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Review and Update of Leukemia Risk Potentially Associated with Occupational Exposure to Benzene

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Since the 1980 U.S. Supreme Court decision on the Occupational Safety and Health Administration's (OSHA) proposal to lower the occupational benzene standard from 10 ppm to 1 ppm, numerous quantitative assessments of the leukemia risk of benzene exposure have been prepared. The primary difference between these risk assessments has been in the way in which benzene exposure has been estimated and in the models applied to describe the dose-response relationship. The more recent assessments, in attempting to estimate benzene exposures on an individual basis, and in applying models which make maximal use of the available data points, represent a substantial improvement over earlier assessments. In this paper, we will review the available risk assessments and the data upon which they are based and will present our own assessment, which builds on prior efforts. Our reevaluation of the underlying data on the cohort that we judged to be most suitable for quantitative risk analysis suggested that past assessments may have overestimated risk by a factor of 3 to 24. In addition, we will present some recently made available data of relevance to the benzene exposure histories of cohort of concern. These data provide additional suggestion that the total benzene exposure of certain members of this cohort has likely been seriously underestimated, the extent to which remains to be determined. Further analysis of these data and pursuit of additional sources to improve the characterization of the benzene exposure of this cohort appear to be warranted in order to define more precisely the benzene-leukemia dose-response relationship.

Introduction

The hazards of benzene exposure to humans and experimental animals are well documented (*1-3*). In humans, exposure to high levels of benzene has caused a variety of disorders of the hematopoietic system, particularly leukemia, especially of the acute myelogenous type, and aplastic anemia (*1,2,4*). Evidence of the leukemogenic properties of benzene has come both from collections of case reports (*3-6*) and from epidemiological studies (*7-9*). There is no substantial disagreement in the scientific community that benzene exposure can cause leukemia in highly exposed humans. What does remain uncertain, however, is the relationship between a particular level of benzene exposure and the resulting probability of developing leukemia. This uncertainty results from incomplete data on the levels of benzene to which individuals in the epidemiologic studies were exposed and a number of other factors that affect the dose-response relationship.

Elevated frequencies of chromosome aberrations in bone marrow cells and peripheral leukocytes have been observed in a number of studies of individuals exposed to benzene (*1*). It is not clear whether these are significant indicators of health damage. Studies of the effects of benzene exposure in animals have shown some similarities to, and also some significant differences from, the effects observed in exposed humans. As with humans, the hematopoietic system in the bone marrow is a critical target of benzene exposure, with anemia, lymphocytopenia, and bone marrow hypoplasia as common responses to repeated inhalation of benzene in the 100 to 300 ppm range (*1*). Also, mice and rabbits exposed to benzene show increased numbers of chromosome aberrations in their bone marrow.

The major difference in response between humans and the species and strains of experimental animals that have been tested is that, although several cases of leukemia have been attributed to benzene exposure by some researchers, no animal model for benzene-induced leukemia has been well established. Several other forms of neoplasms have been found at elevated incidence in rats and mice exposed to benzene by inhalation or ingestion however (*10-15*). The sites at which tumors have been elevated in rodents include the Zymbal gland, the oral cavity, the preputial gland, the Harderian gland, the mammary gland, the lung, and ovaries, in addition to lym-

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phomas and leukemia. The reasons for the differences in response between species are not known, though interspecies differences in metabolism and pharmacokinetics of benzene via different routes of exposure may contribute.

The findings in experimental animals confirm qualitatively the carcinogenic potential of benzene. However, it would be inappropriate to rely on such data to estimate quantitatively the risks of exposure of humans to benzene. Most expert groups, including, OSHA (*16*), U.S. EPA (*17,19*), and the Office of Science and Technology Policy (*18*) agree that where epidemiologic data of reasonably good quality are available, they should be used for risk assessment. Thus, although it may be of interest for the purpose of comparison to use the animal data, greatest reliance should be placed on the more relevant human data when such data are available.

In 1977, OSHA first proposed to lower the occupational benzene standard from 10 ppm to 1 ppm on the basis of its qualitative assessment of the leukemia risks of benzene exposure. A permanent standard was, however, not upheld by the United States Supreme Court on the basis that OSHA had not demonstrated that a significant risk existed at the current standard, nor that this risk would be significantly reduced by institution of the proposed standard. Since this Supreme Court decision, quantitative risk assessments have been prepared by a number of investigators. In addition, exposure data of relevance to the benzene leukemia dose-response relationship have recently become available and should be considered when evaluating this issue.

In the following discussion, we will initially review the epidemiologic data sets available for benzene risk assessment and will consider factors arguing for and against their application for this purpose. We will then review the assessments that have been prepared and their associated strengths and limitations. The data recently made available and their potential effect on the available benzene risk estimates will be discussed. Finally, on the basis of this analysis, our conclusions regarding leukemia risk associated with occupational benzene exposure will be presented.

Epidemiologic Studies Available for Risk Assessment

A number of epidemiologic studies have been used to assess the risk of leukemia mortality to persons exposed to benzene. We will describe the four studies that have been most frequently used for this purpose and their associated strengths and limitations for quantitative risk assessment.

Description of Studies and Their Limitations

Infante et al. and Rinsky et al. Infante et al. (*1*) and Rinsky et al. (*9,20,21*) are reports representing continued follow-up of the leukemia mortality experience of a group of Goodyear workers who had been exposed to benzene in the manufacture of rubber hydrochloride (also known as Pliofilm) at three facilities at two locations in Ohio. We shall limit our discussion to the methodology and results obtained in the latter two Rinsky reports, as these have been the primary basis for the more recent risk assessments.

Rinsky et al. (*9*) divided the Pliofilm cohort from the three facilities into two groups according to the time period worked in the Pliofilm department. Group 1 consisted of 748 workers who worked at least one day between January 1, 1940, and December 31, 1949; group 2 consisted of 258 workers whose first Pliofilm exposure occurred between January 1, 1950, and December 31, 1959. Vital status was ascertained to June 30, 1975, for 98% of the cohort. For each group, the number of workers who died from leukemia between January 1, 1950, and June 30, 1975, was compared to the expected number based on U.S. white male mortality using a modified life table approach.

Among the 748 workers in the first group, 7 deaths from leukemia occurred versus 1.25 leukemia deaths expected, resulting in a standardized mortality ratio (SMR) of 560 ($p < 0.001$). It was noted that the mean duration of benzene exposure was relatively brief, with 437 persons (58%) of the cohort exposed for less than 1 year. Upon data analysis by length of employment, a significant excess in leukemia was observed among workers employed 5 or more years (5 leukemia deaths observed vs. 0.23 expected, SMR = 2100), but not among workers employed for less than 5 years (2 leukemia deaths observed vs. 1.02 expected, SMR = 196, not statistically significant). Among the 258 workers in the second group, only 1 death from leukemia was observed vs. 0.46 expected, representing an increase that was not statistically significant.

Rinsky et al. (*21*) expanded the Pliofilm cohort by including all nonsalaried, white males employed in a Pliofilm department at the two locations for at least 1 day between January 1, 1940, and December 31, 1965 (i.e., 6 additional exposure years). Vital status was ascertained through December 31, 1981 (6.5 additional years of follow-up). This resulted in a total cohort of 1165 white males with at least 1 ppm-day (1 day of employment in a Pliofilm department with at least 1 ppm average benzene concentration) of cumulative benzene exposure.

In this cohort, a total of 9 leukemia deaths was observed vs. 2.7 expected, resulting in an SMR of 337 (95% CI = 154–641). Thus, during the additional 6.5 years of follow-up of the original Rinsky et al. (*9*) 1981 cohort, 1 additional leukemia death was observed; no leukemia deaths were observed in the subgroup of workers whose employment began after 1959.

Rinsky et al. (*21*) further refined their analysis by stratifying the cohort by cumulative benzene exposure. To develop estimates of cumulative benzene exposure, they created 10 broad exposure classes, each associated with a specific job title in the Pliofilm operation. They then constructed job-exposure matrices, which associated an average annual benzene exposure level with each exposure class.

