# RECENT EPIDEMIOLOGIC STUDIES OF BENZENE LEUKEMOGENESIS

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Summary

Numerous case reports and a few epidemiological studies link occupational benzene exposure to leukemia. Taken alone, none of these provides convincing evidence of a causal relationahip between the two. However, the consistency of the epidemiologic findings and the repeated linkage of benzene exposure to a particular type of leukemia results in a body of information which, taken as a whole, leaves little doubt that heavy exposure to benzene increases the risk of acute myeloblastic leukemia and its variants. Evidence that this increased risk is manifested by workers who have been exposed at levels consistently below 100 p.p.m. is lacking. No data exist on the shape of the dose-response relationship even at exposures over 100 p.p.m. There are sound reasons for not accepting the linear model as a basis for extrapolating to low exposure levels. Even if the linear or some other model were to be accepted as a basis for extrapolation there are no solid data points at high exposure levels from which a convincing extrapolation could originate.

## Scope of this review

This review addresses epidemiologic aspects of the Benzene Health Effects Assessment, External Review Draft (1) and the Carcinogen Assessment Group's Preliminary Report on Population Risk to Ambient Benzene Exposures (2) - both documents released by the Environmental Protection Agency in October, 1977. Two recent epidemiologic studies (3,4) which are drawn on in the latter document are also considered.

## Benzene Health Effects Assessment, External Review Draft (BHEA)

The BHEA report (1) is an extremely useful review. It is comprehensive and up-to-date, although, understandably, it does not include some relevant material introduced at the very recent OSHA Benzene Hearings - for example, the study of Ott et al (4). There has been insufficient time for me to review the referenced material in detail, but the report deals accurately with those studies with which I am familiar. The tone is moderate and reasoned and, overall, this strikes me as a scholarly and valuable piece of work.

The report makes a convincing case that high-level exposure to benzene, as occurs in some occupations, is associated with increased risk of acute myeloblastic and mono-myelocytic leukemia. The study of Infante et al. (3) is reviewed in detail and it is concluded that:

> "In general, this epidemiological study provides excellent confirmatory evidence of the causal relationship of benzene exposure to acute myelobytic leukemia". (page 115)

However, the criticisms of this study (5) stemming from information developed in the Benzene Hearings are not addressed - presumably because the BHEA

report was written without benefit of this information. The enthusiastic tone of the quotation must be interpreted with this in mind.

In sharp contrast to the attitude taken in the Carcinogen Assessment Group (CAG) report, the BHEA report concludes:

> "In summary, the available literature concerning the benzene levels associated with the development of acute leukemia is inadequate for generation of dose-response curves or for an analysis of risk related to dose". (page 119)

The CAG Report

Estimates of leukemia risk in the CAG report are based on the assumption that there is a linear dose-response relationship between benzene exposure and leukemia risk, down to the lowest levels experienced by the general population. The slope of the regression line describing this relationship is estimated from the data on occupationally-exposed workers studied by Infante et al (3). The mean benzene exposure of the population at large is estimated from data presented in a recent EPA-supported study (6). From these estimates, the CAG computes that between 31.1 and 77.7 cases of leukemia can be attributed annually to non-occupational benzene exposure in the United States. Whether the figure is 31.1 or 77.7 depends on which of two estimates of the exposure experienced by the workers studied by Infante et al is used. The CAG applies its model to the data of Ott et al, in which no significant excess of leukemia was found. Noting that the number of cases observed (one) did not differ significantly from the number predicted from its model (1.43 to 1.74) the CAG states:

> ",....we can be confident in claiming that the Dow Study (Ott et al) does not offer any evidence upon which to question the validity of our model". (page 15)

If high-level exposure to benzene is leukemogenic - which proposition

must at least be accepted as a basis for prudent action - then, no matter how strong or weak the association, the linear dose-response model must result in some excess leukemias at any dose greater than zero. The principal questions at issue, then, are:

(1) is the linear no-threshold dose-response model a defensible basis for estimation of low level effects (and regulation)?

(2) under this model, are the CAG's estimates valid?

