NIOSH

Testimony to DOL

TESTIMONY OF THE
NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH
ON
THE OCCUPATIONAL SAFETY AND HEALTH ADMINISTRATION PROPOSED RULE:
OCCUPATIONAL EXPOSURE TO BENZENE

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J. Donald Millar, M.D.
Assistant Surgeon General
Director
National Institute for Occupational Safety and Health

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The testimony reviewed the history of benzene (71432) exposure and the development of recommended exposure limits. Data were reviewed on pharmacokinetics, cytotoxicity, long and short term exposures, and skin absorption of benzene. Benzene or its metabolites have been shown to remain in the body for a long period of time following inhalation exposure. Studies in mice revealed exposure related increases in the frequency of sister chromatid exchanges and micronuclei at all exposure concentrations. Some epidemiological standards relating to the benzene standard were cited, including data from the Goodyear rubber hydrochloride cohort which implied a relation between 1 part per million (ppm) benzene exposure for 40 years and incidence of leukemia. Other studies linked benzene to multiple myeloma and myelofibrosis. NIOSH recommended that the Permissible Exposure Limit for benzene be reduced to 0.1ppm as an 8 hour time weighted average and that there be a limit on short term exposures of 1.0ppm for any 15 minute period. These recommendations were made to protect against inhalation of benzene and did not relate to skin absorption. Reports indicated that significant benzene absorption can result among workers exposed to solvents containing about 0.5 percent benzene. It was recommended that steps be taken to eliminate this route of exposure. The use of pressure demand supplied air respirators with an auxiliary self contained breathing apparatus or a pressure demand apparatus was recommended.

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NIOSH staff presenting for Dr. Millar:

Richard A. Lemen Director	Division of Standards Development and Technology Transfer (DSDTT)
Lawrence F. Mazzuckelli Science Advisor to the Director, DSDTT	DSDTT
Robert A. Rinsky Epidemiologist	Division of Surveillance, Hazard Evaluations and Field Studies (DSHEFS), Hazard Evaluations and Technical Assistance Branch
Richard W. Hornung Chief	DSHEFS, Surveillance Branch, Statistical Services Section
Richard W. Hartle Industrial Hygienist	DSHEFS, Hazard Evaluations and Technical Assistance Branch
William E. Halperin Chief	DSHEFS, Industrywide Studies Branch
Allan S. Susten Research Biologist	Division of Biomedical and Behavioral Sciences, Experimental Toxicology Branch
Nancy J. Bollinger Chief	Division of Safety Research, Certification Branch

March 20, 1986

I am Richard A. Lemen, Director of the Division of Standards Development and Technology Transfer (DSDTT) of the National Institute for Occupational Safety and Health (NIOSH). With me today are senior staff from NIOSH research divisions, each of whom has expertise in various aspects of occupational exposure to benzene. Our purpose for appearing at this hearing is to support the Occupational Safety and Health Administration's (OSHA) efforts to promulgate a new standard for benzene.

NIOSH made its first recommendation to OSHA for a benzene standard in the 1974 criteria document Criteria for a Recommended Standard....Occupational Exposure to Benzene. In that document, NIOSH stated that ". . . the possibility that benzene can induce leukemia cannot be dismissed." We further stated that ". . . limited comparisons made for worker populations in Italy and France indicated the distinct possibility that benzene may be carcinogenic."

By 1976, more definitive data regarding the carcinogenicity of benzene were available, prompting NIOSH to revise its 1974 recommendation. A revised NIOSH criteria document was transmitted to OSHA in 1976 which recommended that occupational exposure to benzene be controlled so that its concentration in air does not exceed 1 ppm as determined in a sample collected for 2 hours. NIOSH also presented this same recommendation in support of OSHA's attempt to reduce the permissible exposure limit (PEL) for benzene at its 1977 public hearing.