Rinsky calculated cumulative benzene exposure over a

working lifetime for each individual based upon estimated benzene concentration in a Pliofilm job category during the particular year(s) of exposure and the duration of exposure in particular jobs. The cohort was then divided into four cumulative exposure categories: 0.001–40 ppm-years; 40–200 ppm-years; 200–400 ppm-years; and greater than 400 ppm-years, with SMRs of 109, 322, 1186, and 6637, respectively.

In addition, Rinsky et al. (*21*) performed a matched case-control analysis using conditional logistic regression. This aspect of the Rinsky et al. 1987 report will be discussed later in this paper when the available risk assessments on benzene are reviewed.

There are number of limitations to this study, many of which relate to the characterization of exposure. First, environmental monitoring data for the two locations were significantly less than complete for the years under consideration. For location 1, the location on which the majority of data was available, there were no measurements available for the years prior to 1946 or for the years 1951 to 1963. In 1963, the company began to record benzene concentrations on a standard form. The frequency of company surveys for atmospheric benzene for the years 1963 to 1971, however, was quite low, with an average of only 2.3 surveys/year during this time interval, and an average of only 2.3 samples/year collected for each of the 12 work areas considered. Thus, even for the plant location at which monitoring data were more readily available, the body of evidence may be considered somewhat limited.

Environmental monitoring results for location 2 were extremely limited. For plant 1 (of location 2), only three sample points, determined in an industrial hygiene survey on one day in 1948, were available. Similarly, for plant 2 (of location 2), the only environmental data available were believed to have been taken "around 1957." Thus, apparently no sampling data were available for 27 of the 29 years during which Pliofilm was manufactured at this location. Rinsky et al., for lack of better monitoring data, made the assumption that benzene exposures at location 2 were similar to those at location 1. This assumption has not been verified. This may be particularly significant because it suggests that for greater than 40% of the overall cohort and two-thirds of the leukemia cases, no directly applicable monitoring data were available upon which to base worker exposures.

These significant gaps in the available benzene monitoring data for location 2 in general, and for many of the years under consideration for location 1, necessitated making a large number of assumptions in the investigators' attempts to estimate individual cumulative benzene exposure. Clearly, this is an issue of great importance if one relies on this study to assess benzene-leukemia dose-response relations.

Another area of uncertainty relates to the fact that Rinsky et al. failed to consider all routes of benzene exposure in this cohort of Pliofilm workers. During the 1977 OSHA hearings on benzene, testimony was presented suggesting that dermal exposure in certain work areas in the Pliofilm plants was significant. The Rinsky et al. study, however, did not report on these exposure conditions, nor did it consider that the dermal route might have contributed significantly to total benzene exposure of certain workers in the cohort. The possible contribution to total benzene exposure from the dermal route will be considered later in this paper.

Rinsky et al. did not consider the extent of benzene exposure that members of the Pliofilm cohort may have had in non-Pliofilm jobs within the Goodyear plants. Through a Freedom of Information Act request, the American Petroleum Institute (API) has recently obtained the Goodyear job history records of the Rinsky cohort members who have died. Review of these job history records indicates that most members of the cohort worked in a variety of non-Pliofilm jobs throughout the Goodyear plants, many of which likely involved substantial benzene exposure. As will be discussed, a review of some early published reports by medical personnel of Goodyear suggests that pure benzene or solvents with high benzene concentrations were used by the company in several of these non-Pliofilm operations. On the basis of these reports it is suggested that the total benzene exposure of the Pliofilm cohort may have been seriously underestimated by the failure to consider exposure, both by the inhalation and dermal routes, to benzene in non-Pliofilm jobs throughout the Goodyear plants involved in the study.

Of the 9 leukemias observed in the overall cohort, 6 had worked in location 2. This may be important because location 2 is that for which almost no environmental monitoring data were available for the Pliofilm operations. The higher rate of leukemia mortality in location 2 than in location 1 may be related to the higher potential for benzene exposure in the tire-building (non-Pliofilm) job areas of location 2. The investigations made the assumption, however, that benzene exposures at the two locations were very similar. This assumption may have been in error.

Ott et al. and Bond et al. Ott et al. (*8*) studied the mortality experience of 594 white males who were exposed to benzene in three production areas of Dow Chemical Company in Michigan. The workers had been employed at the plant between 1940 and 1973, with no apparent minimum length of employment required for inclusion in the cohort.

Benzene concentrations in the three production areas (i.e., chlorobenzol, alkyl benzene, and ethyl cellulose) were characterized based upon environmental monitoring data from 1944 to 1973. Overall, benzene levels ranged from 0 to 937 ppm, although the estimated time-weighted average benzene concentrations ranged from 0.1 to 35.5 ppm in the various job categories. Exposures were further categorized for specific jobs in the production areas based upon time-weighted average benzene exposure. A total of 3 leukemia cases was observed from 1940 to 1973 versus 0.8 expected, based upon incidence data from the Third National Cancer Survey. This resulted in an SMR of 375.

There are a number of factors that limit the usefulness of this study for the purpose of leukemia risk assessment.

First, it must be considered that workers at the Michigan Dow plant were reportedly exposed to a large number of chemicals in addition to benzene, some of which have been associated with carcinogenic effects. This lack of specificity of exposure may have had a significant influence on the study results. This concern is magnified upon examination of the work exposure histories of the three leukemia cases, all of whom had documented multiple chemical exposures in past employment.

Another limitation of the study, in terms of its utility for establishing causal associations, was the lack of an observed dose-response relationship. In addition, the small size of the Ott et al. (*8*) study makes it of somewhat limited use for the purpose of risk assessment. Due to the small study size, the standardized morbidity ratio of 375 that was observed for leukemia had a 95% confidence interval that ranged from approximately 77 to 1096. This interval would generally be considered to be too wide to provide confidence in the use of the SMR of 375 as the basis for quantitative risk estimates.

This investigation has been recently updated in an unpublished report by Bond et al. (*22*). In this analysis, 956 Dow Michigan division employees potentially exposed to benzene were studied. The period of observation was 1940 to 1982, representing an additional 9 years of follow-up from the earlier investigation. Four leukemia deaths were observed versus 2.1 expected based upon U.S. white male mortality rates; this increase was not statistically significant. It was noted, however, that all 4 leukemias were of the myelogenous type. When the mortality for myelogenous leukemia was compared with that which would be expected based upon National Cancer Institute Surveillance, Epidemiology End Results (SEER) data, a statistically significant excess was observed (4 observed vs. 0.9 expected; $p = 0.011$). The investigators noted a fifth leukemia case, who was the same individual whose death certificate was classified to pneumonia in the Ott et al. (*8*) study. Thus, this update identified two additional leukemia deaths among benzene-exposed Dow Chemical workers.

The Bond et al. (*22*) update has the same limitations for use in risk assessment as the earlier study of the cohort. Once again, the analysis failed to show a positive dose-response relationship. The number of leukemias observed remains small, and consequently the confidence interval around the risk estimate remains quite wide. The possible influence of additional exposures remains an important issue for consideration.

A conditional logistic regression case-control analysis of the Ott et al./Bond et al. studies (*8,22*) has been conducted by the American Petroleum Institute in order to investigate whether they represent evidence of a relationship between increasing cumulative benzene exposure and increasing risk of leukemia (*23*). The method of analysis was consistent with that employed in the Rinsky et al. (*20,21*) case-control study. Each leukemia case was matched to 10 controls on date of birth and date of first employment in a benzene exposure job. On the basis of these analyses, there was not a statistically significant relationship observed between increasing cumulative benzene exposure and increased risk of leukemia (*23*).

Aksoy. Aksoy (*6*) reported that during 1967 to 1975, a total of 34 workers at shoe manufacturing facilities where benzene was used were admitted to the hematology departments of a medical school in Istanbul, Turkey. The total number of shoe workers in Istanbul was estimated to be 28,500. The crude annual incidence of leukemia in this population was estimated to be 13/100,000 person-years of observation. The annual incidence rate of leukemia in the general population was reported by the investigators to be 6/100,000. The observed incidence was reported to be significantly higher ($p < 0.01$) than the incidence in the general population.