The first question is difficult to answer. The CAG report itself simply states the assumption without attempting to defend it. On page 14, the report recognizes that the "form of the mathematical response model used....is also open to question". The general question has been the focus of much investigation and discussion - too extensive to review here. Certainly, the model is far less easily defensible in the field of chemical carcinogenesis than in that of radiation-induced cancer, in which it arose. In the Appendix to a brief filed at the OSHA benzene hearings by Warren et al (7) on behalf of API, NPRA and others, the evidence for the possibility of thresholds for chemical carcinogens is reviewed. This evidence includes empiric data on the existence of such thresholds for a few known carcinogens in experimental animals as well as knowledge of metabolic and other mechanisms which might be expected to result in threshold phenomena. I have reservations about some of the lines of argument presented by Warren et al - in particular those depending on the generalisability of the relationship between carcinogen dose and induction period - but it seems to me that the principal conclusion of this brief is irrefutable:

"The OSHA hypothesis that there is no threshold for chemical carcinogenesis is contradicted by a considerable body of scientific evidence and opinion". (Ref 7, Appendix, page 1)

It is worth noting that the calculations in the CAG report involve extrapolation to exposure levels less than one thousandth of those estimated to be the levels at which leukemogenesis has been observed.

Suppose one does accept the linear no-threshold model for benzene leukemogenesis, are the existing data sufficient to make the CAG estimates credible? The report itself (page 14) states that "the estimates could easily be in error by several orders of magnitude" - a statement unfortunately not repeated in the Summary. But even this qualification gives insufficient recognition to the vast areas of uncertainty in the data. In my opinion, these are so vast as to make any estimate of risk in the population at large unwarranted. The principal problems are as follows:

(1) The estimate of R (risk in occupationally-exposed divided by that in those not so exposed) is derived from a single study of 748 exposed men among whom 7 died of myelogenous-monocytic leukemia, compared to 1.4-1.5 expected (3). One can accept this study as adding to the evidence linking leukemia to occupational benzene exposure (as does the BHEA report) but still recognize that it is a very insecure basis for estimating either the rate of leukemia in occupationally-exposed workers or the ratio of this rate to that in the non-occupationally-exposed population. There is a slight difference in R as estimated by the original authors (10.0) and by the CAG (11.8), deriving from a difference in the estimates of all leukemias which are acute myelogenous or monocytic. This difference is not so important as the fact that neither group gives confidence limits around their

estimate. The approximate 95% confidence limits around the CAG estimate are from 4.7 to 22.3. Therefore, by generally accepted criteria of "chance" alone, the estimates of benzene-related leukemia deaths could be either half or double the estimates given.

(2) The estimate of dose in the occupationally-exposed cohort - from which the effect of low doses is extrapolated - is, to say the least, uncertain. The estimates of the overall mean average exposure levels are heavily dependent on the 100 p.p.m. assigned for the years 1940-46. This was the Maximum Allowable Concentration during that period but there are no records of measurements taken during those years and the first available measurements, in 1947, were taken in one of the two plants following the installation of new ventilation equipment in 1946. Even after 1946, measurements are available for only one plant and air monitoring information for half the cohort is said to be "almost non-existent" (CAG, page 3). The hearings produced anecdotal evidence that the exposure levels may have been very much higher - at least episodically - than the MACs. To the extent that the occupational dose is under-estimated the attributable leukemia deaths in the general population will be over-estimated. The report (page 13) notes that "The CAG would like to see a realistic estimate of the population weighted average exposure and its uncertainty limits". The implication is that the CAG recognizes that the estimates it has used are unrealistic. How justifiable is it, then, to extrapolate from them?