NIOSH supports OSHA in its proposed rulemaking to promulgate a new standard for benzene. The data on benzene leave no doubt regarding the human carcinogenic potential of this chemical. NIOSH recommends that occupational exposure to benzene be controlled so that no worker is exposed to more than 0.1 ppm as an 8-hour time weighted average (TWA) and that short-term exposure be controlled so as not to exceed 1 ppm as determined in any 15-minute sampling period. Furthermore, since there is the potential for significant amounts of benzene to enter a worker's body by dermal absorption, NIOSH urges producers to continue to make every effort possible to further reduce the benzene contamination of their solvents and other products. It is also necessary for workers to use care when handling benzene and benzene-contaminated solvents, in particular during tire-building operations. We recognize that wearing some types of impermeable gloves may make certain jobs difficult to perform; therefore, we also urge that improved glove design be made a priority for manufacturers of chemical protective clothing.

In support of NIOSH's position, data are described on pharmacokinetics, evidence of cytotoxicity, results from long-term exposures, results from short-term exposures, and the role of skin absorption to the overall exposure to benzene.

Parke and Williams [1953] reported that 2 days after gastric intubation of C^{14}-labelled benzene to rabbits, 80% of the radioactivity could be accounted for in expired air or as urinary metabolites; thus, as much as 20% of the initial dose may have remained in the body either as benzene or its metabolites.

Berlin [1985] has presented data that demonstrate the slow removal of benzene from the body; in this data he described the results of a study of human volunteers experimentally exposed to benzene by inhalation. The subjects were exposed to 4 ppm or 8 ppm for 6 hours per day for 5 days. In order to determine the kinetics of removal of benzene, Berlin determined the concentration of benzene in expired air. Berlin concluded that the kinetics of benzene removal appear to involve distribution and removal from at least two body compartments. Removal from the first compartment was relatively rapid, having a half time of about 2.5 hours; however, removal from the second compartment was much slower, having a half time of about 24 hours.

The implication of these two sets of data is clear; benzene or some of its metabolites persist in the body following inhalation exposure. Over a workweek, a worker exposed to benzene may not be able to eliminate all of the benzene or its metabolites absorbed and produced as a consequence of inhalation or skin absorption during the workshift. Thus, NIOSH concludes that once benzene enters the body, it is removed slowly and may persist either unchanged or as metabolites and that, therefore, cumulative dose is a major consideration in arriving at a recommended exposure limit (REL).

In June of 1985 the Chemical Industry Institute of Toxicology (CIIT) provided a copy of a manuscript to OSHA that described the cytogenetic effects of benzene exposure on rats and mice.

Results obtained from the CIIT mouse studies revealed exposure-related increases in the frequency of sister chromatid exchanges (SCE's) and micronuclei at all exposure concentrations. In rats exposed to benzene at 3 ppm, 10 ppm, and 30 ppm, the frequency of SCE's was also exposure related and statistically significant when compared to controls. The results obtained from rats exposed at 1 ppm were described by the investigators as having borderline significance since they were statistically significant as determined by the Student's t-test but not statistically significant as determined by the Mann-Whitney U test.

The CIIT results are significant from several points of view. First, they demonstrate the cytotoxicity of benzene, an event that may be associated with the induction of cancer. Second, the results obtained at 3 ppm are well below the existing OSHA standard. Third, the effect was observed after only a single exposure to benzene in air, as compared to the day-in and day-out exposure for workers.

In pointing out that these results need confirmation by results obtained from humans, the CIIT investigators state:

> "The present study accurately defines the shape of the dose response curves for these cytogenetic endpoints and indicates that a 6-hour exposure to concentrations of approximately 1 ppm BZ (benzene) and above can induce measurable cytogenetic effects in rodents."

NIOSH has recently received a final grant report. The results described in this report have bearing on the issue of a PEL for benzene, since the effects described below were observed following exposure to benzene concentrations at and below the current OSHA PEL of 10 ppm. In that study, mice were exposed in utero to benzene at 5 ppm, 10 ppm, and 20 ppm for 6 hours per day for 10 consecutive days on days 6 through 18 of gestation. In summary, the investigators reported no evidence of maternal toxicity as a result of benzene exposure, but several indicators of hematopoietic toxicity were observed among fetal animals exposed at 5 ppm, 10 ppm, and 20 ppm. In addition, some of the indicators of toxicity persisted in 2-day-old neonates. Furthermore, in adult male mice re-exposed to benzene at 10 ppm 10 weeks after birth, a significant depression of bone marrow Colony Forming Unit-Erythroid was observed.