The Aksoy study reportedly evaluates the incidence of leukemia among 28,500 shoe workers in Istanbul. In fact, a study of 28,500 shoe workers was not actually performed. Aksoy's study population represents a case series of 34 shoe workers who were admitted to the hematology departments of Istanbul Medical School with a diagnosis of leukemia between 1967 and 1975. The figure of 28,500 was taken from "official records" of Istanbul, which indicate that there are 28,500 workers involved in the shoe, slipper, and handbag industry in which benzene is used as a solvent. Thus, the leukemia incidence in only a small percentage of the Istanbul shoe worker population was actually directly examined.

For a standard population, Aksoy used data on the leukemia mortality in the general population of Western nations, which he obtained from a paper by Gunz (*24*). Aksoy indicated during the 1977 OSHA hearings that the leukemia incidence rate of 2.5 to 3/100,000 for the general population of Turkey was not used in the analysis because vital statistics reporting in Turkey could not be relied upon to draw scientific conclusions.

Questions have been raised about the use of the Gunz rate as a standard, however, because it was actually an estimate of the leukemia mortality rate in Western nations, as opposed to the leukemia incidence rate that was being estimated in Aksoy's population. An additional question in the interpretation of Aksoy's results was the fact that his calculation used crude rates, without adjustment for variations in age or leukemia cell types. Leukemia rates are known to vary widely with age, thereby requiring that comparisons be made between populations with reasonably similar age distributions, or that age adjustment be performed prior to relative risk ascertainment.

Perhaps the area of greatest uncertainty in the Aksoy study was that of characterization of exposure. One must assume that these shoe workers were exposed to a mixture of volatile hydrocarbons, including benzene. In addition, workers may have been exposed to curing agents, dyes, and other chemicals commonly used in the shoe industry. The leukemic effect observed may therefore have been related to these other chemical exposures or to benzene activity in combination with these materials. The exposure data provided in the Aksoy studies were also very limited. Aksoy (*25*) indicated that the concentration of benzene was found to reach a maximum of 210 to 650 ppm when adhesives containing benzene were in use. During

the OSHA benzene hearings in 1977, Aksoy indicated that the concentration of benzene ranged between 15 and 30 ppm outside working hours and between 150 and 210 ppm during working hours. The number of measurements upon which these ranges of benzene concentrations were based was not specified in any of the reports. It is most likely, however, that only a very small percentage of the workplaces under consideration were actually sampled. Applying these environmental data to the entire cohort, therefore, results in a very high degree of uncertainty in any projected exposure-related leukemia risks.

In addition, the Aksoy studies did not consider the issue of dermal exposure to benzene. One can assume, however, that dermal exposure in this occupational setting may have been substantial. In light of recent experimental evidence that suggests that dermal exposure to benzene can result in a high degree of absorption, it would be best advised that this matter be further investigated to determine the likely contribution of dermal exposure to the total benzene exposure of this cohort.

Wong. Wong (*26*) conducted a historical prospective mortality study of a group of 4602 male chemical workers from seven plants who were occupationally exposed to benzene for at least 6 months between 1946 and 1976. They were compared to a group of 3074 male chemical workers from the same plants, but with no occupational exposure to benzene. The vital status of the workers was followed through December 1977 and underlying causes of death coded to the 8th Revision of the International Classification of Diseases. Cause-specific mortality was assessed using a) the comparison group to obtain relative risks and the corresponding Mantel-Haenszel chi-square with one degree of freedom, and b) the U.S. male population as a comparison for obtaining SMRs.

For leukemia, the SMR for the exposed group was 117.4 (7 deaths observed vs. 5.96 expected). This increase was not statistically significant. The relative risk of leukemia could not be determined in the exposed group as compared to the nonexposed group, however, as no deaths from leukemia were observed in the internal control population. The reason for this deficit in leukemia in the unexposed group remains unknown.

The exposed cohort was divided into categories based upon an exposure classification of jobs. In the continuous exposure group a total of 6 deaths from leukemia were observed vs. 4.43 expected, yielding an SMR of 135, which was not significant at the 0.05 level. In the intermittent category, a deficit in leukemia occurred with only 1 leukemia death observed vs. 1.49 expected.

It should be noted that none of the leukemia deaths in the exposed cohort were of the acute myelogenous type, the cell type that has been most commonly associated with benzene exposure in other occupational studies. Rather, 4 of the leukemias were lymphatic, 2 were chronic myeloid, and 1 was an acute leukemia (type unspecified).

The study has a number of limitations, some of which were acknowledged by the investigators. First, it should be noted that each plant collected data on its own workers. Consequently, it is likely that there was a lack of uniformity in data collection procedures, which may have biased the results. Second, data on benzene exposures during the early part of the study were reported to be limited for some of the plants, necessitating estimation of exposures on the basis of uniform tasks in the majority of plants studied. Two of the plants, however, did not use this approach, and estimates of exposures were derived by supervisors or industrial hygienists. This lack of consistency in the methodology for exposure estimation may have further biased the study results, the direction of such bias being impossible to determine. Third, workers in the study were probably exposed to a large variety of additional chemicals in their studied jobs (and in past employment), which may have influenced study results. Fourth, relative risk of leukemia could not be determined between exposed and nonexposed workers, as there were no leukemias observed in the unexposed group. Fifth, the number of leukemia deaths was quite small, limiting the confidence that can be placed in any assessment of dose-response relationships. Sixth, two of the nine plants that originally participated in the early stages of the study reportedly withdrew from the study because of difficulties in data collection and in participation in the study as designed. This occurred after the collection of death certificates, raising the suspicion that the data contained in the death certificates themselves may have been related to the decision to no longer participate in the study. It should further be noted that during the OSHA benzene hearings held in March of 1986, Wong indicated that in his judgment the inadequacies in the benzene exposure estimates made the Wong study (*26*) an inadequate basis for quantitative risk assessment.

Conclusion

This review has emphasized data from epidemiological studies that might be suitable for use in assessing benzene-associated leukemia risk. On its basis, we conclude that the Rinsky et al. (*20,21*) cohort provides the best basis for estimation of benzene-associated leukemia risk. In our judgment, no other available study is suitable for risk assessment, primarily because of a general lack of quantitative exposure information.

Although there are significant limitations in the data on the magnitude of exposures of the Rinsky et al. cohort, it nevertheless appears possible to estimate a dose-response curve (or range of curves) with the degree of reliability usually considered appropriate for such studies. We note, however, that some additional information on the exposures experienced by the Rinsky et al. cohort has recently become available that may affect estimates of risk derived therefrom.

Review of Available Benzene Risk Assessments

A large number of assessments of the risk of leukemia associated with benzene exposure have been published since OSHA first proposed its standard in 1977. In the fol-

lowing discussion, these risk assessments will be considered, beginning with the earlier assessments, all of which employ similar methodology, followed by the more recent assessments that have attempted to make some distinct improvements in exposure characterization and consequent estimates of risk.

Earlier Risk Assessments Employing the Linear Model

The Carcinogen Assessment Group of the United States Environmental Protection Agency presented the first major risk assessment following the 1977 OSHA hearings (*27*). It considered three sets of occupational epidemiology data, namely the studies of Infante et al. (*7*), Aksoy (*25,28,29*), and Ott et al. (*8*). EPA assumed that for low exposures, the lifetime probability of death from leukemia may be represented by the linear equation:

$$P = A + \beta x \tag{1}$$

where A is the rate of leukemia mortality in the absence of benzene exposure and x is the average lifetime exposure to benzene in parts per million. The term β represents the increase in the leukemia mortality rate due to each increase of 1 ppm average lifetime exposure to benzene; this term may also be referred to as the slope of the dose-response relation.

EPA assumed that the relative risk of leukemia is independent of the duration of exposure or the age at which exposure occurs in the worker population. Given this assumption, through several algebraic transformations, β can be derived as follows:

$$\beta = P_1(R - 1)/x_2 \tag{2}$$

where P_1 is the lifetime probability of dying of leukemia with no or negligible benzene exposure, R is the relative risk of leukemia for a benzene-exposed worker cohort compared to the general population, and x_2 is the cumulative occupational exposure to benzene, averaged over a lifetime.

