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REVIEW, CRITIQUE, AND RISK EVALUATION OF BENZENE EPIDEMIOLOGY STUDIES

A Report Prepared for the American Petroleum Institute

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OF BENZENE EPIDEMIOLOGY STUDIES

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I. Introductory-Summary and Conclusions

A comprehensive assessment of the epidemiologic evidence concerning the risks of human disease, as related to a particular type of environmental exposure, would ideally resemble the form presented in a summary outline in Figure 1. (For ease of reference, the Figure and all Tables appear at the end of the text.) The present review on the question of leukemogenic effects of human population exposures to benzene is an approach to that ideal, though much restricted in detail.

Because some of the previously reported reviews of this question have been presented as quantitative risk assessments, it is necessary to address three topics prior to consideration of the principal focus of this report. These are: (1) the generic limitations of quantitative risk assessment; (2) the epidemiologic studies selected for use in the reported quantitative risk assessments for benzene exposure; and (3) the resulting assessments themselves. Against the background given by these first three sections, this review concludes with a more comprehensive assessment as suggested by the outline of Figure 1.

Discussion of the generic limitations of Quantitative risk assessment addresses the following issues: selection of studies for inclusion; compilation of exposure data; selection of the effects whose risk is to be estimated; and synthesis of the above into an estimated dose-response function. Emphasis is given to some of the sources of bias in such estimation and to appropriate procedures for representing the uncertainty of the results.

The epidemiologic studies selected by others. for use in quantitative risk assessment are limited to 6 in number, and these are identified and described. Three of these have been used by 3 or more of the reported risk assessments and are discussed in some detail. Of the remaining 3, 2 are unpublished and the third contributes very little to quantitation of risk, and these are therefore discussed only very .briefly. Overall, these studies present data of very uncertain reliability as a basis for serious assessment of a quantitative relation between benzene exposure and the risks of leukemia.

The methods and results of the 6 reported quantitative risk assessments are discussed in relation to the generic issues already addressed. Each of them presents limitations of methods or difficulties of interpretation which make them unsatisfactory as a basis for overall judgment concerning the relation between exposure to benzene and the occurrence of leukemia.

A more comprehensive assessment of the epidemiologic evidence concerning benzene and the risk of leukemia is developed in accordance with the outline of Figure 1. More than 50 reports are considered which address the occurrence of leukemia in occupational settings where the potential for exposure to benzene is stated or implied. These reports are grouped according to their explicit mention of benzene or, alternatively, the type of occupation or industry studied --- refinery workers, chemical and petrochemical workers, and rubber workers. The main conclusion from this review is that this broad - based approach gives only weak or mixed support to the widely-held view that

benzene is causally related to the occurrence of leukemia in the occupational setting. The inconsistency of the evidence might be explained by such factors as unreliability of the information concerning potential exposures, various methodologic issues, or the necessity of particular conditions of exposure in order that an effect to occur.

Conditions of exposure and their assessment are discussed, with a resulting contrast between the conditions described formerly by European hematologists, at one extreme, and those found in recent studies in U.S. industries, at the other. A continuous trend toward lower levels of potential exposure has been claimed for one population from the early 1940s until the 1970s (42). Such a trend may offer one explanation of a decreasing SMR for leukemia in that population with extended data collection (68). One source indicated that U.S. industrial benzene levels were typically at or below 1 ppm (8-hr TWA) between 1977 and 1983 and suggested that benzene-induced leukemia might no longer be occurring (72).

A test of one reported quantitative risk assessment (89) against the experience of one U.S. industry, refinery workers, demonstrated failure of the risk assessment to project accurately the numbers of leukemia cases actually observed. Even the lower bounds of the risk estimate generally gave projected numbers of cases which would clearly have been in excess over the expected number, whereas deficits of cases were actually reported. This was true whether a 10- or a 1-ppm 8-hr TWA exposure level was assumed. These results indicate that the

risk estimate used does not represent actual experience, at least within the limited number of populations where the necessary data were readily available. This suggests, that the effective exposures were in fact below a 1 ppm 8-hour TWA or that the model substantially overestimates the risk. In either case, the results from this one risk assessment do not lend support to the view that there is a prevailing risk of leukemia to U.S. workers which would be reduced by lowering the current benzene standard to 1 ppm 8-hr TWA or below.

Further investigation is strongly desired to help resolve this and other questions concerning benzene and the risk of leukemia. Of particular importance would the be extension of the approach presented here, by testing each of the available quantitative risk assessments against as much as possible of the accumulated experience of working populations. Unpublished data may be accessible which would permit both broader and more specific evaluation of the existing quantitative risk assessments-. as well as adding to the main objective of as comprehensive as possible an evaluation of the epidemiologic evidence. If there is potential for reducing the risk of leukemia among U.S. workers generally, by adoption of a revised. benzene standard, this remains to be demonstrated satisfactorily.

11. Issues in Risk Assessment: Generic Limitations

A quantitative risk assessment for benzene exposures is an attempt to estimate some theoretical response probability as a function of benzene dose. The data used for this process are generally derived from a small number of occupational studies where past exposures to benzene have been unusually high. The estimated probability is then used to extrapolate from effects observed at these relatively high doses to those at some lower "acceptable" level of probability, with a view to decreasing human exposures to the corresponding "safe" dose level implied by this. Also, they are frequently used to predict effects at lower doses.

Such extrapolations must necessarily be done via mathematical models (63). However, current knowledge of carcinogenic processes is inadequate to determine in a given situation which mathematical model is most appropriate.-- Regulatory agencies have opted, as a matter of policy, to use very conservative models for risk extrapolation to low dose, so as to render it less likely that the risk is under'stated (see below). There are a number of other facets in the risk assessment process which may markedly influence the estimated risk function. For many of these, the situation is similar to that for the mathematical model: The requisite knowledge for a proper scientific treatment is not available. Again, regulatory agencies employ conservative assumptions to avoid understating the risk. These actions inevitably bias the risk estimate upward. A plausible, unbiased, and accurate risk assessment,

however, should be constantly strived for. Instances may occur where sources of bias can be recognized. Efforts should be made to reduce or eliminate these biases.

More specifically, the development of a quantitative risk assessment for exposure to benzene can be thought of as made up of four components:

A. Selection of studies for inclusion in the risk assessment.

B. Compilation of exposure data.

C. Selection of effects whose risk is to be estimated.

D. Synthesis of A, B and C into an estimated dose-response function.

These are considered in further detail below. The studies involved are assumed to be human epidemiological studies.

A. Selection of studies.

A key issue in the selection of studies for inclusion in the risk assessment is the set of criteria used for deciding on the inclusion or exclusion of a given study. These criteria should be stated explicitly. Three extreme hypothetical types of criteria come to mind: (1) Include only positive studies where there is a significant excess risk; (2) include only neutral studies where the risk is no different than expected; (3) include only negative studies where there is a significant risk deficit. Obviously, the first criterion will yield inflated risk estimates; the second, zero risk; and the third, inflated benefit estimates.

A related issue is the availability of studies for

consideration. Studies are usually not done unless there is fairly strong interest, locally or more generally, in a perceived problem. There is a tendency for scientific journals to publish only "positive" and not "negative" studies. As a result, neutral or negative studies are less likely to have been conducted; if conducted, they are less likely to be submitted for publication; and if submitted, they are less likely to be published. Even if published, neutral or negative studies are unlikely to be selected by regulatory agencies in conducting their risk assessments, as noted above.

It is the unusual industrial plant, the extreme, with headlines in local newspapers and television interview about excessive cancers or deaths, that is of interest and that is consequently studied with the results published in the scientific literature. The unusual leukemia patterns within these few plants will not be representative of leukemia for all the plants within the industry, nor will the risk estimates generated therefrom.

B. Compilation of exposure data.

Occupational studies usually lack reliable historical exposure data, even in the sense of environmental monitoring rather than direct personal exposure. Attempts have been made to alleviate this type of problem in the risk assessment process by selection of convenient dose scale. One dose scale which is in common use is the amount of total intake of a substance. This choice is especially appealing in some situations, because upper and lower bounds for the total intake may sometimes be estimated from historical data, whereas more precise estimates cannot.

However, the dose units for any substance should ideally be tailored to its biological mode of action, but the total intake, expressed in units such as ppm.years, may be biologically unsound. For instance, a man taking two aspirin tablets a day for 300 days has the same total intake as another man taking 600 in one day, yet the effects are different. Total intake dose units are inappropriate when small amounts of the test substance are safely excreted or detoxified, but where large amounts overwhelm these defense mechanisms.

Abuse of the dose scale occurs when a number of different scales are employed in the risk assessment process, and only that single scale which minimizes, or maximizes, the risk is selected in the report of the results. Since in the case of the benzene, the most appropriate scale is not known, it would be better to report the results for each of a variety of plausible dose scales.

Bias in risk assessment can also arise by grouping dose categories in various ways so as to maximize or minimize the risk, or so as to give the appearance of a smooth or monotonic dose-response function.

Confounding factors are also important. Bias may be introduced through multiple exposures to other substances and through the failure to account for these in the risk analysis.

C. Selection of effects or groups whose risks are to be estimated.

Bias can occur through pooling of two or more separate effects to enhance or diminish the estimated risk. Bias is

automatically introduced when surrogate effects (e.g., lung cancer) are employed in place of the target effect (e.g., acute non-lymphocytic leukemia). An effect may also be diluted through pooling of selected subgroups of the study population, or it may be exaggerated by redefining groups, or focusing on selected subgroups while ignoring others. These forms of bias fall under the category of statistical pitfalls known as shifting definitions or categories.

Bias can also occur when the comparison or control group is different, or is treated differently, than the exposed group. For example, specific death rates for the general population are used to calculate SMRs. They are based on the underlying cause of death as stated on death certificates. It is inappropriate to use additional conditions on death certificates for the exposed group, say, since these are not available for the comparison group. Doing so would bias risk estimates upward.

The healthy worker effect is a problem in occupational studies because workers tend to be healthier than the general population. Thus a comparison of workers to the general population tends to underestimate risk, especially for long-term chronic illnesses such as diabetes or atherosclerosis. The healthy worker effect is less of a problem for cancers.

D. Synthesis into an estimated dose-response function.

When all the studies to be included have been examined and the doses and effects to be used have been determined, there remains the task of synthesizing these in some manner into an

estimated dose-response function.

The manner in which the studies are to be combined should permit the inclusion of all relevant studies, be they positive, neutral or negative. There is also the question of weighting the studies in some fashion, which is no easy matter. Yet surely larger and longer-term studies should carry more weight than smaller or short-term studies of otherwise equivalent quality.

