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Letter To The Editor

Benzene Toxicity: Studying a Subject to Death

Key words: benzene toxicity, leukemia, regulation, cancer, politics

In November 1983 the Collegium Ramazzini held an International Conference on Benzene, which had as its objective a scientific update on the toxicity associated with occupational exposure to benzene [*Am J Ind Med*, 1985]. A second meeting to discuss benzene risk assessment was held by the Collegium and hosted by the New York University Medical Center in March 1985. Subsequent to these meetings, in a preface to the publication of the proceedings of the 1983 Collegium meeting, Dr. Mehlman focused his comments on "the apparent need to develop information" and suggested that despite the considerable research already undertaken more information was needed before the scientific community could properly *urge* substantial reduction of worker exposure to benzene [Mehlman, 1985].

I suggest that *this* type of approach to the regulation of toxic substances can be characterized as "*Take no protective action until definitive evidence becomes available.*" Since "definitive evidence" itself is subject to varying interpretations and debate, we face situations in which appeals to scientific meticulousness and extensive repetition may serve to delay and abort the promulgation of health *standards* necessary to protect American workers and the general public.

The preface further declares that "to avoid all exposure [to benzene] until all questions relating to its toxicity are determined is neither likely nor practical." Unfortunately, that is hardly the problem. On the contrary, commonly very little or no protection against toxic substances is afforded until exhaustive research relating to toxicity has been performed. This prevailing practice results in continuing exposure to toxic materials while scientific *inquiry* raises more questions than it *answers*. "Studying a subject to death" unfortunately sometimes includes the deaths of those exposed.

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HOW MUCH INFORMATION IS NECESSARY?

The crux of the matter is how much information is necessary to trigger public health intervention. This may be quite different from how much we would like to know about the mechanisms of action for benzene toxicity because of scientific curiosity or for approaches to medical management. For example, aithough the determination of whether then is a "practical threshold dose" or a 'no effect" level [Mehlman, 1985] may be of scientific interest. it would seem to have little bearing on the issue of promulgating a standard to protect workers from needless exposure to benzene in light of currently available data demonstrating toxic effects below any *exposure* limit that could be required of *industry at* this time. Yet, argument for the prior establishment of a "no effect" level is the most recent in the series of reasons that have often been the basis for arguments that oppose OSHA promulgating a new benzene standard.

POINT/COUNTERPOINT: A PROLONGED OVERTURE

A brief review of past major arguments shows interplay between knowledge of benzene's toxicity and a *series* of arguments raised sequentially that obstructed rule-making. In the late 1960s and well into the 1970s there were some who argued that leukemia observed in workers exposed to benzene *could* not be due *to* benzene exposure because studies of benzene toxicity in experimental animals had not demonstrated the induction of cancer (Olson, 1977]. *Although* this argument was never convincing, it has been answered resoundingly. Several studies presented *at* the Collegium meeting demonstrate the induction of multiple site-specific cancers in experimental animals.

In 1976, NIOSH updated its criteria document *on* benzene and judged the clinical and epidemiologic evidence that benzene is leukemogenic to be conclusive. Although there is no evidence for safe exposure levels for carcinogens, because of feasibility limitations NIOSH recommended that no worker be exposed to benzene concentrations in excess of 1 ppm. Subsequently. OSHA proposed lowering the permissible exposure limit (PEL)to 1 ppm as an 8-hour time-weighted average. In response to this effort. industry witnesses raised several questions [Tabershaw and Lamm, 1977] about one of the major epidemiologic studies [Infante *et* al, 1977a] submitted to the OSHA record. These issues were responded to and clarified by NIOSH in 1977 [Infante et al, 1977b]. More recently, in an article entitled "Statistics and Ethics in Medical Research" [Altman, 1980], the reanalysis by industry witnesses of data from the MOSH benzene cohort was found to be inappropriate.

At the OSHA fact-finding hearing on the proposed benzene standard held in 1977. an additional argument was raised that an increased risk of leukemia in workers exposed to benzene was in conflict with 'the general experience of physicians practicing occupational medicine" [Olson. 1977]. This form of negative clinical impression. of course. is of highly limited utility for many reasons, including. its inability to demonstrate that a substance is not a carcinogen. Moreover, clinical observations among Italian occupational health physicians wen used more than a decade prior to the OSHA hearing to support evidence of benzene's carcinogenicity [Vigliani and Saita. 1964].