At least six additional risk assessments were subsequently developed by other groups, all accepting EPA's general model (*30–35*). These risk assessments differed primarily in their judgment of the adequacy for risk assessment of the three studies originally considered by EPA, and in their choice of values for P_1, R, and x_2 to be used in deriving β; several of the assessments rejected the Aksoy and Ott data sets entirely. This resulted in these assessments producing a wide range of estimates for the slope β of the linear dose-response function at low doses.

Because of the limitations of the Ott et al. (*8*) and the Aksoy studies (*6,25,28,29*) as described above, it is our judgment that of the three epidemiologic data sets considered in these risk assessments, the Infante et al. (*7*) and Rinsky et al. (*9*) data are the best suited for quantitative risk assessment. Consequently, for the remainder of this discussion of these seven risk assessments based on the linear model, the results presented will be limited to those derived from the Infante et al. (*7*) and Rinsky et al. (*9*) studies.

Table 1 presents the ranges of additional lifetime leukemia deaths predicted due to occupational exposure to benzene in these seven risk assessments based upon the Infante et al. (*7*) and Rinsky et al. (*9*) data. Risks are predicted specifically for workers exposed at the former 10 ppm standard for 45 years (450 ppm-years) and at the new 1-ppm standard for 45 years (45 ppm-years), assuming an average 70 year lifetime.

Because of variations in these risk assessments in values selected for P_1, R, and x_2, the resultant predictions of risk at 45 and 450 ppm-years varied by a factor of approximately 8. Variations in assumptions about exposure (x_2) had the greatest influence upon the range of predicted leukemias in benzene-exposed workers. Differences in assumptions about background probabilities and relative risks in the Infante/Rinsky cohort had a far less significant influence.

Table 1. Comparision of risk assessments using a linear model based on epidemiological data of Infante et al. (*7*) or follow-up reported by Rinsky et al. (*9*).

Assessment	Relative risk	Average lifetime exposure, ppm	Assumed background probability	Lifetime risk for an average lifetime exposure of 1 ppm[a]	Additional lifetime leukemia risk/1000 workers due to benzene exposure	
					45 ppm-years	450 ppm-years
U.S. EPA (*27*)	9/1.25 = 7.2	2.81	0.006732	0.015	2.1	21
API/Lamm (*30*)	7/1.25 = 5.6	2.81	0.006732	0.011	1.6	16
Hattis and Mendez (*31*)[b]	9/0.84 = 10.7	0.84	0.004517	0.052	7.4	74
IARC (*32*)[c]	7/1.25 = 5.6	N.A.	0.007	0.009–0.037	1.4–1.7	14–17
Luken and Miller (*33*)	7/1.25 = 5.6	1.30	0.006732	0.024	3.3	33
A. D. Little (Gilbert) (*34*)[b]	9/0.84 = 10.7	3.27	0.00452	0.013	1.88	18.8
ELI (*35*)	7/1.25 = 5.6	Low 0.37	0.006732	0.084	4.9–11.8	49–118
		High 0.88		0.035		

[a]All based on a linear model of the dose-response relation. Note that IARC did not project the estimated slopes beyond the range of observed dose-response relations.
[b]These authors use background rates for nonlymphatic leukemias only.
[c]IARC did not estimate average lifetime exposure.

In our opinion, all seven of these risk assessments suffer from poor characterization of the benzene exposure history of this cohort and, consequently, little faith can be placed in the risk estimates derived therefrom. Subsequent risk assessments have attempted to make improvements in the characterization of exposure in the Infante/Rinsky cohort.

White, Infante, and Chu. White, Infante, and Chu (*36*) performed a risk assessment based upon the data presented in Rinsky et al. (*9*) and Ott et al. (*8*). For the Rinsky et al. cohort, the risk assessment was based solely on the experience of workers who had been employed for 5 years or more. It was further assumed that the upper limit on duration of employment was 30 years, because workers who had been employed for more than 30 years contributed less than 0.01 to the number of leukemia deaths expected. White, Infante, and Chu made the general assumption that during the years 1941 to 1975, workers were exposed to benzene at the environmental concentrations recommended during these years. They further assumed that benzene concentrations before 1941 were 50% higher than a recommended level for 1941. On this basis, the range of cumulative benzene concentrations for workers in the cohort with 5 to 30 years of experience was estimated to be 415 ppm-years (83 ppm × 5 years) to 1500 ppm-years (50 ppm × 30 years).

The one-hit model was then selected for low-dose extrapolation, primarily because of its simplicity. This model states that excess cancer risk (P_d) is related to the dose (d) by the equation

$$P_d = [1 - \exp(-\beta \times d)](1 - P_o) \quad (3)$$

where β represents the rate at which the excess probability of leukemia increases with each increment in dose, d represents dose, and P_o is the background risk of cancer. Thus, the total risk of leukemia (P_t) to an individual exposed to benzene is the sum of the background risk (P_o) and the risk associated with benzene:

$$(P_t = P_o + [1 - \exp(-\beta \times d)](1 - P_o) \quad (4)$$

The relative risk of leukemia death in the Rinsky et al. (*9*) study was approximated by the SMR. It was assumed, for the purpose of this risk assessment, that:

$$P_t = \mathrm{SMR}/100(P_o) \quad (5)$$

On the basis of Equations 4 and 5, it was shown that β, the slope of the dose-response relation, can be determined as follows:

$$\beta = -\ln[(1 - (\mathrm{SMR}/100)P_o/(1 - P_o)]/d \quad (6)$$

β value were determined for the upper and lower range of estimated exposure of the cohort. The excess leukemia risk was thereby estimated to be 44 to 152 per 1000 workers exposed for 45 years at 10 ppm benzene and 5 to 16 per 1000 workers exposed for 45 years at 1 ppm benzene. (On the basis of the Ott et al. (*8*) study, which we consider less suitable for risk assessment, the excess leukemia risk was estimated to be 48 to 136 per 1000 workers exposed for 45 years at 10 ppm benzene and 5 to 15 per 1000 workers exposed for 45 years at 1 ppm benzene.)

In our judgment, one of the primary deficiencies in the risk assessment was its bias in its elimination from consideration of workers in the Rinsky et al. study who were exposed for less than 5 years. It appears the 5-year period was chosen arbitrarily. Clearly, it is inappropriate to exclude the observed mortality data on workers who were actually subject to the lower range of exposure to which the model will actually apply. Rather, the entire exposed cohort and its corresponding SMR should have been used in the assessment of risk of this worker cohort.

Further, it should be realized that the range of risks estimated by White, Infante, and Chu on the basis of these data is highly unlikely to represent the true range of risks. The SMR selected (2100) represented the average SMR for the subset of workers with 5 years or more of exposure. White, Infante, and Chu applied this average SMR to their range of cumulative exposure estimates. This average risk estimate, however, does not correspond to the risk at either the upper or lower estimates of exposure. It would have been more appropriate to have applied this average SMR to an estimate of the average cumulative exposure of the cohort.

Review of the environmental monitoring data in the Rinsky et al. (*9*) study calls into question White, Infante, and Chu's assumption that workers were exposed to benzene at the environmental concentrations recommended during the time periods under consideration. The data indicated that in certain areas of location 1 (on which the large majority of data were available), environmental benzene concentrations well exceeded the recommended concentrations for the respective time period. Thus, data contained in the study itself suggest that White, Infante, and Chu may have underestimated the exposure of the Rinsky et al. (*9*) cohort.

Overall, it is our view that the White, Infante, and Chu risk assessment, like the earlier risk assessments described, was deficient primarily in its characterization of exposure of the cohort. The method of exposure estimation applied was relatively crude in its lack of consideration of actual duration of exposure of individuals in the cohort or of exposure measurement data available for specific work operations during the years under consideration. Consequently, the risk estimates derived by White, Infante, and Chu should be given less weight than those obtained in more recent assessments that considered such data.

The general methodologies employed in the subsequent risk assessments of benzene and leukemia, namely those by Crump and Allen (*37*) and Rinsky et al. (*20–21*) are, in our view, superior to those employed in the other benzene risk assessments described. A description of these latter assessments and their strengths and limitations is given in the next section. We also add our own risk assessment, based on a synthesis of the desirable features of all available assessments.