One of the most important components of a risk assessment is the choice of mathematical models for the dose-response function (27). If a truly unbiased estimate of risk is sought, then the model must be completely adaptable. That is, it must allow for the possibility of positive, zero, and even negative risk estimates (28). Such models are not known to be employed by regulatory agencies. For a substance like benzene, for which leukemogenicity may apply at very high dose levels, but not at lower ones, such models are essential for obtaining unbiased risk estimates and would be especially useful in resolving some of the issues concerning risk.

Current approaches to risk assessment leave much to be desired. There is an overemphasis throughout on' one-sided, "conservative" assumptions and models; But if conservative assumptions are used throughout the process of estimating a risk, then the resulting estimate is necessarily an approximation to an upper bound; and "liberal" of equal. plausibility should be used throughout for estimating a lower bound. Failing this sort of parity, what are represented as the upper bounds and lower bounds may not be such at all. One consequence of such bias in the results is to misrepresent, by underestimation, the magnitude of

unreliability of the estimated upper and lower bounds. An erroneous impression of the precision of the risk estimates is likely to result. Thus, whenever a procedure, selection, method, or assumption is accepted for calculating one bound of the risk, its complement of equal plausibility but opposite in direction should be accepted for calculating the other bound. Some examples will illustrate this:

If the lower bound of risk is calculated using a subgroup of the data with the lowest SMR, then the upper bound may be calculated using the subgroup with the highest SMR, and conversely.

If the lowest plausible estimates of exposure concentrations are used in calculating an upper bound, then the highest plausible estimates may be used for the lower bound. And conversely.

If a linear model is used to estimate detrimental aspects of an exposure in studies with positive risk gradients, then a linear model is applicable for estimating beneficial aspects of the same type of exposure in studies with negative risks gradients, and conversely.

If one surrogate outcome occurring with relatively low frequency is selected for determining the lower bound of risk, then alternative surrogate outcomes, selected for relatively high frequency, are permissible for calculating an upper bound. And conversely.

Consider a study wherein the SMR is greater for the very low-exposure category of workers than for the higher exposures. If this evidence were used to argue that an exposure is causally related to an effect even at such very low doses, then it may also be used to argue that the same type of exposure is beneficial at the higher doses. And conversely.

Should proponents of one risk estimate object, say, to using the lowest plausible estimates of exposure concentrations for calculating an upper bound, then they would have no grounds for employing the highest plausible estimates for estimating a lower bound of risk. And conversely.

A scientifically valid risk estimation process must be impartial in calculating the uncertainties involved. The above examples, though exaggerated, do serve to illustrate the

following point: The extent to which the estimated upper and lower bounds on risk appear to diverge depend heavily upon the approach taken. The approach of using assumptions or procedures which are "equal but opposite in direction," as suggested above, would provide at least a more balanced indication of the uncertainties involved in a risk assessment.

Of course, the foregoing examples include several procedures which would be seriously biased. Making such bias balanced by use of extreme approaches on both sides would exaggerate the impression of unreliability of the risk estimates. The range of uncertainty can in fact be reduced, properly, by avoidance of such biased procedures in either direction. Adoption of an approach which is both balanced and reasonable should thus offer the most desirable results, on the assumption that those involved earnestly seek the most precise and unbiased estimates of risk that can be obtained.

III. Critical Evaluation of the Selected Epidemiologic Studies Which Were Utilized in the Reported Quantitative Risk Assessments

A. Studies addressed

Six quantitative risk assessments concerning possible carcinogenic effects of benzene on human populations have been reported to date (15, 16, 19, 44, 68, 89). All have been highly selective in their reliance on particular studies, in relation to the whole of the epidemiologic literature on this question. This is due in part to the very limited number of epidemiologic studies with any quantitation of benzene concentrations in air to serve as an index of possible exposure. In addition, not all of these studies were available at the time of each of the risk assessments. Beyond these limitations, however, the selection among the studies available at particular times has varied still further.

Table 2.1 indicates, in alphabetic order, both the six reported quantitative risk assessments and the six epidemiologic studies which served as the basis for one or another of them, The differences in the selection of studies is clear from this Table. All of the quantitative risk assessments utilized the study of Infante and others published in 1977, either alone or as extended in some respects by the report of Rinsky and others published in 1981 (42, 69). This latter extension was not available to the CAG at the time of its report in 1979, so their analysis was limited to the original publication of 1977 (42). The 1981 extension of the Infante study was in effect subsumed by Rinsky and others in the 1985 report, which further

expanded the report by Infante in 1977 (68).

The study of Ott was included by all except Rinsky (68), The report of Vigliani in 1976 was incorporated only by the IARC reviewers (44, 85). The Wong report of 1983 was available to Crump and Allen, who included it, and to the authors of the CDHS report, who did not (15, 19, 91). The latter group relied instead upon the CAG and EPA interpretations of the Aksoy, Infante/Rinsky, and Ott reports (7, 15, 42, 65, 69).

Some of these six studies, utilized in one or another of the quantitative risk assessments, have been reviewed by others, especially the studies of Aksoy, Infante and others, and Ott and others. White, Infante and Chu, for example, presented arguments against the use of the Aksoy or Vigliani reports for the purpose of quantitative risk assessment (89). Where appropriate, the comments of previous reviewers are acknowledged in the discussions of the respective reports which follow.

B. Approach

It is not practical to present in this document an exhaustive evaluation of each of the six reports which were identified above as the bases for the various quantitative risk assessments. The central issues, with respect to quantitative risk assessment, are the evidence of risk and the evidence of exposure presented in connection with each study. Each of the reports utilized in more than one of the risk assessments is therefore examined specifically as to the reported frequencies of leukemia, the conditions of exposure to benzene, and the

potential for bias in these critical respects. For each of the remaining three reports, utilized in only one of the risk assessments (two of these reports still unpublished), only brief comment will be given here.

C. Comments on each study

Aksoy 1974 ff.

In December, 1974, Aksoy and colleagues at the Section of Hematology of the Istanbul Medical School reported on a case series or cluster of leukemia cases among shoe-workers exposed chronically to benzene (7). That report purportedly addressed the question of the risk of leukemia in this worker population relative to that in the Turkish population at large.

Over a 7-year period the authors had identified 26 cases which they attributed to an underlying population of 28,500 such workers. A calculation was described the result of which the authors took as evidence of "a marked and statistically significant increase" in the incidence of leukemia among such workers over that of the general population. They claimed to have provided "cogent evidence for the clinical impression of a leukemogenic effect of benzene in man." Their conclusion was based on a ratio of 13/100,000 events observed to 6/100,000 expected, or 2.17. However, attentive reading of both their report and the source cited for the expected value indicates some problems with this calculation. The observed cases were incident cases of preleukemia and acute leukemia in Istanbul hospitals from 1967-73. The expected number was based on a report of leukemia deaths in 24 countries in 1965 (35). No adjustment was

made for age differences between the populations compared, incidence was compared with mortality, and no evidence was provided to suggest that the leukemia rates for Turkey resembled those of the 24 countries. These and other issues dictate great caution in evaluating the risk estimate presented by these investigators.

Equally crucial to the immediate discussion is the information on exposures to benzene related to this estimate of risk. The 1974 report already cited identified all 26 cases and their source population as shoe workers, exposed to benzene as a solvent, said to be present as 9 to 88% of the composition of the adhesives in use (4,7). The authors stated, "The working conditions in the industry are not good; their shops are usually small, not hygienic, and poorly ventilated; the concentration of benzene was found to reach a maximum of 210–650 parts per million when adhesives containing benzene were in use." In six additional reports, variously citing these cases and others, other information is given to suggest benzene concentrations of 150–650 ppm, as exposures occurring for 8 hours or more daily, for a mean duration of 6.7 years, among these cases (1, 4, 5, 6, 8) Benzene concentrations in the range from 15–30 ppm were reported outside working hours (4).

These reports do not indicate which locations were monitored or how many, how they were selected, when the reported measurements were obtained in relation to the detection of cases of leukemia, or precisely what the exposures were in terms of 8-hour Time-Weighted Averages (TWA). They do not, with few

exceptions, provide estimates of exposure .specific to individuals. However, they do suggest that in a large occupational group exposed for several years at levels commonly reaching into the hundreds of ppm an excessive rate of leukemia occurrence may have been observed. This appearant excess risk of leukemias in the late 1960s and early 1970s was Considered to have abated by 1974–5, the apparent decline being attributed to substitution of other material for benzene beginning in 1969 (2).

Infante 1977/Rinsky 1981

On April 18, 1976, the Akron Beacon Journal carried a front-page headline which read, "Leukemia killed 7 at Coodyear who worked with same chemical" (93). It was noted that "A team of Beacon Journal reporters has been investigating cancer deaths in the rubber industry." The article stated further that "Nine days ago, federal officials sent a letter to Goodyear asking permission to enter its Akron plant to investigate the former pliofilm operation. The government eventually will examine the cause of death of every person involved in pliofilm production. ...Investigators for the National Institute for Occupational Safety and Health say the study will take at least nine months to complete." The study which followed the work of these reporters was thus an investigation of a case cluster, analogous in important respects to the Aksoy report discussed above. That is, in both situations it was necessary to construct some source population as the denominator from which the cases might' have come, after the fact of case identification. Thus, in neither situation was

there prior definition of a population at risk with subsequent observation for the new occurrence of disease. The necessity to contrive a source population for the cases after the fact is the basis for some of the limitations of this study (as well as of Aksoy's), as is discussed below. Another issue critical to such studies is the prior probability that even a properly constructed denominator will suggest an excessive rate of disease, given the exceptional character of the cluster as the stimulus for the investigation in the first place.

In any case, in July, 1977, Infante and colleagues, of the U.S. National Institute for Occupational Safety and Health, reported the results of a study of 748 pliofilm workers, at two localities in Ohio, all of whom were judged to have had "direct exposure to benzene" in the period 1940–49 (42). Two overall estimates of leukemia risk were presented, one being an SMR of 474 when pliofilm workers and fibrous-glass workers were compared, with 7 deaths observed vs. 1.5 expected. When white U.S. males were the comparison group, the SMR was 506. (An incidental observation is that there is no evidence in these data of a "healthy worker effect," and the authors chose to emphasize the SMR provided by the external, not the internal, reference population.) Further analyses were reported on the basis of a restricted numerator or denominator within the same data set. Thus an SMR specific for myelogenous and monocytic leukemia of 1004 was presented later in the report, challenged in subsequent published correspondence, and revised to 857 (42, 43, 78); and a still later calculation, restricted to workers with greater than

5 years of exposure, resulted in an SMR of 2100.