There are several epidemiologic studies that have bearing on the issue of a new benzene standard. The NIOSH update of the Goodyear rubber hydrochloride cohort clearly implies that even for 1 ppm benzene exposure for 40 years, there is a probability of developing leukemia. This is supported by the estimates of risk arising from the modeling of the data obtained for this cohort by Rinsky et al. The results of the modeling conducted by Rinsky et al. [1985] "indicate that an exponential decrease in risk of death from leukemia would be achieved by a lowering of occupational exposure to benzene. As discussed in our comments, the results of this modeling are in close agreement with the risk estimates generated by Crump and Allen for OSHA.

The Crump and Allen [1985] risk assessment examined not only the Rinsky cohort, but also the cohorts of Wong and OTT. In this update, Dow reports the occurrence of a death from multiple myeloma as well as a death from myelofibrosis; both conditions have been observed in excess in other studies of benzene-exposed populations. OSHA has determined that at 1 ppm as an 8-hour TWA there will be 5-16 excess deaths per 1,000 exposed workers from leukemia due to exposure to benzene.

NIOSH recognizes that there are a number of assumptions and caveats inherent in the modeling performed by Rinsky et al. [1985]. Among these are the fact that the environmental data used are incomplete; therefore, where gaps in measurement existed, estimates were constructed. Furthermore, the data that did exist probably did not account for exposures caused by any spills or leaks that may have occurred. It is also important that the potential for skin absorption was not examined. It is also possible that the workers in the pliofilm department were exposed to benzene in other departments where they may have worked.

Despite these caveats, (1) there is a positive exposure-related increase in leukemia among the workers described in this study and (2) the estimates described by this model indicated that even at a benzene exposure of less than 1 ppm for 40 years, there is a risk of developing leukemia. In a recent update of the OTT study, two additional leukemia deaths have occurred, bringing the total now to five, all of which were of the myelogenous cell type, while only 0.9 was expected. An important fact about these deaths is that four of the five had cumulative exposures ranging from only 1.5 to 54 ppm years.

The historical prospective study by Wong [1983] reviewed by OSHA in the proposed rule is also important in deriving an exposure limit for benzene. In his study, Wong [1983] found that chemical plant workers intermittently exposed to peak benzene concentrations of less than 25 ppm had a relative risk of about 3.4 for death from lymphatic and hematopoietic cancer. This study was also limited by the lack of detailed historical exposure data, but as Wong [1983] described, this problem was partially dealt with by classifying benzene-exposed workers into groups having uniform tasks for which current benzene exposures could be determined.

There are several other aspects of the Wong [1983] study that are notable. First, the job of each member of the exposed cohort in this study was characterized by an 8-hour TWA as well as a peak benzene exposure. Second, a statistically significant dose-response relationship between leukemia as well as all lymphopoietic cancer and cumulative exposure in ppm · months was found.

Recognizing that the workers examined in this study may have had exposures to other chemicals in addition to benzene, Wong [1983] compared the results of the benzene-exposed workers to those obtained from workers in other areas of the plant where benzene was not present. Such an approach should, in the opinion of NIOSH, reduce the potential for confounding of results.

In summary, the pharmacokinetic data, the evidence of cytotoxicity, and the results of recent epidemiologic studies of workers exposed to benzene by inhalation provide a consistent basis upon which to predicate a recommendation for a new PEL for benzene.

While the OSHA proposed standard of 1 ppm does in fact "substantially reduce the risk of leukemia," NIOSH believes that the 5-16 deaths per 1,000 workers that would be expected based on the OSHA estimate is far greater than warranted. Therefore, NIOSH recommends that the PEL for benzene be reduced to 0.1 ppm as an 8-hour TWA and that there be a limit on short-term exposures of 1.0 ppm as determined in any 15-minute sampling period.

It is important to understand that the basis for the recommendation of 0.1 ppm is founded upon the data described above. The single exposures described in the CIIT [1985] study plays a significant role. The findings obtained from these more traditional studies are supported by the results of the modeling conducted by Rinsky et al. [1985] and Crump and Allen [1985].