Crump and Allen. Crump and Allen (*37*) made a significant improvement over earlier assessments of the Rinsky et al. (*9*) cohort in their characterization of its benzene exposure history. In their analysis, an exposure profile was constructed for each worker in the Rinsky et al.

(*9*) cohort. In order to accomplish this, they used the benzene measurement data provided in the Rinsky et al. study (*9*), an updated data tape on the cohort, and data provided by Rinsky, permitting the association of work areas with occupational codes.

Estimates of benzene exposure were based on available measurements in eight major areas and were derived for seven time periods that corresponded to the years in which recommended occupational benzene concentrations were changed. Time periods were so categorized based upon the assumption that the company's procedures with respect to benzene concentrations would remain unchanged unless revisions in the recommendations or standards had occurred. Available measurements within time periods were averaged, based upon the assumption that roughly equivalent measurement procedures would have been used within a given time period.

In the event there were no measurements for a given area in a given period, Crump and Allen multiplied the estimate from the following period by the ratio of the recommended occupational concentration for the period to the recommended occupational concentration for the following period. The general assumption was made that monitoring data from one plant location were applicable to the other.

On the basis of these assumptions about exposure in specific work areas during specific time intervals, estimates of cumulative benzene exposure in ppm-years were determined for each worker. Crump and Allen included dry-side workers in their analyses and recalculated the SMRs for the cohort, both for all workers combined and for six subgroups categorized by cumulative exposure. Their calculations were also different from those in the White, Infante, and Chu assessment [based on Rinsky et al. (*9*)] because they included follow-up between 1940 and 1950, and between 1975 and 1978. For the overall cohort, 8 leukemias were observed versus 2.98 expected, resulting in an SMR of 268 ($p = 0.01$). Mortality from leukemia was dose related, with 6 of the 8 leukemias occurring in the two highest cumulative dose categories.

Crump and Allen also used the data on leukemia mortality from the Ott et al. (*8*) study for deriving their risk estimates. The data tape from the study was furnished to Crump and Allen so they could perform some additional calculations beyond those in the published study. On the basis of this tape, the SMR for leukemia was estimated to be 208 (two leukemia deaths observed/0.96 expected) versus the SMR of 375 estimated in the Ott et al. analysis. Crump and Allen made the judgment that the Ott et al. study, involving only two deaths from leukemia and lack of a dose-response relationship, would not be used independently to make risk estimates, but only in conjunction with data from other studies.

Crump and Allen also used the data set of Wong et al. (*26*) in deriving some of their risk estimates. They indicated however, that without some explanation for the leukemia deficit in the unexposed group, the Wong et al. study does not provide strong evidence of a relationship between occupational exposure to benzene and leukemia. Crump and Allen, however, proceeded to use the Wong et al. data set to estimate excess leukemia risk on the basis of cumulative dose only.

Crump and Allen fit the available Rinsky dose-response data to both the relative risk and the absolute risk linear dose-response models. The relative risk model assumes that the increased age-specific mortality from an agent is proportional to the background mortality. The absolute risk model, on the other hand, assumes that the added benzene mortality is the same for all ages, given equal doses. The relative risk model applied was as follows:

$$E(O_i) = aE_i(1 + bd_i) \tag{7}$$

and the absolute risk model:

$$E(O_i) = E_i + (a + bd_i)Y_i \tag{8}$$

where:

$E(O_i)$ is the expected number of leukemia deaths in the ith dose category;

a is a parameter which allows for the possibility that the background leukemia rates in the cohort differ from those of the reference population;

E_i is the expected number of leukemia deaths in the ith group based upon mortality rates in a comparison population;

b is the potency of benzene for causing leukemia mortality;

d_i is the average benzene dose in the ith group; and

Y_i is the total number of person-years in the ith group.

Next, Crump and Allen described the four different measures of dose that they selected to be fit to these dose-response models. The first was cumulative dose, which, in this analysis, represented cumulative dose in ppm-years up to the beginning of the 5-year age interval under consideration. The second measure was weighted cumulative dose, in which all exposures occurring in the last 2.5 years before the beginning of the 5 years of observation are assumed not to affect leukemia mortality; exposures in the next earlier 5 years are given full weight; those in the next earlier 5 years are given 1/3 weight; and all earlier exposures are given 1/6 weight. The weighted cumulative dose methodology was based upon data on the latency pattern of leukemia in Japanese atomic bomb survivors.

The third measure was termed "window dose," in which full weight is given to exposures during the 10-year period between 2.5 and 12.5 years prior to the 5-year age interval of interest, while exposures outside of this 10-year window are ignored. This window dose measure assumes that doses further than 15 years in the past have no effect on mortality from leukemia.

Finally, peak exposure dose calculations were defined as cumulative exposure in ppm-years in work areas with daily average concentrations above 100 ppm. Exposures to short-term peak concentrations were not identified for these calculations. As there were no areas with exposures between 76 and 100 ppm, it was noted that, in effect, the peak exposure measure assumed that only levels above 76 ppm contributed to leukemia risk.

The peak exposure measure was not used to develop

risk estimates. This was because an analysis comparing leukemia dose-response in workers in the Rinsky et al. (*9*) study exposed to levels of benzene in excess of 100 ppm to those exposed to less than 100 ppm did not support the hypothesis that peak exposure has any effect upon risk over that which can be explained by the contribution of these exposures to cumulative dose. No attempt was made to determine whether levels other than 100 ppm (to represent peak exposure) had a significant effect.

Table 2 compares Crump and Allen's estimates of extra leukemia deaths per 1000 workers using both the relative and absolute risk models and three different measures of dose. Projections were based upon maximum likelihood estimates and the most comprehensive data set available under each model.

Crump and Allen also presented the estimates of extra leukemia deaths per 1000 workers based upon the Rinsky et al. cumulative exposure data alone, to which the relative risk model was applied. For 40 years of exposure beginning at age 20, the estimated extra leukemia deaths were 6.6/1000 workers exposed at 1 ppm and 63/1000 workers exposed at 10 ppm. Estimates based upon the Rinsky et al. data alone using the alternative dose measures and the absolute risk model were not presented in the Crump and Allen paper.

Crump and Allen received a comment on their report which suggested that some of their exposure estimates may have been too high, as levels above 200 ppm, as a time-weighted average, would have been associated with an increased rate of anemia in as little as 4 months, and such an effect was not documented. Crump and Allen developed an alternative exposure matrix to respond to this comment, which in effect instituted a ceiling of 131 ppm for certain job categories. Crump and Allen indicate that use of this alternative exposure matrix will increase risks by about 25%. (This would result in an excess of approximately 8 leukemia deaths/1000 workers exposed at 1 ppm for 40 years, and of 79 leukemia deaths/1000 workers exposed at 10 ppm for 40 years.)

Table 2. Estimates of extra leukemia deaths per 1,000 workers exposed to benzene using relative risk and absolute risk models and three exposure measures.[a]

Model and exposure	40 years of exposure beginning at age 20	
	1 ppm	10 ppm
Relative risk model		
Cumulative exposure (*8,9,26*) (b = 0.033)	9.5	88
Weighted cumulative exposure (*8,9*) (b = 0.048)	3.0	29
Window exposure (*8,9*) (b = 0.035)	1.2	12
Absolute risk model		
Cumulative exposure (*8,9*) ($b = 1.6 \times 10^{-6}$)	2.0	19
Weighted cumulative exposure (*8,9*) ($b = 4.1 \times 10^{-6}$)	1.5	15
Window exposure (*8,9*) ($b = 3.1 \times 10^{-6}$)	1.1	11

[a]All estimates based upon maximum likelihood estimates of dose-response slopes.