As a result of the 1977 OSHA fact-finding hearing, a final benzene standard allowing a PEL of 1 ppm was promulgated by the Secretary of Labor. This standard

was challenged in court and invalidated because a plurality of Supreme Court justices accepted the industry argument that OSHA had not determined whether a significant risk existed at the 10 ppm PEL. Some incorrectly conclude that the Court found no hazard associated with benzene exposure below 10 ppm. To the contrary, the Court did not question the validity of the Secretary of Labor's findings "on *the* basis of substantial evidence, that (1) *exposure* to benzene creates a risk of cancer, chromosomal damage, and a variety of non-malignant but potentially fatal blood disorders, even at the level of 1 ppm " or *that* "(2) no safe level of exposure has been shown. " [Industrial Union Department, AFL-CIO v American Petroleum Institute, 1980].

As a result of the Supreme Court decision. a quantitative leukemia risk assessment of benzene was undertaken by OSHA staff, submitted for peer review, and published *in* 1982 [White et al, 1982]. The results indicate that a "significant" risk of developing leukemia is associated with lifetime occupational exposure (45 years) to 10 ppm benzene averaged over an 8-hour day and that a significant reduction in that risk could be achieved by lowering the PEL to 1 ppm. In response, toxicologists empioyed by the petroleum industry have argued that the assessment overestimated the leukemia risk because the benzene exposures experienced by the cohorts used for the assessments were underestimated [Van Raalte et al, 1984]. This does not appear to be the case based on the best available data [Infante et al, 1984].

More recently, Mehlman [1985] stated that the exposure data used in the risk assessment are "generally believed to be in error." This assertion was unsupported. *Although* representatives of industry or their consultants have challenged the exposure assessment, relatively few. if any, independent scientists have done so. The assessment assumed that 8-hour time-weighted average exposures to the NIOSH cohort ranged between 10 and 150 ppm depending on the calendar time period that the benzene exposures occurred. The assumption seems conservative *since* it, in fact, overestimates average exposure based on available data for *the* NIOSH cohort. Reasonable assumptions also were made for the Dow Chemical Company cohort, which experienced *average* exposures of about 5 ppm [Infante ami white, 1985].

RISK ASSESSMENTS

In April 1984 a draft copy of the new OSHA-proposed benzene standard with its preamble was submitted informally by OSHA to the Office *of* Management and Budget (OMB) for review. OMB requested that OSHA have a benzene risk assessment performed by a source external to the Agency. As a result, OSHA requested Dr. Kenny Crump to perform an independent exposure assessment of the NIOSH cohort and a risk assessment. This risk assessment was based *on* data tapes of the benzene cohorts *studied* by NIOSH and the Dow Chemical Company cohort. and on the report of a *Chemical* Manufacturers Associati'on(CMA) cohort study of benzene exposed workers. Using a cumulative dose and relative risk model (similar to that used by White et al [1982] and data from the three studies just mentioned, *Crump* and Allen [1984] *estimated that* 40 years of occupational exposure to 10 ppm benzene would result in 88 (95% confidence interval = 34–174) excess leukemia deaths per 1,000 workers. This estimate is very similar to the risks of 44–152 per 1,000 projected by White et ai [1982] or to the risks of 9.5–170 per 1,000 estimated by extrapolation of the IARC assessment [IARC, 19821 to benzene levels of 10 ppm [Infante and White, 1985]. For excess leukemia risk associated with lifetime occupational exposure

to 1 ppm benzene. Crump and Allen [1984] estimated 9.5 per 1,000 based on 40 years exposure while White *et al* had estimated 5–14 per 1,000 based on 45 years exposure. The results of these risk assessments support the assumptions and estimates of leukemia risk made by White et al in 1982. Moreover, the benzene risk assessments conducted independently [White et al, 1982; LARC, 1982; Crump and Men. 1984] lead to estimated risks of death from occupational leukemia that have been characterized by OSHA as significant [OSHA, 1983] as a result of average benzene exposures to the current PEL of 10 ppm or to the OSHA *draft* proposal of 1 ppm.

