Risk Analysis, Vol. 4, No. 1, 1984

Letter to the Editor

Tackling a Very Difficult Problem

H. G. S. Van Raalte, P. Grasso, and D. Irvine

We were interested to read the article by White *et al.* published in *Risk Analysis*. The authors made a commendable attempt at tackling a very difficult problem, but that an a number of points we would like to make, particularly in relation to the estimation of exposure levels since any errors introduced in these estimations an bound *to* have a major impact on the assessment of risk at low levels of benzene exposure.

As the authors themselves admit, exposure levels in the plants selected for study by Infante *et al.*[1] were not well documented prior to 1951. and at the location where five out of Seven leukemia deaths occurred, there were no exposure data prior to 1957.

Thus, the actual exposures of the leukemia cases during the aetiologically meaningful period (1939–1951) are largely unknown. There are however some indications that concentrations inside the spreader and dryer units have been occasionally measured and indicated "a highly dangerous level of benzene, rang ing from 200 to 350 ppm" to which employees might have been exposed while making adjustments to the machinery. Although employees were required to wear protective equipment when performing this task, this requirement was frequently ignored.[2]

At the other location where two deaths occurred, there were no exposure data until 1946 when an extensive exhaust system was installed. From 1946 *to* 1950 only 15 measurements were taken on four *dif*ferent days. Of these, 11 (73%) were above 35 ppm, the standard in effect at the time. There is also additional evidence of exposure in excess of *500* ppm in certain instances.

Thus, in *our* view, the authors' "arbitrary" assumption that benzene exposures before 1941 were on "average" 50% higher than those during the period 1941–1946 is based on very poor data indeed, and we consider it to be most unreliable to form the basis of a risk estimate.

It is highly questionable indeed whether the "average" concentration of benzene, even if based on reliable data, *can* be considered as the only, or *even* the main, relevant exposure factor associated with the disease, ignoring the possibly more relevant "peak" values. This view would appear to be supported by the fact that the 5 workers who developed leukemia and who formed the basis of the risk analysis were employed in occupations which made exposures to "peak" levels very likely indeed.[2]

The importance of peak exposure levels is also apparent in the study conducted by Ott *et al.* In this study, the authors concede that pak exposure levels of 937 ppm were measured. We are not however told how frequent was the exposure to these high levels nor how many workmen were exposed to them. Sia we bold that exposure *to* high concentrations is crucial in determining the onset of leukemia, we feel that important and relevant information is missed when the mathematical modelling is based on a cumulative dose model.

The authors mention, but do not include in their analysis, the papers by Askoy[4] and Vigliani.[5] Despite their deficiencies these were the first publications to indicate that benzene was leukemogenic to man. They also indicate that for the leukemia to occur, exposure Io benzene vapours has to he substantial. This is in keeping with what we believe the study by Rinsky[2] and by Ott[3] really demonstrate.

With regard to the assumption that a cumulative dose relationship exists for benzene, we would like to point out that although there is, strictly speaking, no acceptable means for testing the assumption, it would not seem to accord with what is known about the toxicology of benzene. In fact an analysis of epidemiological data concerning the incidence of leukemia and marrow hypoplasia suggests that both these conditions occur in persons exposed to levels of benzene

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concentrations above 100 ppm.[6] Although it would seem sensible to assume a cumulative damage at levels of 100 ppm or above, the assumption seems to be less applicable to lower concentrations.

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Letter to the Editor

Benzene

D. Irvine[1]

The authors have carried out a useful exercise in an attempt to demonstrate how existing epidemiological studies *can* be utilized in estimating the risk of leukemia after long term exposure to low levels of benzene concentration.

The authors mention in detail many of the assumptions they have had to make and give plausible arguments to counter many of the objections that one may raise. However, before one *can* accept the extrapolations that they produce, some further points need to be addressed.

Firstly, no matter how the data of the Rinsky[1] and Ott[2] studies *are* modelled mathematically using a cumulative dose model, large excesses of death due to leukemia *are* suggested at low levels of exposure. Since this is the case, the natural conclusion should be that *if* these two studies are representative of benzene-exposed workers worldwide then potentially large excesses of leukemia deaths will result with prolonged follow-up.