In our judgment, the Crump and Allen estimates based upon cumulative dose should be given the most weight. The window exposure assumption that benzene exposures more than 15 years in the past have no effect on leukemia mortality seems improbable and is at variance with data on leukemia mortality of Japanese survivors of the atomic bomb, in whom excess leukemia mortality has been observed as late as 30 years after exposure. Further, in our judgment, the data upon which the weighted cumulative dose measure was reportedly based [leukemia mortality in Japanese atomic bomb survivors (*38*)], provided an insufficient basis to support the development of the weighted cumulative dose measure for leukemia. Specifically, the relative excess of leukemia mortality in the bomb survivor population does not appear to be independent of age at exposure. In addition, the observations that relative excess mortality decreased by 2/3 from the second 5-year interval after exposure to the third 5-year interval and further decreased by 1/2 in subsequent years apply only to the subgroup exposed at ages 30 to 44; observations for subgroups exposed in the remaining adult age groups showed inconsistent decreases in leukemia mortality over time.

There is little available basis upon which to form an opinion whether the absolute or relative risk model applied by Crump and Allen is most appropriate. Crump and Allen indicate a preference for the relative risk model because it seems most probable that the effect of benzene should be larger when the background rate of leukemia is higher. We tend to concur with this preference. On the basis of expert hematological opinion submitted during the 1986 OSHA benzene hearings, it is suggested that there is little support for the Crump and Allen alternate exposure matrix. Specifically, the apparent absence of deaths related to bone marrow toxicity among workers in Pliofilm areas (i.e., casting) with estimated benzene concentrations in excess of 130 ppm does not indicate that such estimated concentrations were higher than actual concentrations (*39,40*).

According to Goldstein, the benzene literature indicates that even in the worst of situations in the past (with regard to high exposure to benzene), there were relatively few individuals with clinically overt pancytopenia; similarly, acute myelogenous leukemia has not been observed in more than 1 to 2% of such highly exposed workers (*39*). Bennett observed that the literature on benzene-induced aplasias and cytopenias, although extensive, does not permit reliable prediction of a specific number of such cases at any given exposure level. Further, given the relatively small number of Pliofilm workers (approximately 50) who experienced benzene levels that one would generally associate with aplastic anemia, the apparent absence of cases is unexceptional (*40*). The opinions of these hematology experts suggest that the Crump and Allen original exposure estimates, derived from industrial hygiene data, are preferable to the Crump and Allen alternative estimates (*37*). Thus, in our judgment, application of the relative risk model and the original Crump and Allen cu-

mulative dose measure to the Rinsky et al. data provides the risk estimates that are the most plausible in the Crump and Allen assessment.

Rinsky et al. In addition to the cohort analysis of 1196 white male Pliofilm workers described earlier Rinsky et al. performed a matched case-control analysis on a subset of this Pliofilm worker cohort (*20,21*). In this analysis, each of the 9 leukemia cases was matched to 10 controls by year of birth and year first employed. This analysis was performed in an attempt to evaluate the effect of certain indicators of exposure on the relationship between risk of death from leukemia and exposure to benzene; to evaluate the effect of potential confounders and effect modifiers on this relationship; and to identify the functional form of the exposure-response relationship.

The investigators initially considered the following exposure variables separately and fit a separate model for each variable: cumulative exposure, duration of exposure, and average exposure rate. Cumulative exposure, expressed in ppm-years, was reported to be the strongest predictor of death from leukemia ($\beta = 0.0126$, 95% C.I. $= 0.0028 - 0.0224$; $\chi^2 = 6.4$; $p = 0.011$) (*21*).

An evaluation of the shape of the exposure response function was performed in which several models for cumulative exposure were applied. The finding indicated that a log linear model best represented the observed exposure-response relationship. On the basis of this model, the equation describing the odds ratio (OR) for leukemia in relation to cumulative benzene exposure was reported to be OR = exp (0.0126 × ppm-years). At 45 ppm-years, the model predicts 5.3 excess leukemia deaths per 1000 workers, and at 450 ppm-years, 667 excess leukemia deaths per 1000 workers are predicted.

The Rinsky et al. (*20,21*) method of conditional logistic regression is a valuable approach to analyzing dose-response information, as it makes maximal use of the information available on individual exposure. In its inclusion of individual exposure levels in the statistical analysis, it avoids the loss of information and resultant imprecision that may occur in analyses that dichotomize [e.g., the earlier linear (*27,30–35*) and one-hit model risk assessments (*36*)] or categorize (*37*) cumulative benzene exposure.

It should be noted, however, that this methodology will only result in truly improved risk estimates if it is based upon sound estimates of individual exposure. As was the case in the Crump and Allen assessment involving individual exposure estimation, numerous assumptions were necessarily made about past benzene exposure. Further, complex decision rules were developed to estimate exposures for individual years. The validity of the assumptions and decision rules applied by both Rinsky et al. and by Crump and Allen should be reconsidered in light of additional relevant exposure information that has recently been uncovered through searches conducted by the American Petroleum Institute.

Present Authors

We have performed several additional analyses of the Rinsky et al. data set (*20*), in which the case-control, conditional logistic approach was applied. Because currently there is uncertainty regarding actual past benzene concentrations in the Pliofilm plants of concern, we have performed separate analyses in which the Rinsky et al. (*20*) and the Crump and Allen (*37*) assumptions about exposure were applied.

We have also examined the Rinsky et al. (*20*) data tapes and noted several inconsistencies in the case-control data. Specifically, upon examination of the work histories of the controls selected by Rinsky et al. (*20*) (control set 1) it was noted that 15 of the 90 controls had 0 ppm-day cumulative exposure; according to the Rinsky et al. (*20*) study criteria, individuals with less than 1 ppm-day of benzene exposure in Pliofilm should have been excluded from the cohort.

Upon examination of the Rinsky et al. (*20*) data tapes, it was noted that the investigators had used inconsistent cohort definition criteria for the case-control and the cohort studies. In the cohort study, Rinsky et al. apparently considered only a smaller group of 1196 wet-side workers, whereas in the case-control study, a larger group involving 1868 wet-side and dry-side workers was included. We believe it is more appropriate to consider workers from both the wet and dry side in the analysis, as there is evidence of benzene exposure in both of these Pliofilm work areas. In our reanalysis of the data tapes, we considered all 1868 workers in our subsequent selection of controls.

We selected another group of 90 controls from the cohort, applying the Rinsky et al. matching criteria (control set 2). In addition, we selected a third control group, matched according to the criteria of Rinsky et al. (date of birth and date of first employment), but applying the additional criterion of matching according to plant (control set 3). We elected to match by plant because the two plants were located more than 100 miles apart and because of differences in non-Pliofilm benzene exposure, which may have influenced plant-specific mortality patterns.

Table 3 presents our estimates of the additional lifetime leukemia mortality risks (assuming a background leukemia mortality risk of 0.0071) for workers exposed to benzene at 1 ppm for 45 years (45 ppm-years) and 10 ppm for 45 years (450 ppm-years), using the various exposure assumptions and control sets described above. The Crump and Allen I exposure assumptions are those originally derived by these investigators. The Crump and Allen II exposure assumptions are their alternate estimates in which a ceiling of 131 ppm for each job category was enforced.

Our analyses demonstrate that use of the Crump and Allen I (*37*) exposure assumptions instead of those of Rinsky et al. (*20*) will reduce the leukemia mortality risks projected substantially (by factors of approximately 10 and 77, at 45 and 450 ppm-years, respectively). Further, use of control groups in which more stringent and alternative matching criteria are applied will also affect the estimates of risk.

We propose that selection of controls from the larger cohort, which included both the wet- and dry-side workers, is appropriate. We believe our additional criterion of

Table 3. Summary of present authors' analysis of Rinsky et al. (*19*) data using conditional logistic regression and alternative exposure assumptions and control groups.