(3) The use of data from a single study is unfortunate - particularly when the risk estimates from that study have such wide confidence bounds and the exposure data are so deficient. On page 4, apparently in explanation of its selection of the data from this study for its estimates, the CAG states:

"In spite of these difficulties, the Infante study is the only one currently available which reports an excess rate of leukemia among benzene-exposed populations". It is not clear whether the CAG thinks that this study is unique in that a rate can be computed from the data or in that this rate is in excess. It would clearly be unjustified to use only data from studies that show an excess of leukemia, and it seems that the former characteristic must be what is referred to. In fact, the BHEA report indicates that Aksoy and colleagues also present rates for occupationally exposed groups and although there are difficulties with those data - uncertainty as to the general population rate and lack of age adjustment - it is a matter of debate as to whether they are greater than those with the data of Infante et al. There is reference, for example, to the fact that over 400 workers exposed to low levels have been excluded from the Infante study (CAG, page 4). If this is so, the estimate of the relationship of risk to dose might have been considerably distorted. Furthermore, the CAG model does not in fact involve the use of a rate in the occupationally exposed. If it did, the inadequacy of a rate based on 7 cases might be too readily apparent. The model instead uses the relative risk (R) and this parameter is as readily estimated from the study of Ott et al (4) as from the Infante study (3). In fact, while the ability to estimate a rate in the occupationally-exposed is implicit in the computation of R, neither the original authors nor the CAG do compute such a rate. The selection of this study as the single basis of the CAG estimates is not adequately justified in the CAG report.

It was noted early in this review that the CAG applied their model to the data of Ott et al, in which no significant excess of leukemia was found.

The fact that the Ott study "is consistent with the Infante study on statistical grounds" (CAG, page 2) is simply a reflection of the small size of the Ott study. If the expected number of cases of leukemia in the Ott study is 1.43 or 1.74 (CAG, page 15) the occurrence of even no cases of leukemia would be "within the limits of normal statistical variability". The study is therefore not supportive of the validity of the CAG estimates - it is simply uninformative.

The study of Infante et al (3)

This is a study of 748 workers occupationally exposed to benzene between 1940 and 1949 in the manufacture of "Pliofilm". Between 1.1.50 and 6.30.75, seven deaths from leukemia occurred in the cohort, whereas 1.4 would have been expected had U.S. rates for white males prevailed. Comparison with another occupational cohort, not exposed to benzene, gives a similar expected value for leukemia deaths. The excess number of deaths from leukemia and the fact that all were myelogenous or monocytic make this study consistent with other evidence linking occupational benzene exposure to leukemia risk. However, as noted above, the small numbers and the deficiency of information on exposure levels make these data entirely inadequate for estimation of any quantitative relationship between exposure level and risk.

A great deal more information than appears in the published version of this paper was developed at the OSHA Hearings, and has been the basis for extensive criticism of the study. I have not reviewed the transcript of the Hearing, but the main points of criticism have been presented by Tabershaw

and Lamm (5). These include the following:

(a) The study was not of a single cohort, as implied in the paper, but of two cohorts which had different exposures and in which the results were different. It was therefore inappropriate to combine them.

(b) Certain groups of workers were inappropriately excluded or omitted.

(c) The authors' characterization of the exposure levels was incorrect.

(d) The distribution of deaths by type of leukemia was inappropriately compared with an incidence series.

(e) The authors' implication that more leukemia cases might be expected because follow-up was only 75% complete was incorrect in that with 95% follow-up no more cases have been identified.

These criticisms have different levels of validity and importance. Overall, however, they do not change my opinions that (1) the study does suggest an increased risk of leukemia in the cohort, and (2) the data are totally inadequate for estimation of a data point on a dose-response curve.

The study of Ott et al (4)

This is a rather similar study of 594 workers exposed to benzene at the Michigan Division of Dow. The strengths of the study include the good characterization of exposure levels and relatively complete follow-up (91%). The principal weakness is the small numbers - particularly of workers exposed at high levels and with long latency. Thus, there were two deaths attributed to acute myelogenous leukemia and one death attributed to bronchopneumonia in which myeloblastic leukemia was listed under "other significant

conditions". The expected number of leukemia deaths was 1.0. While the excess number of leukemias is not statistically significant, it is clear that the numbers are inadequate to rule out a substantial increase in risk in the cohort. While the results of the Infante and Ott studies are seemingly at variance, the two are not statistically imcompatible ($p > 0.1$) - a reflection of the small numbers in both studies.

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