The pharmacokinetic data, the data reported by CIIT, and the data reported by Wong [1983] also provide a basis for the recommendation for a limit on short-term exposures. The pharmacokinetic data demonstrate the persistence of benzene in the body following its inhalation. The CIIT animal data demonstrate the ability of single benzene exposures of at least 3 ppm and perhaps as low as 1 ppm to induce cytotoxicity, and the study by Wong [1983] demonstrates the ability of intermittent exposures to peak benzene concentrations of 25 ppm and less to cause leukemia in humans.

The recommendation presented by NIOSH and the proposed OSHA standard are designed to protect against the effects of inhaled benzene; they do not account for the possibility of skin absorption.

As OSHA has recounted in the preamble to the proposed rule, the data of Susten et al. [1985] clearly demonstrate that significant benzene absorption can occur among workers who use solvents that contain about 0.5% benzene. As OSHA stated in the preamble:

> "NIOSH calculated that a worker building 150 tires per day could absorb approximately 6 mg of benzene daily through intact skin . . . . The 6 mg of benzene absorbed through the skin may be compared to an estimated 14 mg of benzene that would result from inhalation of 1 ppm over an 8-hour day."

Thus, under these conditions, a worker may absorb about 20 mg of benzene over an 8-hour shift. It should be noted that this study was conducted using a petroleum distillate that contained 0.5% benzene. If a worker is exposed to solvents containing a greater percentage of benzene, then the total amount of benzene absorbed would be greater than the 6 mg reported by Susten et al. [1985]. Therefore, it is possible that any benefit derived from an airborne exposure limit such as that described by either NIOSH or OSHA will not provide full protection if workers are not protected from potential skin absorption. The NIOSH study of percutaneous benzene absorption demonstrates the necessity for eliminating this route of exposure. If a worker has the potential for skin absorption, it could render any proposed airborne exposure limit ineffective. NIOSH concludes that when there is the potential for skin absorption, personal protective equipment and clothing that is impermeable to benzene must be provided to ensure the adequacy of the standard.

Under the current OSHA standard, NIOSH recognizes that a properly conducted program of medical surveillance may enhance worker protection. Such a program should be designed so that it accomplishes the goal of identifying exposed populations and can give early indications of potential disease, thereby allowing intervention. We do suggest that if workers are exposed to benzene at greater than the proposed standard without benefit of a STEL or when significant skin contact has occurred, determination of the formed elements in the blood may be a useful technique in preventing disease. Also we suggest that determination of urinary phenol is valuable in deterring extent of exposure in individuals with accidental or cutaneous exposure.

Finally, since benzene is a carcinogen, NIOSH currently recommends only pressure demand supplied-air respirators with an auxiliary self-contained breathing apparatus (SCBA) or a pressure demand SCBA. If OSHA, however, decides to allow the use of the respirators described in their proposal, we urge them to reexamine their published workplace protection factors in light of our previously submitted data on powered air purifying respirators.

Before responding to specific questions germane to the scientific issues surrounding NIOSH's recommendations, I would like to address certain issues that have recently arisen.

First, I want to make the Institute's position on the uses and limitations of quantitative risk assessment perfectly clear. This position was clearly described in NIOSH's comments on the OSHA advanced notice of proposed rulemaking for 29 CFR 1990, Identification, Classification and Regulation of Potential Occupational Carcinogens. As we stated:

> Because our understanding of the mechanism of carcinogenicity is incomplete, our use of mathematical models to predict its outcome must be employed with extreme caution. To select a model or models from among the many choices and to have them incorporated into Administration policy will not resolve those issues.
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> Since there is no single model that will satisfy all the requirements for performing risk assessments, NIOSH believes that any attempt to mandate use of specific models or techniques of risk assessment for regulatory purposes will only prolong the controversy and will detract from the goal of public health protection.
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> In order to further define the role of risk assessment as a method for recommending standards for worker protection, a review of the NIOSH approach that addresses the complexities of these techniques follows.
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> Historically, NIOSH recommendations for workplace standards employed a variety of methods to establish conditions that NIOSH believed would best prevent adverse effects. In most cases, a safety factor was applied to further ensure that even the most susceptible individual would realize a degree of safety. When addressing tissues of carcinogenicity, NIOSH typically assumed that no exposure could be considered safe. This assumption is not unique to NIOSH. The 1958 Delaney Amendment imposed a zero tolerance for carcinogenic food additives. This position, which continues to guide NIOSH, was supported in 1970 by the Ad Hoc Committee Report to the Surgeon General:1
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> > "The principle of a zero tolerance for carcinogenic exposure should be retained in all areas of legislation presently covered by it and should be extended to cover other exposures as well. Only...where contamination of an environmental source by a carcinogen has been proved to be unavoidable should exception be made (and then) only after the most extraordinary justification is presented...Periodic review...should be made mandatory."
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> On July 2, 1980, the Supreme Court stated that OSHA had exceeded its statutory authority by failing to show that the benzene standard was "reasonable, necessary or appropriate." The Court ruled that Section 3(8) of the Occupational Safety and Health Act required OSHA to produce "substantial evidence" which demonstrates that the regulated substance