Before we accept this reasoning we must determine whether the two studies do in fact reflect typical working exposures of industrialized populations to benzene. The studies are special in the sense that complicating interactions with other chemicals do not occur. but an attempt at quantifying exposure, by necessity, concentrates on the available data and produces 'average' values. The exposures during the early period in the Rinsky study are not documented but one surmises that the situation was much worse than the period after installation of extensive exhaust equipment, with a potential for temporary exposure to high concentrations.

This point is of particular relevance in the mathematical modelling of the dose response relationship since a heavy reliance on a cumulative dose, ignoring the possibility that high exposures, albeit for brief periods, may be necessary for the induction of the leukemia, could produce completely erroneous results in an extrapolation to lower cumulative doses.

There is nothing to be gained here by simply objecting to this modelling since the biological knowledge is not sufficient to propose any alternative. What is essential is *some* further information concerning the shape of the dose response curve in the lower dose region.

One can either produce negative studies as in the case of the OSHA hearings, as counter examples (albeit with their inherent deficiencies—White *et al.*)[3] demonstrating that the projected risk values from these two studies do not hold, or one can attempt to see if the results do apply to actual populations. Adopting this latter approach there are two groups of workers that can be cited who provide a good framework on which to judge the applicability of the risk estimates.

The first corresponds to the "dry side" workers referred to by Hannis[4] who apparently did not satisfy the cohort definition applied by Infante in his original study. It has been stated that *this* group of 404 workers were exposed to up to 20 ppm levels of benzene, and yet by the 1975 follow-up date no *cases* of leukemia had been observed. Arguably a sufficient latent period has not ban allowed, and the quantification of exposure may not be accurate. but it *is* possible that here is a group of individuals from the same ethnic/geographical background for which these extrapolations do not apply.

The second group is taken from the Rinsky follow-up to the Infante study and is composed of all those workers referred to as group 2 in the study who first had exposure to benzene during the period 1950–1960.

[1]The British Petroleum Company, Chertsey Road. Sunbury-on-Thames, Middlesex TY16 7LN, England.

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In carrying out an exercise of this sort, several assumptions have to be made to test the extrapolation since no details are given of the duration of employment in benzene-exposed occupations. Following the authors' approach in the risk analysis, the best and worst cases have been adopted and are presented below. They aim to give a feel for the typical range of deaths that might be anticipated from this group.

Corresponding to a dose of 415 ppm years associated with the observed SMR of 2100 in group 1 we obtained a range of deaths equivalent to (1.3, 12.1). The lower limit was derived assuming that all 258 workers worked for periods of less than one year (six months), while the upper limit had three implicit assumptions. The first was that workers at locations 1 and 2 had a turnover rate among short term workers equivalent to that in group 1—that is 58% less than one year. The second assumption was that the remainder of the 148 workers at location 1 had periods of employment proportional to the number of 'units' in operation; this was a simplified attempt to reflect that the size of the workforce would diminish as the number of operational units was reduced. Finally, that the 46 individuals at location 2 who worked for longer than one year, all worked for a period of ten years from 1955 to 1965 at which time it was considered the benzene exposures altered considerably due to the change from rubber hydrochloride manufacture to vinyl film.

The same exercise was repeated using the model coefficient corresponding to 1500 ppm years associated with an SMR of 2100 which led to (.3, 3.9) as the range of deaths under the assumptions described above.

By 1975 only one death had occurred against an expected figure of .46 giving an excess of .54. It can be seen that although the figures are only rough approximations, that .54 just overlaps the (.3, 3.9) interval and is not contained in the (1.2, 12.1). In this context the lower limit is not regarded as being particularly representative of the actual work profile of the cohort, and there is a suggestion that the actual excess is not as large as anticipated. This may be due solely to the assumptions made in calculating the figures, that sufficient time had not elapsed to manifest the excess, or that the original projections were derived for individuals with greater than 5 years exposure (we have extrapolated to 6 months for the lower estimate, and used periods of less than five years for the proportionality assumption in location 1.).

