



Letter to the Editor

Assessment of Leukemia Mortality Associated with Occupational Exposure to Benzene^{1,2}

Peter F. Infante,³ Mary C. White,⁴ and Kenneth C. Chu⁵

We appreciate the opportunity to respond to the interesting comments concerning the benzene risk assessment. (White *et al.* Risk Analysis, 2:195-203, 1982) Dr. Van Raalte of Shell and Drs. Grasso and Imine of British Petroleum have raised issue with the exposure levels and relative risks observed in the various studies of benzene exposed workers. Dr. Gaffey of Monsanto has raised concern about the concept of assuming constant relative risk, and Dr. Chandler of Washington, D.C. is concerned about the justification for selecting the linear model for determining a dose response relationship for benzene and leukemia.

We have divided our response into four separate areas, namely: (1) estimated benzene exposure levels experienced by the study cohorts selected for the risk assessment; (2) results of studies not selected for the risk assessment that were mentioned by the commentators; (3) the concept of relative risk used in the risk assessment; and (4) model selection.

(1) Estimated benzene exposure for the study cohorts

In regard to the Infante *et al.*⁽¹⁾ and Rinsky *et al.*⁽²⁾ study of Pliofilm workers, the authors concluded that, based upon a review of available data, benzene exposures to the cohort were generally within the limits recommended at the time [i.e., the 8-hour time-weighted-average (TWA) exposures ranged between 10 ppm and 100 ppm]. In their letter, Van Raalte *et al.* questioned this assessment. Thus,

we shall summarize benzene exposure for the National Institute for Occupational Safety and Health (NIOSH) cohort as published in 1981 by Rinsky *et al.*⁽²⁾

For one Pliofilm manufacturing facility, information on benzene concentrations between 1946 and 1976 was available from a series of reports by the Industrial Commission of Ohio, the Ohio Department of Health, the company, the University of North Carolina and a NIOSH survey. According to NIOSH investigators, most of the data in these reports appears to have been derived from area samples measured with detector tubes over a sampling period ranging from 2-3 minutes. The company surveys of 1973-75 and the NIOSH walk through survey conducted in 1976, measured concentrations in personal breathing zone air. While the short-term area samples measured over the years indicated that some benzene levels were above 100 ppm, most were below 100 ppm. These latter data points seem to have been ignored by Van Raalte *et al.*

In addition, the area samples are often measured in an effort to determine point source emissions and may exaggerate actual worker exposure. Furthermore, exposure determined from short-term area samples corresponds to relatively lower personal 8-hour average concentrations because workers are mobile and take breaks away from manufacturing

The Rinsky *et al.*⁽²⁾ report cites documents indicating that workers were required to wear respirators when exposed (even momentarily, to levels considered above those recommended at the time. These levels ranged from a maximum allowable concentration of 100 ppm in 1941 to an 8-hour TWA of 10 ppm from 1969 to the present." One of the several documents does indicate that respirators were not

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³Office of Standards Review, OSHA DOL, Washington, D.C.

⁴Brookline, Massachusetts.

⁵Gaithersburg, Maryland.

used. Overall, the evidence indicates that respirators generally were used when exposures were over the recommended limit. Van Raalte *et al.* mentioned only the one report which indicated this was not the case.

Van Raalte *et al.* further mentioned that the White *et al.* assumption that exposures were 50% higher (i.e., 150 ppm, between 1937–40, as compared to 1941, when the allowable concentration was 100 ppm) was "based on poor data." The 100 ppm level was set in 1941. We thought it was a reasonable assumption based on the data available for the 1940's. Better data are not available.

We believe that the actual exposure levels to individual workmen comprising the NIOSH study^(1,2) will never be known precisely. However, much effort has been made to characterize their exposure, resulting in reasonable estimates that are better in quality and in detail than for most historical prospective occupational mortality studies. Only studies of asbestos and arsenic exposed workers have provided better exposure data.

Limited information on exposure levels was available from the second location. One report from the Ohio Department of Health dated 1948 indicated there were "a few conditions wherein an employee might be subjected to an extremely high concentration of benzol," but that employees were "well aware of the toxicity of benzol and have been instructed to, and do, wear respirators when they are required to enter" these areas. Environmental data from this location believed to have been derived around 1957, when the recommended 8-hour TWA was 25 ppm, indicate atmospheric levels ranging between zero and 100 ppm based on short-term area samples. Since respirators were used at this facility and management was aware of the toxicity of benzene, the assessment that personal exposure to benzene at this facility as well as at the earlier mentioned plant was generally within the recommended limits at the time of exposure seems reasonable. Upon review of the Rinsky *et al.* report, it seems that our assumption in fact overestimates average exposure to the cohort.