Subsequent to the review of these benzene risk assessments, OMB asked the Agency to have Crump and Allen perform an additional risk assessment based solely on the CMA study of benzene *exposed* workers. This was done. The results indicated an even higher estimate of 121 excess leukemia deaths per 1,000 workers *exposed* for 40 years to benzene levels of 10 ppm and 13 per 1,000 for those exposed to 1 ppm for 40 years [Crump and Allen, 1984].

REPRISE

As the above issues seem to have been exhaustively explored, there is now a new demand for scientific certainty [Mehlman, 1985]. It calls for information showing that bone marrow lesions do not occur below a certain level of benzene exposure in order to establish a "no effect level" for such exposure. In response to requests by OSHA [1985], a study addressing low-level benzene exposure has recently been released by the Chemical Industry Institute of Toxicology [Neal, 1985; Erexson et al, 1986]. The results demonstrate that a single 6-hour exposure to 1 ppm benzene in rats resulted in a significant increase in micronuclei in bone marrow polychromatic erythrocytes and sister chromatid exchanges in peripheral blood lymphocytes. These findings are both qualitatively and quantitatively consistent with other recent experimental findings [Baarston et al, 1984; Rosen et al, 1984; Tice et al, 1982; Gad-el-Karim et al, 1984] and epidemiologic study results [Picciano, 1980; Sarto et al, 1985). While one may argue about the existence of a "no effect level" for benzene-induced bone marrow lesions or their necessary relevance to the long-term carcinogenicity of the chemical, such a level is clearly lower than the 1 ppm permissible exposure limit that OSHA has recommended in its widely circulated *draft* proposal. The proposal was transmitted formally to OMB for review in April 1985.

Every day the scientific and political debate over benzene continues to delay necessary mandated control of exposure, workers are subjected to the risk of unnecessary disease and suffering, and costs to society as a whole are increasing. For the most part, these costs, to date, have not been paid by industry. In "An Interim Report to Congress on Occupational Diseases" [U.S. Department of Labor, 1980], for example, the Secretary of Labor concluded that 86% of the income support for *those* severly disabled from an occupational disease was provided by public programs, *ie.* 53% from social security, 17% from veterans benefits, and 16% from welfare, whereas only 5% was paid by workers' compensation, which is paid by industry as part of its cost of production. The increase in successful plaintiff toxic tort liability suits has raised questions whether the (inexpensive) workers' compensation system will suffice to shield industry from these liabilities [Kittrell, 1985).

Through passage of *the* Occupational Safety and Health Act of 1970, Congress clearly intended to control and eliminate, as far as possible, Occupational disease and death. Congress also intended to place the economic cost of occupational illness

squarely on the shoulders of the responsible party — industry. However, because of strong lobbying pressures and, in considerable part, the indecisiveness of the scientific community, the promises to workers that Congress made in the OSHA Act of 1970 are still unfulfilled.

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Author's Response

Benzene: Evaluation of Control Measures not Competitive With Basic Research Requirements

Dr. Infante has characterized my statement in the Ramazzini Proceedings on benzene [Mehlman, 1985] that "more research is needed before the scientific community can properly urge substantial reduction of worker exposure to benzene" as "take no protective action until definitive evidence becomes available." The *two* quotations are not even approximately equivalent.

The reduction of exposures to a safe level is a well-established principle in the fields of occupational and environmental health. Many scientists believe that a level of 10 ppm is adequate *to* reduce the incidence of leukemia in workers occupationally exposed to *benzene* to a level undetectable in the human population. Recent proposals to lower the standard further to 1 ppm are based on a concept of preventive prudence.

I have no quarrel with Dr. Infante's conclusion that there exists evidence in his study for a qualitative relationship between benzene exposure and leukemia. However, since Dr. Infante has also stated that the underlying scientific basis for risk assessment is less than *certain* [White *et* al. 1982], further scientific *inquiry* into the mechanism of action of benzene may increase our knowledge not only for application to risk assessment methodology but also for understanding treatment and cures for the disease. Scientific inquiry may indeed raise more questions than it answers. but that is the nature of science.

As Goldstein and Snyder [1982] have noted, 'Considerable funds have been spent on the regulatory process and only a relatively small amount on the scientific efforts which could resolve the problem." Surely regulatory policy should be based on a solid foundation of valid information.

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