Regardless which risk estimate one considers, the levels of benzene exposure which may have been experienced by these workers are of particular interest. The available reports give differing impressions. The authors of the original report described the process of pliofilm production during which benzene exposure could occur and cited monitoring data for one of the two localities (42). Levels from 0 to 10 or 15 ppm had been described in a 1946 document which was cited, although the authors made the less specific claim that "employees' benzene exposure was generally below the recommended limit in effect at the time of each survey." A chronological table of these recommended limits was then presented which ranged from a maximum allowable concentration of 100 ppm in 1941 to an 8-hour TWA of 10 ppm in 1971. However, the 10 ppm standard is irrelevant in this context, since it was not in effect until 10 years after the death of the last of their 7 cases, as indicated in a later report (69)).

In that later report, Rinsky and others provided very extensive detail as to the available exposure information. They emphasized the conclusion, based on this study, that "benzene is a human carcinogen at a range of exposures not greatly above the current legal standard," which, at the time of that report, was an 8-hour TWA of 10 ppm (69). However, that same report gave contrary information on individual exposure estimates for the leukemia cases, with 5 of 7 having 35 or 40 ppm 8-hour TWA exposures, one having "probably less than 100 ppm," and one, among those employed prior to any ventilation of the work area,

having no quantitation provided. In a still later report, White, Infante and Chu stated: "The average benzene exposure over the period of 1937 to 1954...was 83 ppm. Over the period 1937-75, the average benzene exposure was 50 ppm" (89). Since, according to Rinsky and others, the great preponderance of the potential exposure period among the 7 cases occurred in the 1937-1954 interval, the figure of 83 ppm appears to be the more relevant of the two (69). The basis for these estimates is unclear, however, since no monitoring data were available, according to the Rinsky report, for the location where 5 of the 7 workers were employed, until a date after all but the last case had discontinued employment there (69).

Some addition-a1 information can be gleaned from the reports, as follows. Limited benzene monitoring data were available for one location well within the actual exposure period for the population under-study, and from two locations near the close of the exposure period of interest or later (69). The authors estimated the personal benzene exposure histories for 6 of the 7 cases but indicated a lack of information both on the earliest years of exposure, for all but one case, and on possible benzene exposures additional to those involved in the pliofilm process, for 4 of the 7 cases. The reported values could therefore be interpreted as more likely to underestimate than to overestimate the actual exposures of these workers, especially if the authors' argument is valid that potential exposures were in general decreasing from the early 1940s onward. Use of respiratory protective equipment by workers at some times and locations was

mentioned, but not in reference to any of the leukemia cases themselves. For 6 of the 7 cases, exposures apparently occurred prior to any workplace ventilation, such conditions perhaps accounting for 50% of the cumulative exposure period among these workers. No attempt at characterization of personal exposures among other members. of the study population was reported. Notably, also, the last of these 7 deaths occurred in 1961 (69), 15 years prior to even the newspaper account of 1976 and now 25 years ago.

Ott 1978

In 1978, Ott and colleagues, from the Dow Chemical Company, reported on mortality among workers considered to be occupationally exposed to benzene (69). Of 594 such workers, 335 were regarded as having been exposed prior to 1950, the three work areas involved having been operated from 1920, 1935, and 1936, respectively. In the analysis most specific for potential benzene exposures, the occurrence of one death coded as leukemia was related to 0.9 cases expected on the basis of US white male mortality over the corresponding calendar period, which would yield a relative risk of 1.11. In a larger group with other potential chemical exposures, 53 additional subjects added 0.1 expected cases of leukemia and one observed leukemia death, which would yield a relative risk of 2. A third death was necessarily excluded from these calculations since it had not been recorded as due to leukemia as the underlying cause on the death certificate.

Potential benzene exposure levels, by work area, were

reported as 8-hour TWA values from 1944 at the earliest, in one area, to 1952-53 in the other two areas. The 8-hour TWA values over the period of study were estimated from varying numbers of samples, at specified locations. The minimum and maximum values of these estimates were 0.1 and 35.5 ppm, respectively. For the individual cases, the work histories permitted estimates of 18 months of potential exposure below 2 ppm 8-hour TWA, for one case, and 2 years of potential exposure at 2-9 ppm, in addition to other chemical exposures, for the other case.

The workplace monitoring data for the mid-1940s and early 1950s, when these workers were exposed, were limited, but the corresponding estimated 8-hour TWAs were in the 9-35.5 ppm range. Multiple occupations, and multiple potential exposures while employed by Dow, occurred for the first and second of these two cases, respectively.

An incidence estimate was also given, in a single sentence in the Discussion section of the Ott report. However, there is a difficulty with this calculation, in that the expected number of cases excluded lymphocytic and monocytic cell types, while the cell types were not known for all 3 of the cases included. For one case, death was ascribed to "leukemia" and not further specified; a statement later in the report and more recent correspondence (84) give the impression of myelocytic leukemia, type not specified. The basis for this reclassification, evidently more detailed than that on the death certificate, is not stated and is not likely to have been applied equally to the events contributing to the reference or expected rates.

Accordingly, the expected value may have been underestimated, the ratio of observed to expected therefore overestimated, and the impression of a statistically significant excess incorrect. Further, the sensitivity of all risk estimates from this study to the addition or subtraction of a single case is to be noted, although the expected numbers of deaths are only slightly below those of the Infante study (42).

Rinsky 1985

This unpublished report by Rinsky and others presents a risk assessment based on an extension of the original study of Infante and others (68). It is thus both a further analysis of the original data, supplemented with additional mortality experience (2 cases of leukemia added), and a risk assessment based on these data. Thus many of the limitations of the original study discussed above remain. In connection with the bias cited above with respect to use of a previously-identified cluster of cases in estimation of population rates of disease occurrence, it is of interest that the reported SMR from the expanded study population and extended duration of study appears to have decreased, from 506 to 328. If valid, this change would support the interpretation of an initially inflated rate with the artifact of the original cluster effect diminishing over time. Perhaps further extension of the study will confirm this apparent trend. Additional evaluation of this report will be deferred until its publication. (See also IV. E. below.)

Vigliani 1976

The report of Vigliani cited in the IARC risk. assessment refers to two series of cases accumulated over periods of 34 and 17 years, respectively, in Milan and in Pavia, Italy (85). These were cases among workers in rotogravure and shoe-manufacturing occupations. Air concentrations of benzene in these work places were described as typically from 200 to 400 or 500 ppm. Vigliani noted as well: "It must be remembered that in the many cases occurring in the shoe industry, the people worked not only in the factory but also at home, doing the same job and using glues with a high benzene content without the slightest precaution."

As to the estimation of a relative risk of leukemia among such workers, this report gives only the following statement: "Saita and myself [10] calculated that for workers heavily exposed to benzene in the rotogravure and shoe industries of the Provinces of Milano and Pavia, the risk of acute leukemia was at least 20 times higher than for the general population." The citation is to the 1964 report of Vigliani and Saita which focuses on a series of 6 cases of leukemia occurring over a period of 21 years, 1942-1963 (86). As with the Aksoy report, this one seeks to attribute an observed series or cluster of cases to an assumed underlying population in order to obtain an estimate of risk. The procedure was as follows:

For the four years, 1960-1963, the total number of leukemia cases attributed to benzene exposure was 12, with 11 deaths in the same period. (In 1962-63, 11 and 10 of these events,

respectively, occurred.) The population at risk by virtue of benzene exposure was claimed to be 5000, "and probably less than 3000 were exposed to dangerous concentrations of benzene." The rate of occurrence of acute leukemias in the period 1959–1961 was claimed to be 1/20,000/year in the general population. No reference was given to support either of these estimates. The authors stated, "The incidence of acute leukemias in 1962-63...was about 20 times higher than expected, even assuming that 5000 people were exposed to benzene."

The calculation required to give approximately this result was to compute the ratio of 11 cases/ (5000 persons x 2 years) or 11 cases/10,000 person-years to the reference estimate of 1 case/ 20,000 persons/year. The result is **22,** or "about 20 times higher." Of course, if the period 1960–61 were chosen instead of 1962-63, the number of cases was 1/2 years instead of 11/2 years, and the ratio of the assumed rates would be exactly 1 instead of 22. (The contrast between the two results demonstrates clearly the effect of selecting data to make a point.) With no other basis for the estimate given by Vigliani and Saita, it seems clearly inappropriate to use these data for any serious attempt to assess risk quantitatively. Their citation by **IARC** is therefore surprising.

Wong 1983

The report by Wong to the Chemical Manufacturers Association, dated 8 December 1983, remains unpublished **and** received extensive critical comment following its submission (29, 30, 33, 36, 47, 49, 50, 59, 67, 70, 71, 91). Among its **major**

limitations were the apparent deficit of leukemia cases in the comparison group, the small number of cases available for analysis at the level of detail intended, and the very wide confidence limits at each degree of exposure where dose-effect estimation was attempted. The author's conclusions in this respect are not supported by the data presented. More thorough commentary will be deferred until the report has been published.

IV. Critical Evaluation of Previous Risk Assessments

Brief comments on each of the benzene ,risk assessments available are described below.

A. California Department of Health Services (CDHS), (1984)(15).

The CDHS used the 95% upper confidence bound on preputial cancers in mice to calculate an upper bound for the estimated total cancer risk from benzene exposures, and used the Carcinogen Assessment Group (CAG) estimate as a lower bound.

The CDHS, throughout its discussion, consistently employed conservative assumptions and techniques, on the grounds of inadequate scientific knowledge. But, on the same grounds then, liberal assumptions and techniques should be employed for calculating a lower bound of risk, and the CAG risk assessment hardly qualifies for this.

The inappropriateness of the CDHS approach and the resulting unrealistic risk estimates were emphasized by Dr. Spivey in testimony before the California Air Resources Board (76).

B. Carcinogen Assessment Group (CAG), (1979) (16).

The final benzene-leukemia risk assessment performed by the CAG used data from the Infante, Ott and Aksoy studies. They estimated the lifetime probability of leukemia death, P, from a lifetime (71 years) exposure to x ppm of benzene, to be:

$$P = Bx, \text{ where } B = 0.024.$$

The numbers used by the CAG for estimating this relationship have been thoroughly and soundly criticized by Lamm (46).