Exposure assumptions	Control set[a]	Additional lifetime leukemia deaths per 1000 workers due to benzene exposure	
		45 ppm-years	450 ppm-years
Rinsky et al. (*20*)	1 Rinsky et al. controls matched on: date of birth date of entering Pliofilm	5.1 (0.83–11.7)[b]	635 (15.6–986)
Rinsky et al. (*20*)	2 Present authors controls matched on: date of birth date of entering Pliofilm	6.4 (1.2–14.7)	819 (26.4–991)
Rinsky et al. (*20*)	3 Present authors controls matched on: date of birth date of entering Pliofilm plant	4.2 (1.0–8.7)	449 (21.3–953)
Crump and Allen (*37*) I	1	0.5 (0.13–1.0)	8.3 (1.4–20.4)
Crump and Allen (*37*) I	2	0.7 (0.1–1.3)	11.0 (1.4–30.9)
Crump and Allen (*37*) I	3	0.5 (0.1–1.0)	7.9 (1.1–20.4)
Crump and Allen (*37*) II	1	1.3 (0.3–2.3)	29.8 (4.2–106)
Crump and Allen (*37*) II	2	1.6 (0.3–3.1)	47.0 (4.0–218)
Crump and Allen (*37*) II	3	1.2 (0.3–2.3)	27.8 (3.3–103)

[a]Control sets: 1) Rinsky et al. controls matched on date of birth, date entering Pliofilm work; 2) present authors controls matched on date of birth, date entering Pliofilm work; 3) present authors controls matched on date of birth, date entering Pliofilm work, and plant.
[b]Numbers in parentheses are 95% confidence intervals.

matching by plant is also appropriate, because it eliminates potential location bias. We therefore have a preference for the risk estimates based upon our control set 3. In the following section, we will describe additional data on the benzene exposure history at the Pliofilm plants studied by Rinsky et al. These data are of importance because they provide a basis for selection from or adjustment of the various benzene risk assessments.

Additional Factors Regarding Benzene Exposure in the Rinsky Cohort

There are a number of additional factors that were not accounted for in the assessment of the total benzene exposure of the Rinsky et al. Pliofilm cohort that may significantly affect the estimates of risk projected on its basis. First, employment of members of the cohort in the non-Pliofilm jobs involving benzene exposure was not accounted for in any of the exposure assessments of the Rinsky et al. cohort. Preliminary review of the subset of the job histories of the cohort (within the Goodyear plant) indicates that a large percentage of the workers also worked in non-Pliofilm jobs in other areas of the plant. These jobs dated back to the early 1900s and involved areas of the plant (e.g., tire building, cement mixing) for which there is evidence that pure- or high-benzene concentration solvents were used up to at least 1942.

A review of the literature has indicated that in the early decades of the 20th century, rubber workers appeared to be highly exposed to benzene-containing solvents and rubber cements (*41*). These substances were often applied by hand or in relatively poorly ventilated environments. Based upon a 1924 survey of the industry (*42*), benzene vapor exposures of rubber workers ranged between approximately 100 and 900 ppm. A survey of four rubber plants in 1942 reported benzene levels ranging from 10 to 350 ppm (*43*).

Wilson (*44*) described the blood examinations and symptomatology of 1104 workers at Goodyear who had used benzol. He indicated that the concentration of benzol to which patients seen at the company hospital were exposed varied between 50 and 500 ppm, with an average concentration of 100 ppm; occasional sharp exposures of 500 to 1000 ppm benzol were also cited. Of this group of 1104 workers, 83 (7.5%) showed mild blood changes, and 25 (2.2%) showed severe blood changes (aplastic anemia) with symptoms of severe benzene intoxication. Three of these 25 patients died as a result of the aplastic anemia. At a 1942 conference on health hazards in the rubber industry, Conn of Goodyear specifically cited the spreader operation of Pliofilm production as an area of elevated benzene concentrations that resulted in two deaths from severe aplastic anemia (*45*). He indicated that prior to the introduction of ventilation measures, benzene exposures ranged from 500 to 700 ppm directly above the spreaders. Data contained in the work histories of the Rinsky et al. Goodyear cohort indicate that during the 1940s a number of hospitalizations and fatalities secondary to acute exposure to high levels of benzene also occurred in the neutralizer area of the Pliofilm plant (*46*). This is particularly noteworthy in regard to the Rinsky et al. cohort, in which 6 of the 9 leukemia cases worked in the spreader-neutralizer area during the 1940s, when other workers performing the same jobs sometimes suffered fatal blood dyscrasias. In addition, Davis (*47*), who was assistant medical director of Goodyear, wrote of examining about

7000 workers who had used various substances containing benzene over a 12-year period. These reports suggest that Goodyear used benzene in various operations at least as early as 1917 to 1942 or later.

A preliminary analysis of the work histories of the leukemia cases and controls selected by Rinsky et al. (*20*) indicated that the 9 cases had substantially more potential exposure to benzene than did the 90 matched controls, both in Goodyear non-Pliofilm and Pliofilm operations. Overall, it was observed that the cases worked, on average, nearly three times as long as controls in solvent-related non-Pliofilm jobs, in which benzene exposure was likely. When the analysis was broken down by time periods, this distinction between cases and controls was greatest during the years prior to 1942, when the use of high benzene content solvents was most prevalent (*48*).

Another factor not considered in the available risk assessments was the contribution of dermal exposure to benzene, both within Pliofilm and non-Pliofilm jobs at the Goodyear plants. There was testimony presented during the 1977 OSHA hearings that certain workers in Pliofilm were sometimes drenched in benzene. Further, in a study recently conducted by NIOSH investigators (*49*), it was estimated that workers in tire building (a non-Pliofilm job in which some of the Pliofilm workers had spent some of their years at Goodyear) have 150 contacts of the palmar surface per workday involving exposure to benzene in solution. Assuming a 0.5% benzene content in the solvent, 150 cm^2 of exposed palmar surface, 6.25 μL solvent/cm^2, 0.88 g/mL benzene density, and 1% dermal absorption, they estimated that 6.19 mg benzene would be absorbed per workday. Additional studies by Maibach (*50–52*), Franz (*53*), and Hanke et al. (*54*), however, suggest that the dermal absorption value applied by Susten et al. (*49*) was possibly too high by a factor of approximately 3. This would lower the amount of benzene absorbed in tire building in which 0.5% benzene in solvent is presently used to approximately 2 mg/day (vs. approximately 15 mg/workday absorbed from inhalation of 1 ppm for 8 hr) (*55*). If 100% benzene were used, as was likely the case in certain jobs prior to 1942, the amount absorbed by the dermal route would increase by a factor of approximately 200, to a level of approximately 400 mg/workday (*56*).

The American Petroleum Institute has made some preliminary estimates of the potential effect upon leukemia risk of the addition of non-Pliofilm airborne and dermal benzene exposures to the Pliofilm-specific benzene exposure estimates applied in the case-control analyses. For these analyses, three different sets of exposure assumptions were developed for the non-Pliofilm jobs of the workers, representing potential low, moderate, or high benzene exposure. At the time when these calculations were performed, NIOSH had only made available a subset of the work histories of the Rinsky et al. cohort. Consequently, to perform these calculations it was necessary to develop a procedure in which non-Pliofilm exposure of workers for whom no work history was available was estimated from the experience of workers for whom a work history was available (*57*).

These analyses suggested that the additional consideration of non-Pliofilm airborne and dermal exposure of the Rinsky et al. (*20*) cohort could result in a substantial lowering of the excess leukemia risk associated with benzene exposure. For example, on the basis of the high non-Pliofilm benzene exposure assumptions, excess risk associated with 45 years of exposure at 1 ppm in the workplace would decrease by a factor of 17 assuming the Rinsky et al. (*20*) exposure matrix, and by a factor of 2 assuming the Crump and Allen I exposure matrix. It should be noted that these estimates are by necessity crude as they were based on limited additional industrial hygiene data for non-Pliofilm work areas and because complete work histories were not available on all members of the cohort at the time of the analysis.

Nevertheless, these estimates suggest that the lack of consideration of inhalation and dermal absorption of benzene in non-Pliofilm areas in calculating cumulative exposure of the Rinsky et al. cohort resulted in an underestimation of total exposure and possibly an overestimation of risk. API intends to investigate additional sources of information on airborne benzene levels in non-Pliofilm areas and on the extent of dermal exposure in Pliofilm and non-Pliofilm jobs. Such data will be incorporated into future assessments of benzene-associated leukemia risk.