Dr. Irvine argues that a "group of 404 workers were exposed to up to 20 ppm levels of benzene, and yet by the 1975 follow-up date no cases of leukemia had been observed," hence the extrapolations of the risk assessment do not apply. He attributes this statement to Harris and Thorpe on behalf of the American Petroleum Institute. This statement is inconsistent with information presented and discussed 6 years ago.⁽³⁾ Prior to selection of the cohort, a thorough evaluation of industrial hygiene data available plus

the NIOSH walk through survey determined areas in which benzene exposure occurred. As stated in 1977⁽³⁾: "Data previously requested of industry, but never supplied, were introduced at the U.S. Department of Labor hearings on a proposed benzene standard, which alleged that exposure to benzene existed in an area not selected for study. No details (i.e., sampling location, duration, analytical procedure, or definition of department) were given to permit a valid interpretation of the only data points (0.11.8 and 20 ppm) in that report." Thus, it is difficult to understand how 3 data points of unknown origin can be extrapolated to the statement that 404 workers exposed to benzene levels up to 20 ppm have not developed leukemia.

When commenting on the study by Ott *et al.*⁽⁴⁾ used in the risk assessment, Van Raalte *et al.* cite the highest single exposure peak (937 ppm) measured in the study, and state that they are not told how frequent such exposure occurs. It is clear from the Ott *et al.*⁽⁴⁾ report that the 937 ppm level was the highest and was a rare occurrence. Van Raalte *et al.* cite this single data point to support their opinion that high concentrations of benzene are crucial in determining leukemia and thus mathematical modeling based on a cumulative dose concept misses "important and relevant information." The average benzene exposure to workmen in this production area was estimated to have been 35 ppm.

None of the three leukemia cases (versus 0.8 expected, RR = 3.75) worked in the area of the plant where the highest exposure existed. To the contrary, two of the individuals who died from leukemia worked in areas characterized as low benzene exposure 2–9 ppm TWA, while the third worked in an area characterized as very low (i.e., TWA exposures less than 2 ppm).

Further assessment of atmospheric benzene levels in the three production areas from which workers were selected for study by Ott *et al.* indicated that exposures to the cohort had always been fairly low, reflecting the use of closed continuous systems. In production area 1, estimated TWA benzene exposures based mostly on breathing zone samples ranged between 0.1 and 6.2 ppm for the years 1944 to 1973. In production area 2, TWAs ranged between 0.3 and 14.7 ppm between 1953 and 1972 while in production area 3, the averages ranged between 4 and 35.5 ppm for the years 1952–1974. On the basis of data presented in the Ott *et al.* study, the average exposure for the entire cohort was about 5 ppm. Thus, in the absence of any mathematical modelling

for this study, one could be left with the impression that fairly low average exposure to benzene results in the development of leukemia.

(2) Results of studies not selected for risk assessment

Dr. Irvine comments that one can produce negative studies demonstrating that the projected risk values from White *et al.* "do not hold." He sites for his example the study of petroleum refinery workers by Thorpe. The International Agency for Research on Cancer (IARC)⁽⁵⁾ reviewed the Thorpe study and in addition to its criticisms of low power and limited methodology stated "the study suffers from problems of ascertainment, specificity and validity of diagnosis, and the 'health worker effect' in the calculation of SMRs" (Standardized Mortality Ratios). More detailed discussions of the limitations of the methodology used by Thorpe have been published.⁷

Dr. Irvine also mentions that the extrapolations of the risk assessment do not apply to a small group of individuals who first worked in a benzene-exposed department between 1950-1959. The data do not support his contention. For individuals who were first exposed between 1950-1959 there were two deaths from myelogenous leukemia when the expected deaths based on total leukemia was 0.46. For one of these deaths due to acute myelogenous leukemia (AML), however, the hematologist who diagnosed numerous leukemia victims who worked at the plant noted that the discharge diagnosis was changed from AML to aplastic anemia so the widow would receive \$10,000 in industrial compensation. If the death was from leukemia the widow would have been entitled to no compensation.⁽⁸⁾ Although this death was not included as attributable to leukemia in the NIOSH study (as appropriate), there is justification for including it in a maximal risk estimate which would result in 2 leukemia deaths versus 0.46 expected, for a relative risk of 4.0 based on total leukemia mortality, or a higher relative risk based on myelogenous leukemia mortality only. The numbers upon which the observation is based are small, but nevertheless they are contradictory to Dr. Irvine's interpretation of the results for these workers.