There are a number of other deficiencies in the CAG approach. First, a very conservative linear model was used with no explanation or justification given. Second, neutral or negative studies on benzene and leukemia were not considered. However, two of the studies that were used (Ott and Aksoy) required shifting definitions in order to render them sufficiently positive. (In its Preliminary Report (16), the CAG did not include the Aksoy study at all and said of the Ott report: "The Ott study indicated no excess leukemia risk with relatively well-documented exposures.") These definitional changes included changing leukemia mortality to incidence of myelogenous leukemia for the Ott study, and to non-lymphatic leukemia for the Aksoy study.

In addition, the revised data from each of the three studies were essentially reduced to two points, and a line drawn between the two. The enormous variations within each study were ignored in this process, with the result that the upper and lower bounds set forth by CAG are too low and too high, respectively, within the confines of their linear model. Indeed, the Ott study shows, if anything, a negative dose-response slope. The highest SMR is in the lowest dose group and the lowest SMR is in the highest dose group (Crump and Allen, Table 1) (19). A similar criticism applies when SIRs are employed. This evidence, being directly counter to a positive dose-response pattern, raises doubt whether any of the observed cases is attributable to benzene exposure.

C. Crump and Allen (1984) (19).

This risk assessment was done for OSHA and also employed

linear models (relative risk and absolute risk). Of the six risk assessments reviewed, this one raises the fewest objections. Crump and Allen rejected the Ott study by itself on the grounds there is no dose-response. For the other two studies, they attempted to account for within-study variation by grouping the workers into a variety of dose categories and applying each of two linear models to each category. On the other hand, the analyses were confined to the conservative class of linear models, with the result that the extrapolations to 10 ppm exposures, and less, will yield elevated risks. Even the lower bounds so calculated are elevated and thus cannot be considered as true lower bounds.

D. International Agency for Research on Cancer (IARC), (1982) (44).

The IARC developed several risk estimates for benzene using data from Aksoy, Infante, Ott and Vigliani. Their general approach was similar to that of the CAG: linear model, conservative lineavity and proportionality assumptions throughout, shifting definitions and categories, ignoring or obscuring variation, and numerous conservative assumptions about dosage. However, they prefaced the very brief development of their risk estimates with several pages of such caveats as the use of many assumptions, the variability in the data, the lack of exposure data, and the lack of scientific knowledge.

E. Rinsky et al (1985) (68).

Rinsky and others, in an update of the Infante study of pliofilm workers, employed a logit model to estimate the odds ratio for leukemia. Only a preliminary draft of this work is available, and the details provided by the authors are so scanty that it is impossible to critique this document in detail.

F. White, Infante and Chu (1984) (89).

These authors put forth an obviously biased risk estimation procedure for leukemia and benzene. They described the context in which they performed this task as scientific rather than regulatory. Yet they employed the same conservative techniques to reduce the entirety of data in averaging each of the two studies which they considered to a single point, with these results extrapolated to one ppm.

From the formulae in White, et al., it may be deduced that a lower bound for the relative risk (or standardized mortality ratio) may be expressed, for small x

$$R = 1 + .014x$$

where x is the cumulative dose of benzene in ppm*work-years. This was derived from the Rinsky (1981) study. The corresponding upper bound is

$$R = 1 + .0518x$$

Therefore, if E represents the expected number of leukemia deaths used in calculating an SMR, the observed number, n, should be close to (R)(E). Data from Crump and Allen (Table 2) (19) for

the Rinsky study were used to calculate the following table:

Cumulative Dose x	Lower R	Upper R	Expected E	Lower RE	Actual Observed n	Upper RE
11.0	1.154	1.570	.55	.635	0	.864
42.2	1.590	3.186	.52	.827	0	1.657
129	2.806	6.682	.32	.898	0	2.138
Total	-	-	1.39	2.360	0	4.659

Thus, for this subgroup of the Rinsky study, the procedure of White and colleagues (which is based on the Rinsky study) predicts a lower bound of 2.360 leukemia deaths, and an upper bound of 4.659 leukenia deaths, whereas zero was the number actually observed.

For the highest dose group, where x = 1482.5 and E = .051 (Table 2 of Crump and Allen), the lower and upper limits are 1.110 and 3.967, whereas only one death was observed. These failures of the White model to predict accurately relations within their own data demonstrates the extreme biases in their model. These results are in accord with the comments of Dr. Philip Cole, who severely criticized the White risk analysis for its biased approach (18).

V. Comprehensive Assessment of the Risks of Leukemia Related to Benzene Exposure

A. Studies addressed

A large number of epidemiologic studies have been reported which pertain to potential occupational exposures and the risks of leukernia. Reference to benzene is sometimes explicit and includes environmental measurement data. More often benzene is considered to be one of the substances to which exposure potentially could occur in a particular type of process or industry, but environmental data specific for benzene are lacking. The quantitative risk assessments have been very selective in their use of the available epidemiologic studies, as reviewed above. It is intended here to present a more comprehensive review of the epidemiologic evidence, to permit a more adequate overall evaluation of the relation between benzene in the work environment and the risks of leukemia.

B. Approach

The approach taken here in compiling the epidemiologic literature on the relation between benzene exposure and the risk of leukemia is in accordance with the outline presented as Figure 1 above. The first phase, that of identification of all available evidence and screening it for relevance is necessarily continuous. New evidence may come to light at any time, and earlier reports which were unrecognized or unavailable may materialize. Relevance may be judged differently at different periods in the continuing evaluation of a body of evidence such

as that under discussion here.

Notwithstanding these limitations, a reasonably comprehensive assessment of the evidence is possible at any given time if the procedures as outlined are implemented with diligence. The result of the first phase of this comprehensive assessment is a listing of 57 reports, which are categorized more or less satisfactorily as follows: (1) reports of studies with explicit reference to benzene exposure, regardless of the type of occupation or industry (Table 4.1); (2) reports of studies of refinery workers not included in (1) (Table 4.2); (3) reports of studies of chemical and petrochemical workers not included in (1) (Table 4.3); and (4) reports of rubber workers not included in (1) (Table 4.4). Known additional reports of studies of miscellaneous occupational or other conditions of potential benzene exposure are currently 11 in number; these and such other possibly relevant documents as come to light will require review as the opportunity becomes available.

The second phase entails the evaluation of each relevant report. Formally, this involves the critical assessment of each report individually, with respect to the nature of the research question, and the design, conduct, analysis and interpretation of the research. This process culminates in the reviewer's judgment of the validity of the evidence provided by a given report on the question of association between the exposure and the disease or condition of concern. It should be noted that validity of evidence does not imply the unqualified acceptance of the results, whether supportive or not supportive of an association. Rather, it implies a judgment of sufficient soundness of the

results that they may reasonably be taken as contributing something to the later overall assessment.

Some of the elements of each report considered in this second phase are presented in the respective Tables 4.1 - 4.4. Each subset of reports is summarized briefly below by reference to these Tables. Thereafter, an overall summary is addressed in accordance with the third phase of assessment outlined in Figure 1.

C. Comments on each category

1. Studies with explicit reference to benzene (Table 4.1)

The 13 papers cited refer to studies described in the several pages of Table 4.1. Studies 1, 3, 4, 5, and 8 are discussed in Section 2 above. Five were cohort and five were case-control studies, and three were investigations of clusters of cases, viewed in one or another population context. The studies were predominantly in the US (7/13), and they varied widely in the sizes of the study populations and total experience observed. Where inclusion criteria for members of the study population were specified, they also varied widely, from only 1 day to 6 months of employment being required.

Data on-potential exposure were very limited, and more often qualitative than quantitative information was presented in this respect. Only infrequently was exposure information provided which was concurrent with the observation period for the study subjects. Seldom were data presented on the duration of employment or of followup.

The results are expressed in Table 4.1 in accordance with the type of analysis reported, in terms of the SMR or the OR, with confidence intervals calculated wherever possible. In addition, the power of several studies to detect a relative risk of 2.0 or 5.0 is presented in the final column of the Table. Classification of the data for purposes of analysis differed among the studies. Subgroups were separately analyzed in accordance with the type of leukemia, the nature of the exposure, or other characteristics.

The SMRs and ORs were generally greater than 1 (corresponding to values > 100 for the SMRs) but much less consistently significant in relation to a 95% confidence interval. In the cohort studies, very small numbers of cases were expected or observed, usually fewer than 5. The two cohort studies with the greatest power did not suggest a significant increase in leukemia risks in relation to the reference population.

2. Studies of refinery workers (Table 4.2)

The 14 reports on refinery workers not already included above relate to 12 studies. All but one were of the cohort design, and nearly all were conducted in the U.S. Typically 15,000 or more employees were studied, over periods beginning from as early as 1928 to as late as 1973. Eligibility required anywhere from 1 day to 5 years of employment, and exposure classification was generally based upon job descriptions. Periods of employment of 15 years or more were common and the

mean duration. of followup was approximately 15 years or greater in 4 of the 9 studies where this was both relevant and reported.

The numbers of cases expected and observed in several of the analyses were notably greater than in the previous set of studies. In 8 of the 12 studies, the power to detect a relative risk of 2.0 or greater was at least .80. In only 4 of 11 calculations for total cohorts in these studies was the SMR greater than 1.00, and in only 1 of those 4 was the lower bound of the 95 % confidence interval greater than 1.00. By this criterion, the only study with a significantly increased frequency of leukeaia was that of McCraw, for the AML type only; the published discussion indicated that those experiencing this excess were not those most likely to have had occupational exposure to benzene (53).

3. Studies of petrochemical workers (Table 4.3)

The six reports included here refer to six cohort studies, two of which concerned the same plant. All but one of the studies were conducted in the U.S., and they were generally much smaller studies than those just described. Most of these settings involved multiple types of potential chemical exposures, in all but one case including nearly the whole decade of the 1940s within the population experience. The eligibility criterion was either one day or more or one year or more of employment in the given facilities. Where the duration of followup was reported, the range was from a mean of about 14 to 21 years.

Although the SMRs were generally greater than 1.00, none was

significantly elevated by the criterion already stated. One SIR, for lymphatic leukemia, was significant by the same criterion. This was in a cohort of workers in styrene-based processes.

4. Studies of rubber workers (Table 4.4)

The 22 reports in this set refer to 9 studies, of which 6 were conducted in the US. These were cohort studies of relatively large size, for workers employed from the 1940s or earlier (6 studies) or from the mid-1960s (3 studies). Eligibility was typically based upon 1 or more years of service. Classification by potential exposure status was based upon various job or department titles, and concurrent industrial hygiene data were lacking in all but one of the study settings. The duration of followup, when reported (4/9 instances) was most often 18-20 years.