poses a significant risk of material impairment of health and that the new standard would reduce that risk. The Court stated, however, that "substantial evidence" does not necessarily mean scientific certainty. The Court cited Section 6(b)5 of the Act to stress that regulation cannot attempt to produce a risk-free workplace by regulating "insignificant" or "acceptable" risks, but it left to OSHA the determination of what "significant" or "unacceptable" means.

The District of Columbia Circuit Court of Appeals decision on August 15, 1980, upheld the lead standard, in which an acceptable risk was estimated for a material that is not known to be a carcinogen. These two decisions provided the impetus for the inclusion of a quantitative risk assessment effort in the standards recommending program of NIOSH.

Other federal agencies have had experience with quantitative risk assessment. Many of those agencies provided testimony before the House of Representatives Subcommittee on Science, Research and Technology hearings on "How Risk Comparison Can Become a Valuable Instrument of the U.S. Regulatory Policy." The prevailing opinion is that quantitative risk assessment can be useful in establishing priorities and in estimating the anticipated reduction in risk as a result of regulatory actions. However, the testimony indicates that quantitative risk assessment should not be used as the sole basis for the decision whether or not to promulgate regulations because of the uncertainties inherent in the process. Our analysis of the utility of quantitative risk assessment agrees with this.

Over the last several months, there has been much discussion between NIOSH and the American Petroleum Institute (API) concerning the release of certain records maintained by NIOSH. These records were used by NIOSH in our ongoing epidemiologic investigation of workers exposed to benzene in two Goodyear pliofilm factories in Ohio. Among other things, API's request sought the personnel and medical records for approximately 1,700 workers, entailing approximately 19,000 documents.

In testimony submitted to OSHA, the representative of API states in part:

> "No cohort of benzene-exposed workers has been studied as intensively or has as much documentation about exposure. For these and other reasons, the NIOSH study is a critical foundation of virtually every risk assessment that has been prepared for benzene...."

The API representative then recounted API's efforts to acquire the copies of the NIOSH records, originally obtained from Goodyear, relating to this study.

I am assured by the Director of NIOSH, Dr. Millar, that upon receipt of the Freedom of Information Act request from API dated August 29, 1985, NIOSH immediately began to respond while seeking to fulfill its legal and ethical duties to protect the privacy of living persons in this study cohort. I am certain API is well aware of the care which must be taken to safeguard against the inadvertent release of information which may violate the privacy of individuals.

Because we knew from past experience with such requests that preparation for releasing such records is an arduous, time-consuming process requiring great care, NIOSH suggested that the API might more speedily satisfy their desire for these records if it made a request directly to the Goodyear.

Nevertheless, we proceeded to comply with the API's request. On September 30, 1985, an API representative visited NIOSH to help narrow the scope of the request. Beginning October 29, 1985, NIOSH has to date provided API with 11,155 pages of the requested information. NIOSH anticipates that all of the documents will be provided to API by the end of April.

The bulk of the records now requested by API have been in NIOSH's possession since 1977, yet API waited until very recently to submit its request. NIOSH has worked diligently to respond expeditiously to this complex matter which has consumed, and continues to consume, an inordinate amount of staff time and energy. NIOSH is devoting significant staff and other resources, including evenings and weekends worked by its staff, to respond to this request while protecting the privacy of individual workers.

Today we are here to meet our statutory public health obligations in support of OSHA's attempt to promulgate a much-needed new benzene standard. We have presented OSHA and the public with the scientific basis for our recommendation. We will be happy to respond to questioning intended to clarify and explore the basis for a recommendation.