Van Raalte *et al.* state that we did not include the Aksoy and Vigliani studies in our risk assessment and that these studies indicate benzene exposure has to be substantial for leukemia to occur. In our paper we previously stated they were not included because we felt the benzene exposure information from the studies was not as detailed as that in the

Infante-Rinsky and Ott *et al.* studies and that the estimates of risk were uncertain. However, we recognize that Aksoy, Vigliani, and their co-workers have made tremendous contributions in their pioneering work addressing the clinical manifestations of an entire spectrum of blood abnormalities associated with benzene exposure. Workers described in the Vigliani and Aksoy reports were exposed to high levels of benzene resulting in the occurrence of over 200 cases of leukemia. However, Vigliani and Aksoy did not have data upon which to assess the carcinogenicity of benzene among workers exposed to low levels.

(3) The concept of relative risk used in the assessment

Dr. Gaffey has illustrated the confusion that can arise from the use of the term relative risk. Rates of the disease may be expressed in units of time, such as the number of deaths per 1000 persons per year, or may be expressed as proportions which are unitless, such as cumulative mortality. It may be useful to distinguish a ratio of time-dependent rates from a ratio of proportions, since both types of ratios are referred to as relative risks.

When mortality rates are for a very small interval of time, the ratio of two rates can be viewed as an instantaneous rate ratio. An instantaneous rate ratio need not be age dependent, and at least theoretically could be constant over time and across ages. On the other hand, cumulative mortality expressed as a proportion is upper-bounded by one. A ratio of two proportions cannot exceed one if the denominator proportion is equal to one.

In our calculations, we treated the SMR as an estimate of the ratio of two cumulative mortalities. As such, the SMR can be thought of as a composite measure of instantaneous rate ratios for all age groups. When one compares SMRs between study populations with different age compositions, one is implicitly making the assumption that the instantaneous rate ratio is constant across age groups. The appropriateness of the comparison is dependent on the validity of this assumption. The assumption of a constant instantaneous rate ratio also is made when one uses the SMR from one study to calculate a risk for another population with a different age composition.

In our calculations, we expressed the probability of death from leukemia as the cumulative risk over an adult lifetime (i.e., a proportion). The SMR was treated as an estimate of the ratio of the cumulative

mortality from leukemia following occupational exposure to benzene over the cumulative mortality from leukemia in the absence of occupational benzene exposure. In our model, the ratio of cumulative mortalities was dose dependent. The use of Abbott's correction assured us that the estimate of the total cumulative mortality from leukemia would not exceed one.

Thus, the measure of relative risk that we relied on was the ratio of cumulative mortalities, which could be estimated from the SMRs. The assumption of a constant instantaneous rate ratio was not integral to our calculations. However, this assumption is important to consider when assessing the validity of the risk estimates.

(4) Model selection and cumulative dose relationship for benzene and leukemia

Dr. Chandler has questioned the appropriateness of using the one-hit, or linear model, and suggests that molecular mechanisms which determine the dose response relationship for benzene toxicity should be evaluated in estimating the risk of benzene.

We believe that an assessment of benzene toxicity could be improved by knowledge of biological factors such as the dose of the ultimate metabolite(s) in bone marrow (and other organs), the toxicity of these compounds, and the rates and sites of their transformation as well as the cumulative nature and pharmacokinetic distribution and action along with modifying effects of intrinsic and extrinsic factors. However, after decades of study, the basic mechanism by which benzene affects bone marrow precursor cells is still unclear. Furthermore, even if these factors could be identified, it would be difficult to determine the weight that should be given to each factor in the development of a mathematical model. Nevertheless, selection of this model seemed appropriate since linear dose response relationships exist for several end points measuring the toxic effects of benzene on the bone marrow. (These are discussed below.)