Conclusions About Leukemia Risk

When epidemiological data of reasonably good quality are available, these data should be used to assess risk to human populations. In the case of benzene leukemogenesis, the Rinsky et al. study of benzene-exposed Pliofilm workers (*20,21*), because of its relatively large amount of exposure information, appears the best suited for assessing quantitatively the leukemia risk of benzene. The risk assessments that have made use of the Rinsky et al. data therefore form the basis of our conclusions about the risk of leukemia associated with occupational benzene exposure.

We have reviewed seven earlier benzene risk assessments of the Rinsky et al. cohort that employed the linear model (*27,30–35*); the assessment of White, Infante, and Chu that employed the one-hit model (*36*); the Crump and Allen assessment that used both the relative and absolute risk linear models (*37*); the Rinsky et al. assessment that used linear logistic regression for a case-control subset of the cohort (*20,21*); and the present assessment that used linear logistic regression with various modifications to the Rinsky et al. (*20*) case-control analysis.

The earlier assessments, and that of White, Infante, and Chu (*36*), in our judgment, all inadequately characterized the benzene exposure history of the cohort, and consequently, estimates of risk derived from these assessments should be considered more limited than those of Rinsky et al. (*20,21*), Crump and Allen (*37*), and the present report. Our conclusions about benzene-associated leukemia risk are therefore based upon these three latter analyses.

The Crump and Allen (*37*) and the Rinsky et al. (*20,21*) assessments should be considered preferable to the earlier assessments as they both attempted to character-

ize the benzene exposure histories of individual members of the Pliofilm cohort, as opposed to making generalizations about benzene exposure of the cohort as a whole. The manner in which exposure in individual work areas of the Pliofilm plants was assessed appears to be the factor of greatest influence on the number of excess leukemia deaths projected in these various assessments. The Crump and Allen (*37*) methodology of exposure assessment differed from that of Rinsky et al. (*20,21*) in a number of respects. Crump and Allen calculated time-weighted average benzene levels over seven multiyear time periods, whereas Rinsky et al. derived single-year values on the basis of actual values or by linear interpolation. In cases where there were no data available for earlier time periods, Rinsky et al. extrapolated the benzene concentrations for the earliest year back to the plant opening. In fact, for 3 of the 10 exposure classes considered by Rinsky et al., levels from the 1960s were extrapolated back into the 1930s. Crump and Allen, in the event that there were no measurements for a given area for a given period, multiplied the estimate from the following period by the ratio of the occupational standard or recommendation for the period to that of the occupational standard or recommendation of the following period.

Both groups used data from location 1 as a surrogate for location 2. Crump and Allen used data from the two locations interchangeably, whereas Rinsky et al. applied data from location 2 only to this location. Rinsky et al. also excluded from their estimates data documenting high benzene levels in the storage area of the plant; these were included by Crump and Allen in their average exposure category. These various differences resulted in the exposure estimates of Crump and Allen being generally higher than those of Rinsky et al. for the majority of the job titles and time periods covered.

In the absence of additional monitoring data, it is not possible to render a judgment as to which methodology best estimates the absolute exposures experienced by the cohort. As described above, a major difference between Rinsky et al. and Crump and Allen was in their methodologies for estimating exposures in the earlier years, when no industrial hygiene data were available. The result of this methodologic difference is that the Crump and Allen estimates for the early years generally exceeded those of more recent years, while the Rinsky et al. estimates for early years were often the same as for more recent years. We have a preference for the Crump and Allen methodology for estimating relative benzene exposures during the earlier years, as it seems more plausible that such exposures were higher than those measured more recently. A recent analysis in which an attempt was made to correlate hematology data of the Pliofilm cohort with both the Rinsky et al. and the Crump and Allen exposure assumptions tends to further support the methodology applied by Crump and Allen. In this analysis, the Crump and Allen exposure estimates correlated more strongly than the Rinsky et al. estimates with fluctuations in the white and red blood cell counts of the cohort (*58*). Of the two exposure matrices presented by Crump and Allen, we prefer the original matrix. As detailed earlier, the available data on human benzene toxicity provide some support for this exposure matrix, which was derived from existing industrial hygiene data.

We adopted the exposure methodologies developed by both Crump and Allen and Rinsky et al. in our estimations of benzene leukemia risk. Our analyses used the matched case-control conditional logistic regression methodology. We assessed the effect of applying the Crump and Allen exposure methodology to the Rinsky et al. case-control data set. We selected three additional sets of controls: the first applying Rinsky's criteria of matching by date of birth and date of first employment in Pliofilm; the second in which the controls were matched by plant in addition to the Rinsky matching criteria of date of birth and date of first employment in Pliofilm; and the third in which controls were matched by the Rinsky criteria, plant, and date of last employment.

Table 4 presents the range of additional lifetime leukemia deaths per 1000 workers associated with occupational benzene exposure which were projected in the various assessments in which the Crump and Allen (*37*) and the Rinsky et al. (*20,21*) exposure methodologies were applied. In all cases, risk was associated with cumulative benzene exposure. Based on this table at 10 ppm benzene exposure for 45 years (450 ppm-years), a range of 7.9 to 819 additional leukemia deaths per 1000 workers would be expected. By reducing the OSHA PEL to 1 ppm, again assuming 45 years of exposure (45 ppm-years), approximately 0.5 to 7 additional leukemia deaths per 1000 workers would be expected.

We have a preference for the conditional logistic regression approach adopted by Rinsky et al. (*20,21*) and subsequently by ourselves because it makes maximal use of the data points available. We also prefer the strict criteria for matching that we have used, in which the cases were matched by date of birth, date of first employment in Pliofilm, and plant (control set 3). We prefer the use of Crump and Allen's exposure matrices because they, in effect, assume exposures in earlier years exceeded those in later years. Available data on benzene toxicity in humans appear to provide greater support for Crump and Allen's original exposure matrix. This methodology and choice of control group and exposure assumptions results in our preferred estimate of 0.5 excess leukemia deaths per 1000 workers exposed for 45 years to 1 ppm benzene, and 7.9 excess leukemia deaths per 1000 workers exposed for 45 years to 10 ppm benzene.

It should be noted, however, that these estimates do not take into account the influence of benzene exposure of workers via inhalation and dermal absorption in non-Pliofilm areas of the plants studied by Rinsky et al. On the basis of our preliminary analyses, it is suggested that accounting for such exposures will likely result in a substantial lowering of the occupational leukemia risks which were estimated on the basis of this study.

Additional data on the extent of inhalation and dermal exposure to benzene in the Rinsky et al. cohort may be revealed through the analysis of Goodyear workers' history records recently made available by NIOSH and by

Table 4. Comparison of available benzene risk assessments in which Crump and Allen (*37*) or Rinsky et al. (*20,21*) exposure assumptions were applied.

Risk assessment	Data set used	Exposure assumptions	Model applied	Additional lifetime leukemia risk per 1000 workers due to benzene exposure	
				45 ppm-years	450 ppm-years
Rinsky et al. (*21*)	Rinsky et al., 1986 case-control analysis	Rinsky et al. 1986 cumulative exposure estimated on an individual basis	Conditional logistic regression	5.3	667
Present authors I[a]	Rinsky et al., 1985 alternate case-control analysis	Rinsky et al. 1985 cumulative exposure estimated on an individual basis	Conditional logisitic regression	4.2–6.4	449–819
Present authors II[a]	Rinsky et al., 1985 alternate case-control analysis	Crump and Allen 1984-I cumulative exposure estimated on an individual basis	Conditional logistic regression	0.5–0.7	7.9–11.0
Present authors III[a]	Rinsky et al., 1985 alternate case-control analysis	Crump and Allen 1984-II cumulative exposure estimated on an individual basis	Conditional logistic regression	1.2–1.6	27.8–47.0
Crump and Allen (*37*)	Rinsky et al., 1981 cohort study (8 leukemias)	Crump and Allen 1984-I cumulative exposure estimated on an individual basis	Relative risk (linear)	6.6 (for 40 ppm-years) beginning at age 20	63 (for 400 ppm-years) beginning at age 20

[a]Ranges reflect the use of three different control groups.

pursuing additional sources of data of past exposure practices in the industry. Clearly further investigation of the actual extent of additional benzene exposures of the cohort is warranted in order to improve susbsequent estimates of the leukemia risk associated with human exposure to benzene.

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