For 6 of these studies, no SMR for leukemia for any category of workers was significantly greater than 1.0, and most ranged between .80 and 1.20. For one setting addressed in several reports, results varied for different groups of workers, with two SMRs of 1.3 and 2.4 being significantly greater than 1.00. For the remaining study, the SMR for lymphocytic leukemia among active workers was significantly greater than 1.00, based on 8 cases observed and 1.1 expected. Several additional results were presented as ORs or RRs without reported significance.

D. Summary of the epidemiologic evidence

The third phase of the comprehensive assessment entails

the judgment of the overall body of evidence as it bears on the question of causality and the particular circumstances under which a causal relation may hold. The often-cited "criteria" for judging causality (which actually only describe factors which influence such judgments and are not true criteria) are expressed in one of their conventional forms in part 3.1 of the outline in Figure 1. From this point of view, the summary of the epidemiologic evidence concerning benzene exposure and leukemia would, in its most concise form, appear as follows:

1. Consistency: Weak. Given the numerous studies by both the cohort and the case-control approach, in numerous working populations (especially those where explicit reference is made to benzene exposure), and with marked variation in study designs, there is ample opportunity for consistency to be demonstrated. However, the reported results are quite mixed as to the presence or absence of evidence of association between the occupational exposures studied and the occurrence of the leukemias.

2. Strength: Mixed. The ranges of values of the SMRs and ORs reported and of their confidence limits are wide, often being below 1.00. A dose-response relationship is not regularly found, in that those with the greatest likelihood of benzene exposure are not always those with the greatest apparent risk.

3. Specificity: Weak. Results of the kind described above for leukemia are observed for a number of other diseases as well, with generally lesser consistency. Among the leukemias the results are inconsistent as well. Because the great majority of cases of leukemia are not known to depend upon benzene exposure, specificity is lacking in this respect as well. In addition, the common experience of multiple types of chemical exposures even within the available and often incomplete work histories of individuals further weaken the specificity of such a relation.

4. Temporal sequence: Generally supportive if known, but often unclear. The question of temporal relation between potential exposure and the onset of disease is often difficult to address and seldom fully resolved, due to limitations of the data presented. Because work histories are incomplete, the possibility of intervening exposure more proximate than that under study or others more remote and possibly related to the occult onset of disease can seldom be satisfactorily excluded. That the few studies with unusually detailed case information tend to establish the necessary temporal relation is supportive.

5. Coherence: Mixed. The strongest support from disciplines other than epidemiology for a causal role of benzene in the development of leukemia is the range of its known hematotoxic effects in man and the clinical observations of cases of leukemia developing late in the course of recovery from severe bone marrow depression. The lack of an animal model for the

experimental production of leukenia has detracted from but not outweighed this support.

Overall, this evidence is consistent with the view that leukemia may occur as a result of benzene exposure, but only under certain specific conditions. Thus the evidence of increased risk in some studies and the absence of it in others requires explanation. The methodologic issues which could in part explain the differences in results of studies have been discussed or alluded to above. It remains to examine closely the issue of exposure from this point of view.

E. Assessment of current and projected conditions of exposure.

The conditions of exposure to benzene and other substances in several types of occupational settings have been reported in epidemiologic studies in the manner suggested in Tables 4.1 - 4.4. That is, explicit reference to benzene has occurred in only a small proportion of studies sometimes considered relevant to the question of the relation between benzene exposure and the risks of leukemia. Within this small subset of studies, fewer still have provided any quantitative estimate of the benzene present in the environment of the workers studied. The great majority of studies have instead given qualitative descriptions of the work environment, often in terms of the particular jobs, departments, or processes to which subgroups of workers were related.

Although it is not intended here to discuss matters of industrial hygiene in detail, several comments are appropriate as background to the further consideration of exposure, specifically that involving benzene. The extensive program of environmental and personal monitoring common in industry today is a relatively recent development. Exposure estimates going back significantly more than ten years must, in general be regarded as highly and personal monitoring common in industry today is a relatively recent development. Exposure estimates going back significantly more than ten years must, in general, be regarded as highly inferential with respect to actual exposures of individuals. In the general sense, exposure denotes the presence of a substance in the workers' environment, and the assumption that worker contact with the substance therefore occurs.

The determination of worker exposures to chemicals in the occupational environment may be made by two methods: workplace or environmental monitoring or personal dosimetry. Environmental monitoring determines the concentration of substances in workplace air by the placement of a suitable sampler or analytical instrument somewhere in the facility. This approach offers many advantages in terms of simplicity and cost, but also the disadvantage of providing concentration data at only a single location, i.e., the location of the sampler or analyzer. Given the fact that no worker spends the entirety of his work shift at only one place, the environmental concentration measured may be only a limited indication of the potential worker exposures. For this latter reason, personal dosimetry is preferred. In personal

dosimetry the sampler or analytical device is placed on the worker, and thereby affords a much better indication of the material(s) to which the worker is actually exposed. The disadvantages concern cost, and possibly complexity, for a multiplicity of sampling/analytical devices.

Devices known as detector tubes or adsorption tubes for the rapid and simple analysis for benzene have been available for many years. These are generally known by the names of their manufacturers: Draeger, Kitagawa, Unico, Mine Safety Applicances (MSA), and others. They are very easy and inexpensive in use, but suffer a high degree of imprecision, of the order of 10-25%, and sometimes higher. They are also sensitive to other petroleum hydrocarbons, including materials that are very likely to be found wherever benzene might be present. These devices also suffer the disadvantage, already discussed, of indicating workplace concentrations rather than worker exposures.

The preferred technology from the point of view of accuracy, precision and applicability to personal dosimetry involves the use of carbon absorption tubes for sampling, followed by analysis by gas-liquid chromatography. Properly performed, this technique affords. the best indication of exposure potential in both environmental and personal dosimetry modes of application.

It is evident from the earlier discussion that relatively few studies have provided exposure data in a manner approaching that of actual individual exposure. Attempts to do so, as in the treatments by Rinsky and others of the pliofilm worker material, remain largely conjectural and subject to considerable dispute (e.g., 78).

In more qualitative terms, there seems little disagreement that in U.S. industries generally, environments where the potential for habitual exposure to air concentrations of benzene in the hundreds or even tens of ppm existed over past decades, but not recently. It is suggested that in few industries has there been in recent years a potential for habitual exposure to benzene in air at concentrations above 1 ppm, and that exposure potential in excess of 10 ppm may be distinctly unusual (72).

The recent data of which we are aware do not indicate that environments of the kinds described by Aksoy, discussed earlier, exist in US industry, nor do those which may have existed in the pliofilm plants investigated by Infante and his colleagues (42). Indeed, workers whose histories have been studied over the several post-WW II decades have not shown a strong and consistent pattern of excess leukemia occurrence such as might be predicted from continued opportunity for high-dose benzene exposures (see section 4.c., above). Thus, the environmental conditions which gave rise to the epidemiologic evidence supporting an association between benzene exposure and the risk of leukemia may no longer exist in the US.

F. Estimation of risks under alternative sets of conditions.

In the quantitative risk assessments for benzene which have been discussed above, alternative approaches have been. taken on the basis of different choices of mathematical models, different interpretations or selections from the available data, and other differences. Regardless of the particular risk model which might

be invoked, it is important to consider whether or to what degree the projections it provides are consistent with the actual experience of the many human populations which have been studied. An approach to this further evaluative step, the final phase outlined in Figure 1, is presented here to the extent that presently available data and opportunity have permitted. It should be emphasized that many studies not yet examined in the manner to be presented may permit similar analysis, by recourse to the actual data files and not the published reports alone. Also, other risk assessments that the one examined here might be evaluated by use of this approach. The purpose of the following analysis was to evaluate the correspondence between the projected numbers of excess cases of leukemia under the conditions of a given study and the actual results of that study. If the model were found to be in accord with actual results, it would in an empirical sense be supported; if not, its validity should be questioned and its assumptions re-examined.

The risk assessment selected for evaluation here was that of White, Infante and Chu, previously discussed (89). Their Table IV, p. 201, provides the expected numbers of excess cases of leukemia (all types) for specified combinations of years of working exposure (1, 5, 15, 30 and 45 years) and concentration of benzene in air (1 and 10 ppm), each with an upper and a lower bound as estimated by the authors. from the data of Rinsky and others (69).

To apply these projections required the identification of those reported studies for which the presentation included both

the person-years of potential exposure for the overall study population or subgroups of interest, and the corresponding results as to the excess (or deficit) of cases observed in relation to the number expected. Where this could be calculated from the data reported, a study could be included. Those studies in the series of reports on refinery workers which met these criteria were used.

One important adjustment to the reported total person-years of experience in a given cohort or subgroup concerned the frequent practice of including periods of both active employment and retirement within a single reported analysis. Because this admixture of active and inactive periods would tend to inflate the projected numbers of cases without commensurate increase in the potential for exposure, only those studies were included in which an adjustment for this effect could be made.

The adjustment procedure differed somewhat according to the data presentation of each study; in general, however, a method was found in each instance to discount from the total person-years that portion most likely to be free of the exposure potential understood to characterize the occupational setting under study. This was sometimes possible from directly reported data, but more often it was necessary to assume that the proportion of years of active employment was the same for subgroups as for the whole for whom data were directly available. Often the proportion of years which were active was 90 percent or greater, so that little error is likely in this regard. Still, recourse to the original data would be desirable to confirm the validity of such assumptions. In some instances, it was

necessary to compute the expected value for an exposure group from the rate reported for the non-exposed subgroup; adjustment for possible differences in age- and time-composition of the person-years involved was not possible. Because in one study the results were presented only for the whole ICD category 200 - 209 (Eighth Revision), data from the SEER Program were used to estimate the proportion of deaths in that category likely to be due to leukemia of any type (204 - 207) (41). (These and other aspects of the detailed procedure for each study utilized will be provided on request.)

The procedure, once the person-years and the corresponding actual excess (or deficit) of cases were determined, was as follows. First, the 15-year projections from the White, Infante and Chu Table IV were utilized, because this period most closely approximated the mean duration of employment in the several populations selected. Second, the relevant number of person-years was divided by 15 x 1000 to determine the number of thousands of equivalent 15-year "working lifetimes" for each group analyzed. Third, the result was multiplied by the projected number of excess cases of leukemia per 1000 workers, by use of both the upper (UB) and lower (LB) bounds for exposures at both 10 and 1 ppm, as presented by White and colleagues. These projections could then be compared with the actual excess (or deficit) of leukemia cases which was observed in each group.