For a number of carcinogens, the linear non-threshold model has been shown to describe the dose response relationship (i.e., radiation and leukemia, arsenic and lung cancer, and asbestos and lung cancer). This model also has been used for carcinogenic agents by the World Health Organization's Arsenic Working Group, for ionizing radiation on an international basis, by a Task Group on Air Pollution

and Cancer in Stockholm in 1977, as well as by regulatory bodies in the U.S. such as the Carcinogen Assessment Group (CAG) of the EPA.⁽⁹⁾

With specific regard to benzene and leukemia, OSHA requested several reviewers to comment on the model used by White *et al.* for the risk assessment.⁽¹⁰⁾

In response, Dr. Norman Breslow, Dr. Philip Cole, Dr. Charles Brown, and Dr. David Gaylor all thought the linear model was acceptable and that other more complex models were not justified. However, Dr. William Rowe felt other models should be evaluated in addition to the linear model, while Dr. Karrh felt the linear model was unverifiable. In our opinion, the issue of model selection can best be summarized by Dr. Charles Brown who stated⁽¹⁰⁾:

The 'correct' model is unknown, and will remain so until we know the mechanistic relationship between benzene exposure and leukemia; however, I do not believe that the data warrant more sophistication than the simple linear model (to which the one-hit model is a very close approximation at low response rates); in addition, since the range over which the dose extrapolation is performed appears to be relatively small (one order of magnitude?), the dose response model should have a small effect on the risk assessment results.

With regard to benzene and leukemia Dr. Norman Breslow recently stated that dose additivity and low dose linearity should be adopted as biologically reasonable and scientifically prudent assumptions in the absence of specific evidence to the contrary.⁽¹⁰⁾

Van Raalte *et al.* have the opinion that a cumulative dose relationship would not seem to accord with what is known about the toxicology of benzene and, based upon their interpretation of epidemiologic data, further allege that both marrow hypoplasia and leukemia only occur in persons exposed to benzene concentrations above 100 ppm.

In the Ott *et al.*⁽⁴⁾ report, there is no evidence that the leukemia cases experienced high peak benzene exposures. Likewise, studies of several refineries⁽¹¹⁻¹²⁾ and chemical manufacturing facilities⁽¹³⁾ where relative leukemia risks are significantly elevated and average exposures have been low, do not provide data to indicate that the leukemia deaths resulted only from substantial peak exposures to benzene.

The only epidemiologic study to address maximum peak exposure and cumulative exposure to benzene in relation to cancer was the recently reported industry-wide mortality study of chemical workers exposed to benzene sponsored by the Chemical

Manufacturing Association (CMA).⁽¹³⁾ When data were analyzed by cumulative exposure, statistically significant dose response relationships were demonstrated for leukemia as well as for all lymphohematopoietic cancers. Analyses by maximum peak benzene exposure (i.e., below 25 ppm, or between 25–100 ppm, or above 100 ppm) did not demonstrate a significant trend. However, the latter analysis demonstrated a relative risk greater than 3 when maximum peaks were below 25 ppm. The findings suggest that cumulative exposure may be a valid measure of dose in determining dose response relationships for benzene and leukemia and that maximal peak exposures below 25 ppm may also induce lymphohematopoietic cancer.

In order to further evaluate the issue of the level of benzene required to cause toxicity to the bone marrow, one can look to experimental studies where dose and dose level can be controlled. In this regard, the NTP bioassay on benzene demonstrates dose response relationships for multiple cancers as well as for leukopenia in both mice and rats.⁽¹⁴⁾ The low dose in both species is equivalent to an 8-hour atmospheric exposure of 20 ppm. Additional experimental studies have now demonstrated that inhalation of 10 ppm benzene causes significant bone marrow depression (6 hrs/day, 178 days)⁽¹⁵⁾ and disturbances of immune system function (6 hrs/day, 6 days).⁽¹⁶⁾ Since most leukemias and related disorders in man seem to involve stem cell abnormalities and immune system deficiencies these findings may be highly relevant to benzene and leukemia.

Several recent experimental studies have demonstrated adverse effects on chromosomes and bone marrow in relation to low level benzene exposure. Collectively, these studies demonstrate chromosomal damage in bone marrow cells as a result of only one 6-hour exposure to 10 ppm⁽¹⁷⁾ or one 4-hour exposure to 28 ppm,⁽¹⁸⁾ or to an equivalent of two 8-hour exposures to 6 ppm.⁽¹⁹⁾

Thus, numerous recent findings seem to contradict the opinions of Van Raalte *et al.* and Irvine that only peak benzene exposures above 100 ppm can cause leukemia or bone marrow toxicity. Furthermore, both epidemiologic observations and experimental studies support a cumulative dose concept for benzene and leukemia, and indicate that even short-term exposures to 10 ppm are toxic to the bone marrow.

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