 1, line 11: about to over

p. 3, last line: delete "(ohio and elsewhere)"

p. 4, line 16: delete "unusually"

p. 4, line 21: concentrations to consentration

p. 4, line 22: delete "significant level"

p. 4, line 23: rewrite to read: "...million that is thought to represent the exposure of the Infante cohort."

p.5, line 11: ESIMATE TO ESTIMATE

p. 8, line 3: $K_3K_4N)AU$ to $K_3K_4N)/AU$

p. 8, line 6: X_a=VMT/UA to $X_2 \propto$ VMT/AU

p. 11, line 21: plosfilm to Pliofilm

p. 13, line 15: delete "no"

p. 14, line 16: Change "Within this figure..." to "Of the 112 surveys..."

p. 14, line 3 of footnote: areas to surveys

p. 15, line 12: Add after "assumption":"(thought not refutable)"

DBZ0014312

Errata Sheet for

A Supplementary Review of

HUMAN EXPOSURES TO ATMOSPHERIC BENZENE

by

Will M. Ollison, Ph.D.

p. 2, ¶ 2, line 12: "5,000-45,000 tons/year"

p. 4, ¶ 1, line 11: "of 32 ug of benzene"

p. 8, Table II, line 3: "0.05-0.28"