The results of this concluding analysis are presented in Table 4.5, Projected vs. Actual Excess Cases of Leukemia in Studies of Refinery Workers (cf. Table 4.2). Of 11 categories

of workers, in 4 studies, 8 showed deficits of leukemia cases, while excesses of tens or hundreds of cases were projected by the risk assessment, if the exposures were taken to be at the 10 ppm level. Even if the 1 ppm level were assumed, the upper bounds gave projections of excesses of 2.3 to 14.9 cases where deficits of 1.2 to 3.8 were actually observed. In the 3 instances where an excess was in fact observed, but of only 0.5 to 2.5 cases, the upper bounds gave projected excesses of 1.7 to 7.4 cases. In the latter of these instances, the only excess of cases actually observed was in the group with the least potential exposure, as determined by the original investigators, while roughly equivalent deficits of cases were observed in the higher-exposure groups and the overall cohort.

The correspondence between these projections from one of the recently published benzene risk assessments and the actual observations in four studies of working populations --- having in the aggregate nearly 400,000 person-years of active working experience during mortality followup --- is notably poor. The projections from the quantitative risk assessment at an assumed 10 ppm level of benzene concentration are clearly irrelevant to actual experience, and those from an assumed 1 ppm level, even at the lower bound, are also seriously out of keeping with actual experience, as they uniformly predict excesses which in 8 instances did not exist and in the remaining 3 were either several times smaller or were paradoxically present only at the lowest reported level of potential exposure.

Two interpretations of these results which should be considered are (a) whether the levels of benzene concentration

in the work environments of these groups were in fact several times lower than even the 1 ppm level; and (b) whether the model, incorporating the many kinds of assumptions discussed. in detail above, is itself inappropriate and seriously misleading. The evidence considered above suggests that benzene concentrations in some US work environments in the latter 1970s and early 1980s were between 0.1 and 1.0 ppm (72). During the years of these 4 studies, the 1960s and 1970s, the potential exposures may have been higher but such data as may be available for such a determination were not examined as a part of this analysis.

With further investigation, either (a) or (b) or still another explanation for these results must be found. In any case, the results of these studies directly, in contrast to projections of a risk assessment based on a 10- or even 1-ppm concentration of benzene, give no support to the claim of an excess risk of leukemia among such workers on the basis of continuing leukemogenic exposures. That there may be little or no excess risk under prevailing conditions greatly diminishes the possibility that revision of the benzene standard from 10 to 1 ppm 8-hour TWA or lower could produce any appreciable benefit in terms-of the frequency of occurrence of leukenia among workers.

FIGURE 1

Use of Epidemiologic Evidence in Judging Causal Relations and Risks, Including Necessary Conditions of Exposure

1. Identification of all available evidence concerning a possible causal relation

   1.1. Systematic citation searches

   1.2. Standard texts and other documents

   1.3. Cross-references

   1.4. Personal inquiries

   1.5. Screening of all the above for relevant reports

2. Evaluation of each relevant report from (1.)

   2.1. Question: WHY was the study done?

   2.2. Design: WHAT disease or condition was studied?

   WHO was studied?

   WHEN was the study conducted, both chronologically and in relation to the disease process?

   2.3. Conduct: HOW was the study actually carried out?

   2.4. Analysis: HOW were the resulting data analyzed and presented?

   2.5. Interpretation: DOES this study provide valid evidence on the question of association between the exposure and the disease or condition of concern?

3. Summary of all valid evidence as found in (2.)

3.1. What is the nature of this evidence?

(1) Consistency (methods, direction of association)

(2) Strength (magnitude, gradient or "dose-response")

(3) Specificity (uniqueness of exposure-disease relation)

(4) Temporal sequence (exposure preceding onset of disease)

(5) Coherence (support from other evidence)

3.2. What general interpretation is justified on this evidence?

4. Assessment of current and projected conditions of exposure relative to those addressed in (2.)

4.1. Summarization of exposures in all relevant studies, in quantitative or qualitative terms, as available information permits

4.2. Estimation of current and projected exposure conditions

4.3. Judgment of the comparability of potential exposures under the circumstances of (4.1.) and (4.2)

5. Estimation of risks under alternative sets of conditions

5.1. Quantitative assessments, including confidence limits, under appropriate sets of assumptions

5.2. Evaluation and interpretation of the results of (5.1), by consideration of all relevant information

TABLE 2.1

Reported Quantitative Risk Assessments and the Selected Epidemiologic Studies which were Utilized

Quantitative Risk Assessments		Aksoy (1974)	Infante/ Rinsky (1977) (1981)	Ott (1978)	Rinsky (1985)	Vigliani (1976)	Wong (1983)
Calif. DHS (1984)		X	X	X			
CAG (1979)	Preliminary		X	X			
	Final	X	X	X			
Crump & Allen (1984)			X	X			X
IARC (1982)		X	X	X		X	
Rinsky (1985)			(X)		X		
White, Infante & Chu (1982)			X	X			

Table 4.1
Studies of Leukemia in Benzene Exposed Populations

Author Year	Design Observation Period	Location Type of Facility	Total N Person-years (% lost to follow-up)
1. Vigliani, 1964; 1976.	Cluster 1960-63	Occupational hematology clinic.	Unknown N.A.
2. Thorpe, 1974.	Cohort, 1962-71.	8 European refineries	Unknown 383,276 38,000+
3. Aksoy, 1976.	Cluster, 1967-75.	Hematology clinic.	34 N.A. 28,000.
4. Ott, 1978.	Cohort, 1940-73.	Chemical plant U.S.A.	594 No data 0
5. Infante, 1977; Rinsky, 1981.	Cluster, 1940-75.	2 Pliofilm plants, U.S.A.	748 17,020 2
6. Tsai, 1983.	Cohort, 1952-78.	1 Refinery U.S.A.	454 5900 1
7. Decoufle, 1983.	Cohort, 1947-77.	1 Chemical plant U.S.A.	259 5942 11
8. Wong, 1983.	Cohort, 1946-75.	7 Chemical plants U.S.A.	7676 133,967 1
9. Cirard, 1970.	Hospital-based case-control.	Lyon, France	cases 257 cont 124
10. Ishmaru, 1971.	Case-control nested within cohort.	Atomic bomb cohort, Japan.	cases 303 cont 303

Notes and abbreviations can be found at the end of the table. Abbreviations are used consistently throughout all the following tables.

Author Year	Design Observation Period	Location Type of Facility	Total N Person-years (% lost to follow-up)
11. Linos, 1980.	Population-based case-control.	Olmstead County, MN U.S.A.	cases 138 cont 276
12. Rushton, 1981.	Case-control nested w/in refinery cohort.	8 Refineries U.K.	cases 36 cont 144
13. Checkoway, 1984.	Case-control nested w/in rubber cohort.	1 Rubber plant, U.S.A.	cases 11 cont 1350

Study Number	Inclusion Criteria	Exposure Criteria	Comments
1.	Males.	Employment in a job in which benzene was used.	Not a true analytical study. Benzene concentrations in the range of 200-500ppm.
2.	Males, no other mentioned.	Exposed if 5+ years in jobs handling materials involving contact w/ 1% or more benzene	No concurrent industrial hygiene data; possible underascertainment of cases.
3.	Males.	Shoeworkers.	Not a true analytical study. Benzene levels ranged from 30–210 ppm.
4.	Males, employment 1 month between 1938–70 in 1 of 3 production areas.	Three production areas: 1.TWA 0.1-6.2ppm 2.TWA 0.3-14.7ppm 3.TWA 3.8-35.5ppm.	Industrial hygiene data concurrent with exposure; some subjects exposed to vinyl chloride, asbestos. 33% exposed 10+ years.
5.	Males, employment 1 day in exposed department	Departments with benzene exposure.	Sparse industrial hygiene data; TWAs stated to be within prevailing standards. Reported data indicatewide range of exposures. 58% of cohort exposed <1yr.
6.	Males, any employment on production units involving benzene.	Exposure ranged from 0.1 to >25 ppm between 1973 and 1982.	Industrial hygiene data not taken concurrently with exposure to benzene. Meanduration of exposure 7.4 years.
7.	Males with any employment, 1947-1960.	No exposure data available.	Benzene use averaged 5.8 million gallons annually.

Study Number	Inclusion Criteria	Exposure Criteria	Comments
8,	Males, with minimum 6 months employmentin one of three exposure exposure groups.	Three exposure categories: No exposure Intermittent Continuous. Based on occupation.	Exposure expressed as cumulative exposure in ppm-months. No concurrent industrial hygiene data.
9.	Severe hemopathies admitted to Lyon hospitals.	Not available.	Exposure assessment based on interview. 5 of 124 controls (4%) exposed. Controls had non-hematologic illnesses.
10.	303 adult leukemia case and control pairs. Both sexes.	Not available.	Occupational history obtained by interview; exposure based on jobs a priori designated as exposed. Matched on age, sex, residence, exposure to the Atomic bomb.
11.	Cases occurring in Olmsted County, 1955-74.	Not available.	Exposure assessment based on review of medical record.
12.	All leukemia cases in a large cohort of refinery workers.	Not available.	Exposure assessment based on industrial hygiene estimates.
13.	Eleven lymphatic leukemia cases identified in a cohort study of rubber workers.	Not available.	Exposure assessment based on industrial hygiene estimates.

Study No.	Mean Duration of employment (Years)	Mean Duration of follow-up. (Years)	Comparison population.
1.	N.R.	N.A.	Crude rates for the province where the clinic was located.
2.	N.R.	N.R.	National mortality rates.
3.	Range: 3-24 years.	N.A.	Estimated national rates for Turkey.
4.	N.R.	N.R.	U.S. White Males.
5.	N.R.	23	U.S. White Males.
6.	N.R.	13	U.S. Males.
7.	N.R.	23	U.S. Males.
8.	16	18	U.S. Males; non-exposed group.
9.	N.R.	N.A.	Controls with other diseases.
10.	N.R.	N.A.	Population controls.
11.	N.A.	N.A.	Population controls.
12.	N.A.	N.A.	Population controls.
13.	N.A.	N.A.	Population controls.

Study No.	Results for Benzene Exposure and Leukemia	Obs/Exp	SMR	95%C.I.	Power to Detect Relative Risk of 2.0	5.0**
1.	Estimated RR acute leukemia		20.0		N.A.	N.A.
2.	Exposed	8/6.6	1.21	(0.5, 2.4)*	.68	.99
	Unexposed	10/16.7	0.60	(0.3, 1.1)*		
3.	Estimated RR		2.0		N.A.	N.A.
4.	Total cohort (Third leukemia listed as secondary cause of death).	2/1.0	2.0	(0.2, 7.2)*	.21	.79
	AML cases	3/0.8	3.75	(0.8, 11.0)***.		
5.	Total cohort	7/1.25	5.60	(2.2, 11.5)*	.24	.87
	Location 1	2/0.58	3.45	(0.4, 12.4)*		
	Location 2	5/0.67	7.46	(2.4, 17.4)*		
6.	Total cohort	0/0.42	---	(0.0, 8.7)	.16	.89
7.	Total cohort	3/0.44	6.80	(1.4, 19.9)*	.14	.48
8.	Total cohort	7/9.36	0.75	(0.3, 1.5)	.81	.99
	Continuous	6/4.43	1.35	(0.5, 2.9)		
	Intermittent	1/1.19	0.90	(0.2, 37.2)		
	Nonexposed					
9.	Total Cohort					
	Acute leumemia	(OR)	3.29	(1.2, 9.2)*		
	Myeloid leukemia	(OR)	1.70	(0.4, 6.6)*		
	Chronic lympho-cytic leukemia.	(OR)	4.12	(1.3, 12.9)*		
10.	Occupations with benzene or x-ray exposure	(OR)	2.50	(p<.01).		

Study No.	Results for Benzene Exposure and Leukemia Obs/Exp SMR 95%C.I.	Power to Detect Relative Risk of 2.0 5.0**
11.	Occupations with benzene exposure (OR) 3.34 (0.6, 27.6) (3 of 4 exposed cases were chronic lymphocytic leukemia).	
12.	Benzene exposure for controls matched on : a. birth year (OR) 2.00 (0.9, 4.3) b. birth year, length of service (OR) 2.33 (1.0, 5.6)	
13.	Benzene exposure (OR) 2.5 (p> .05) (ORs for. 5 of 24 solvents examined were 5.0 or greater; previous study by Arp reported OR = 4.5 for primary benzene exposure and OR = 1.5 for secondary exposure).	

* Confidence intervals calculated by the present authors.
** Assuming Type I error of .05 and a 1-sided significance test by method of Beaumont, 1981.
***Standardized incidence ratio (SIR).
NR- Not reported.
NA- Not applicable.
RR- Relative risk.
SMR- Standardized Mortality Ratio.
OR- Odds ratio.

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TABLE 4.2
Leukemia Occurrence in Refinery Workers

Author Year	Design Dates of Observation	Location Type of Facility	Total N Person-Yrs % LTFU
1. Tabershaw, 1974, 1975.	Cohort, 1962-71.	17 refineries U.S.A.	20,163 142,652 1
2. Theriault, 1979.	Cohort, 1928-76.	1 refinery, Canada.	1,205 17,545 16
3. Hanis, 1979.	Cohort, 1964-73.	1 refinery Canada.	15,032 82,057 6
4. Rushton, 1980.	Cohort, 1950-75.	8 refineries U.K.	34,781 575,982 2
5. Schottenfeld, 1981.	Cohort, 1977-79.	19 companies refinery, R&D, petrochemical, U.S.A.	86,820 122,607 0
6. Hanis, 1982.	Cohort, 1970-77.	1 refinery & petrochemical plant, U.S.A.	8,666 52,791 10
7. Thomas, 1982. Thomas, 1984.	Decedent case-control.	3 refineries U.S.A.	2,509 deaths
8. Wen, 1983.	Cohort, 1937-78.	1 refinery U.S.A.	15,095 372,505 6
9. McCraw, 1985.	Cohort, 1973-82.	1 refinery U.S.A.	3,976 No data. 8
10. Divine, 1985.	Cohort, 1947-77.	Refining, research & petrochemical facilities, U.S.A.	19,077 358,029 2
11. Hanis, 1985a, 1985b.	Cohort, 1970-77.	3 refineries & petrochemical plants, U.S.A.	21,698 137,702 1
12. Wong, 1986.	Cohort, 1950-80.	2 refineries U.S.A.	14,179 No data.

Study Number	Entry Criteria	Exposure Criteria	Comments
1.	Hourly workers employed 1 yr 1962–1971.	High, medium low exp to hydrocarbons.	Exposure based on most recent job.
2.	5 years employment, 1928–76.	None	High lost to follow-up.
3.	Males actively employed or annuitants, w/ 5 years service, 1964–73.	Refinery, non-refinery; exposed, non-exposed to petroleum products.	Results expressed as RR based on directly adjusted internal comparisons. Results restricted to 40+ age groups.
4.	Males, 1 year employment between 1950-75.	Broad occupational categories.	Occupation based on most recent job.
5.	Any employment	Refinery, petrochemical.	Includes incidence 1977–79. and mortality data; Underascertainment of events likely.
6.	Any employment for 1 month, 1970-77.	8 occupational categories	Occupation based on longest duration job.
7.	Leukemia, brain, stomach cancer deaths, 1943-79 identified in PMR study.	11 occupational categories.	Outcome variable was duration of employment in each category.
8.	Anyone employed 19-37–78.	Hourly, salaried.	Occupation based on longest duration job.
9.	White males ever employed 1973–82	None.	
10.	Anyone with 5 years employment, one day of which fell 1947–77.	None.	
11.	Anyone with 1 month service 1970-77.	General occupational categories.	Cigarette smoking data available. Occupation based on longest job.

Study Number	Entry Criteria	Exposure Criteria	Comments
12.	Males, 1 year service, 1950–1980.	General occupational categories.	No industrial hygiene data reported. First and most recent jobs recorded.

Study #	Mean Duration of Employment (Yearsj	Mean Duration of Follow-up (Years)	Comparison Population
1.	20	7.1	U.S. Mortality Rates.
2.	Not reported.	14.6	Quebec Death Rates.
3.	Not reported.	5.6	Internal comparison group.
4.	13.2	16.6	U.K. Mortality Rates adjusted by geographic region.
5.	(41% >20 years).	1.6	U.S. Mortality Rates.. SEERIncidence Rates.
6.	(61% >15 years)	6.1	U.S. Mortality Rates.
7.	Not applicable.	N.A.	U.S. Mortality Data for the PMR study.
a.	(51% >= 20 years).	24.7	U.S. Mortality Rates.
9.	Not reported.	N.R.	U.S. Mortality Rates,
10.	(50+% > 20 years).	18.8	U.S. Mortality Rates.
11.	(62% >= 15 years).	6.3	U.S. Mortality Rates.
12.	(47% >= 10 years).	N.R.	U.S. Mortality Rates.

Study No.		Leukemia Results Obs/Exp	SMR	95% C.I.	Power to Detect RR=2.0	5.0**
1.	Total cohort	11/12.2	0.82	(0.4, 1.5)*	.89	.99
	High	3/5.6	0.56	(0.1, 1.6)*		
	Moderate	4/5.6	0.72	(0.2, 1.8)*		
	Low	3/1.5	2.71	(0.6, 7.9)*		
2.	1 leukemia death; no risk estimate					
3.	Leukemia included in all hematopoietic (RR):					
	Moderate vs nonexposed		1.88	p>.05		
	Exposed vs nonexposed		0.88	p>.05		
	Refinery vs nonexposed		0.46	p>.05		
4.	Total cohort	30/31.96	0.94	(0.6, 1.3)*	.99	.99
5.	Mortality					
	Total cohort	4/7.83	0.51	(0.1, 1.3)	.75	.99
	Refinery	4/5.98	0.67	(0.2, 1.7)		
	Petrochemical	0/1.15				
	Incidence					
	Total cohort	14/9.93	1.41	(0.8, 2.4)*	.83	.99
	Refinery	11/7.56	1.45	(0.7, 2.6)*		
	Petrochemical	0/1.48				
	Cell Type					
	Lymphatic	7/3.31	2.11	(0.8, 2.4)*	.44	.99
	Other	7/6.17	1.13	(0.5, 2.3)*		
6.	Total cohort	9/9.3	0.97	(0.4, 1.8)*	.81	.99
	Operators, mechanics	7/7.2	0.97	(0.4, 2.0)*		
	Other	1/2.1	0.48	(0.0, 2.7)*		
7.	Total cohort(PMR) (ORs ranged from 0.4 to 1.6 for various occupational groups).	33/18.0	1.83		NA	NA
8.	Total cohort	38/33.3	1.14	(0.8,1.6)	.99	.99
	Hourly	32/25.6	1.25	(0.9,1.8)		
	Salaried	3/3.2	0.92	(0.2,2.7)		
9.	Total cohort	14/6.6	2.13	(1.2,3.6)	.69	.99
	AML	8/2.0	3.94	(1.7,7.9)		
	Other.	6/4.6	1.30	(0.5, 2.8)*		
10.	Total cohort	48/40.7	1.18	(0.9,1.6)	.99	.99
11.	Total cohort	20/25.9	0.77	(0.5,1.2)	.99	.99
	Active	6/8.0	0.75	(0.3, 1.6)*		

Study No.	Leukemia Results Obs/Exp	SMR	95% C.I.	Power to Detect RR=2.0	5.0**
12. Total cohort	22/24.9	0.88	(0.6,1.3)	.99	.99
Maintenance	13/14.4	0.90	(0.5,1.5)		
Operators	10/8.06	1.24	(0.6,2.3)		

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TABLE 4.3
Leukemia Occurrence in Chemical and Petrochemical **Workers**

Author Year	Design Dates of Observation	Location Facility	Total N Person-Yrs % LTFU
1. Alderson, 1980.	Cohort, 1935-1970	3 plants, **U.K.**	708 10,000 0
2. Ott, 1980.	Cohort, 1940-75.	Several plants, U.S.A.	2904 No data. 3
3a. Austin, 1983.	Cohort, 1941-77.	1 plant, U.S.A.	6,588 137,745 3
3b. Waxweiler, 1983.	Cohort, 1941-77.	Same plant as 3a above.	7,595 132,341 3
4. Marsh, 1983.	Cohort 1949-76.	1 plant, U.S.A.	2490 No data. 0
5. Bond, 1985.	Cohort 1940-80.	1 plant, - **U.S.A.**	19,608 407,094 2

Study Number	Entry Criteria	Exposure Criteria	Comments
1.	Production workers employed 1 year, 1937–1970.	Methyl–ethyl ketone (MEK) isopropyl alcohol (IPA) exposed.	Benzene used on MEK and IPA units until 1971.
2.	Production workers employed 1 yr 1937-70. This cohort overlaps #2 in Table 1.	57 common exposure experience categories;	Exposure based on entire job history.
3a.	Males, with one day employment, 1941–77.	None stated.	Potential for many exposures.
3b.	Males, with one day employment, 1941–77.	None stated.	Potential for many exposures.
4.	Males, 1 year employment between 1949-66.	None stated.	Potential for many exposures.
5.	Males, 1 year employment between 1940-80.	Six general categories.	Multiple exposures possible.

Study #	Mean Duration of Employment (Years)	Mean Duration of Follow-up (Years)	Comparison Population
1.	Not reported.	MEK: 13.9 IPA: 15.5	U.K. Mortality Rates.
2.	Not reported.	Not reported.	U.S. Mortality Rates.
3a.	(20% < 6 months).	20.9	U.S. Mortality Rates.
3b.	(31% > 15 yrs).	17.4	U.S. Mortality Rates.
4.	Not reported.	Not reported.	U.S. Mortality Rates.
5.	(38% >10+ yrs).	20.8 years.	U.S. Mortality Rates. Texas Mortality Rates. Local Mortality Rates.

Study #		Leukemia Results Obs/Exp	SM	95% C.I.	Power to Detect RR= 2.0	5.0**
1.	MEK cohort	1/0.35	2.86	(0.1,15.9)*.		
	IPA cohort	0/0.18	----			
2.	All leukemia	6/2.9	1.76	(0.6,3.8)*.		
	Lymphatic (SIR)	7/1.64	4.27	(1.7,8.8)*.		
	Other (SIR)	4/2.89	1.38	(0.4,3.5)*.		
3a.	All leukemia	9/7.73	1.16	(0.53,2.21).		
	Employed					
	< 6 months	1/1.41	0.71	(0.0,4.0)*.		
	> 6 months	8/6.32	1.27	(0.5,2.5)*.		
	Ever hourly	8/5.22	1.53	(0.7,3.0)*.		
3b.	All leukemia	11/8.1	1.36	(0.68,2.43).		
4.	All leukemia	3/4.96	0.61	(0.1,1.8)*.		
5.	All leukemia	30/30.3	0.99	(0.67,1.41).		
	>15 years	23/21.7	1.06	(0.67,1.59).		

* Confidence intervals calculated by the present author.

** Assumes Type I error of .05 and a one-sided test by method of Beaumont, 1981 (see Table 1).

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TABLE 4.4
Studies of Leukemia in Rubber Workers

Author Year	Design Observation Period	Location Type of Facility	Total-N Person-years (% lost to follow-up)
1. McMichael, 1974.	Cohort, 1964-72.	1 tire mfg plant, U.S.A.	6678 51,346 (?)
2. Andjelkovic, 1976.	Cohort, 1964-73.	1 rubber mfg plant, U.S.A.	8938 No data. 3
3. Monson, 1976.	Cohort, 1940-74.	All employees of one company; majority worked in mfg plant.	13,571 253,026 6
4. Fox, 1976. Fox, 1974.	Cohort, 1967-74.	All employees in the rubber and cable-making industries, U.K. (381 plants).	40,867 (?) 3
5. Parkes, 1982.	Cohort 1946-75.	Employees of 13 rubber plants in the U.K.	33,815 (?) 1
6. Matanowski, 1982.	Cohort, 1943-76.	13 Styrene-butadiene plants in the U.S.A. and Canada.	13,920 243,856 7
7. Meinhardt,, 1982.	Cohort, 1943-4/76.	2 Styrene-butadiene plants, U.S.A.	2756 .53,929 3
8. Holmberg, 1983.	Cohort, 1930-75. control.	2 tire and other rubber products mfg plants, Sweden.	13,114 (?) 6

Study Number	Entry Criteria	Exposure Criteria	Comments
1.	Males, age 40-84 at 1/1/64.	Classified by job title into groups with similar exposures.	No concurrent industrial hygiene data available. Cohort included retired persons.
2.	Males, age 40-84 on 1/1/64.	Classified by job title into groups with similar exposures.	No concurrent industrial hygiene data available. Cohort included retired persons.
3a.	Employed at least 5 years 1940-74.	Classified by department.	No concurrent industrial hygiene data reported.
3b.	Employed at least 5 years 1940-74.	Classified by department.	No concurrent industrial hygiene data reported,
4.	Males, 35-65 actively employed 2/1/67 with 1 year's service.	Classified by department and industry.	No concurrent industrial hygiene data reported.
5.	Males, with for 1 month, 1970-77.	Classified by occupational groups.	No concurrent industrial hygiene data reported.
6.	Males, with 1 year service prior to 1979. PMR study.	All plants were styrene-butadiene facilities; general occupational groupings.	No concurrent industrial hygiene data reported.
7.	White males, 6 months service, prior to	This was a styrene-butadiene plant no subcategorization of workforce.	Styrene, butadiene and benzene measured in one plant at the time the study was initiated.
9.	Males, 1 yr of service 1931-75.	Broad occupational groupings employed,	No concurrent industrial hygiene data reported.

Study Number	Mean Duration of Employment (Years)	Mean Duration of Follow-up (Years)	Comparison Population
1.	25	7.7	U.S. Males.
2.	Not reported.	Not reported.	U.S. White Males.
3.	Not reported.	18.6	U.S. Males; Females (White; Nonwhite).
4.	Not reported.	Not reported.	U.K. Males.
5.	Not reported.	Not reported.	U.K. Males.
6.	Not reported.	18.0	U.K. Males.
7.	Not reported.	20.0	U.K. Males.
8.	Not reported.	Not reported.	Swedish Males. Swedish National Cancer Registry.

Study Number		Leukemia Results Obs/Exp	SMR	95% C.I.	Power to Detect RR=2.0	5.0**
1.	Total group	16/12.5	1.28	(0.7, 2.1)"	090	.99
	Active	11/3.5	3.15	(1.6, 5.6)*	.46	.99
	Lymphocytic	8/1.1	7.64	(3.3, 15.1)*	.22	.83
	Myelogenous	3/1.5	2.0	(0.4, 5.8)*	.26	.92
	Lymphocytic and solvents.	OR=	3.3	(Not reported)		
2.	Total cohort	25/18.1	1.4	(0.9, 2.0)*	.97	.99
	Myelogenous	6/6.9	0.9	(0.3, 1.9)*	.70	.99
	Lymphocytic	10/6.6	1.5	(0.7, 2.8)*	.70	.99
	Lymphocytic only.					
	High solvents	OR=	3.2	(p=.07) (Wolf, 1981).		
	Benzene	OR=	4.5	(p>.05) (Arp, 1983).		
	Benzene	OR=	2.5	(p>.05) (Checkoway, 1984).		
3a.	Total cohort (Monson, 1976).	55/43	1.3	(1.0, 1.7)*	.99	.99
	Calendering	RR=	3.6	Not reported.		
	Tire curing (Monson, 1978).	RR=	3.1	Not reported.		
3b.	White males (Delzell, 1981).	68/56.6	1.2	(0.9, 1.5)	.99	.99
	Processing (Delzell, 1982).	10/4.2	2.4	(1.1, 4.4)*	.52	.99
	Aerospace (Delzell, 1984a).	12/9	1.3	(0.7, 2.3)	.80	.99
	Industrial Products (Delzell, 1984b).	22/20	1.1	(0.7, 1.7)	.99	.99
4.	Total cohort	28/23.3	1.2	(0.8, 1.7)*	.99	.99
	Tire mfg	11/8.9	1.2	(0.6, 2.1)*	.79	.99
5.	Total cohort	17/18.6	0.9	(0.5, 1.4)*	.99	.99
	Blue collar	15/15.8	0.9	(0.5, 1.5)*	.95	.99
	White collar	2/2.6	0.8	(0.1, 2.9)*	.38	.99
	Production	3/4.2	0.7	(0.1, 2.0)*	.52	.99
	Utilities	2/1.0	2.0	(0.4, 2.3)"	.21	.79
	Maintenance	7/6.5	1.1	(0.4, 2.3)*	.68	.99
7.	Cohort A	5/2.5	2.0	(0.6, 4.7)*	.37	.99
	War hire	5/1.8	2.8	(0.9, 6.5)*	.30	.95
	Cohort B	1/1.0	1.0	(0.0, 5.6)*	.21	.79

Study Number	Leukemia Results Obs/Exp	SMR	95% C.I.	Power to Detect RR=2.0	5.0**
8. Total cohort	27/26.3	1.0	(0.7, 1.5)	.99	.99
Mixers/weighers	2/3.3	0.6	(0.4, 2.2)*	.44	-99
Other production	21/20.1	1.0	(0.6, 1.5)*	.99	.99
Total cohort	38/39.9	1.0	(0.7, 1.4)*	-99	.99

* Confidence intervals calculated by the present authors.

** Assuming Type I error of .05 and a one-sided significance test by method of Beaumont, 1981.

*** Standardized incidence ratio **(SIR).**

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Table 4.5

Actual vs. Projected Excess Cases of Leukemia

in Studies of Refinery Workers

(cf. Table 4-2)

Study No. (Years)	Group	Person-Years (Basis)	Equivalent 15-yr. "Working Lifetimes" x 1000	Projected Excess Cases @ 10 ppm UB	@ 10 ppm LB	@ 1 ppm UB	@ 1 ppm LB	Actual Excess Cases (O - E) [(-) indicates deficit]
1 (1962 - 1971)	All	148,965 (Adj.)	9.93	536.2	149.0	49.6	14.9	(-) 2.8
	High Exp.	6[illegible]	[illegible]	[illegible]	65.4	[illegible]	6.5	( ) [illegible]
	Med. Exp.	66,0[illegible] (Adj.)	[illegible]	[illegible]	66.0	[illegible]	6.6	( ) 2.4
	Low Exp.	16,799 (Adj.)	1.12	60.5	16.8	5.6	1.7	2.5
3 (1964 - 1973)	Refinery	26,064 (Rep.)	1.74	94.0	26.1	8.7	2.6	(-) 2.1
	Exposed	47,175 (Rep.)	3.14	169.6	47.1	15.7	4.7	0.5
5 (1977 - 1979)	All	121,749 (Rep.)	8 1[illegible]	438.5	1[illegible]1.8	40.[illegible]	12.2	( ) 3.8
	Refinery	87,659 (Adj.)	5.84	315.4	87.6	29.2	8.8	(-) 2.0
	Petrochem.	23,132 (Adj.)	1.54	83.2	23.1	7.7	2.3	(-) 1.2
11 (1970 - 1977)	Active	98 149 (Rep.)	6.5[illegible]	[illegible]3.2	98 1	3[illegible].7	9.8	( ) [illegible].0
	Pot Exp.	73,671 (Adj.)	[illegible].91	[illegible]6[illegible] 1	73.6	[illegible]4.6	7.4	1.[illegible]

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