We can either uncritically accept the projections made by the authors, carry out relatively unproductive exercises similar to the one above to see whether the risk is real, establish whether 'negative studies' exist. or concentrate effort on determining a better understanding of the mechanism involved (which might dictate peak values of exposure being included).

Without a clearer understanding of the mechanism, or data points established in the low dose region so that the shape of the simplified dose response curve is characterized, the debate will never be satisfactorily resolved.

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Letter to the Editor

The Methodology of Risk Assessment

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In their recent paper on a risk assessment of leukemia mortality associated with occupational exposure to benzene, White *et al.*[1] invite comments on their approach. Several things might be said about their choice of dose response model and their exposure estimates. However, I wish to raise a basic question about the methodology that I believe may be more important.

For practically all cancers there is a background mortality that varies with age. In such cases, the assumption that the relative risk associated with some exposure is constant across all age groups is false by algebraic necessity.

To see that the relative risk must be age dependent, consider the author's Eq. (4), but denote the dose response curve by $f(d)$. That equation states in effect that the relative risk is

$$(P_1/P_0) = 1 + f(d)(1 - P_0)/P_0$$

When d is constant the relative risk is a decreasing function of P_0. In plain words, if you have a dose that produces a relative risk of 5 when $P_0 = .2$, it cannot produce a relative risk of 5 when $P_0 = .5$.

Since the authors state that the assumption of a constant relative risk justified their use of the SMR to estimate that relative risk, and since the assumption cannot be true, it seems to me that their procedure is not valid. It isn't so much that the SMR may overestimate or underestimate the relative risk, as they state on page 202, it's that there is no relative risk to be estimated, since it isn't constant in the first place.

At the risk of jousting with a sacred cow (and of mixing metaphors) I suggest that the real problem is with the concept of relative risk, which has a seductive appearance of straightforwardness until you look at it carefully.

It may be time to rethink the way in which we characterize the possible hazards associated with chemical exposures.

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Letter to the Editor

Benzene and the One-Hit Model

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Future adverse health consequences subsequent to occupational exposure to benzene were estimated from epidemiologic data by White *et al.* A fundamental scientific *and* legal issue is the question of the relative health risks associated with chronic "low" level exposure to benzene. If fact-based science and value-based social policy are to be articulated with veracity, then the best estimate of the true human risk should be sought The best estimate of the true human risk demands the systematic evaluation of *all* relevant facts which may quantitatively influence the risk estimate. In addition, the assumptions and the implications of the predictive health model must be evaluated for consistency and coherency with the known facts.

White *et al.* "selected the one-hit model for benzene, primarily because it is a simple model." The one-hit model is not merely a statistical distribution but is mathematically derived from a set of specific assumptions which relate the "dosc" to an irreversible biological process. Mathematically, the one-hit model describes a continuously increasing saturation function which starts at zero and asymptotically approaches one with increasing dosc. Chemically, the logic of the one-hit model requires that a single unique chemical event constitutes the causal biological event. The causal biological event must be initiated in a single cell in order to be unique. In addition, the *chemical* event must be irreversible to be in accordance with the mathematical assumptions for a Poisson process. A critical determinant of the model's risk predictions is the assumption that the number of irreversible biological events is directly proportional to the dose. hence the ***critical public health conclusion that a ample proportional relationship exists*** between the dose and the response at "low" doses.

Is the one-hit model an accurate predictor of the future incidence of leukemia in exposed populations? White *et al.* state "the current biological evidence concerning the chemical induction of leukemia was considered insufficient to defend the use of a mort complex model" Unfortunately, the nature of the evidence considered to be insufficient was not stated.

The notion that "simplicity" is adequate justification for predicting future incidence of human disease disguises at least four substantial scientific issues:

1. The fundamental issue of whether or not the dose-response relationships for benzene are continuous functions or are discontinuous functions is side-stepped by the simplicity argument. From a public health perspective, the critical issue of the existence of risk outside the observable range is thereby avoided.
2. Justification of selection of the linear model by noting its simplicity also leads to the notion that the response is proportional to dose. Of the infinite set of possible relationships between dosc and response, the assumption that a simple proportional relationship exists needs to be justified. *Since* it is possible that the molecular mechanism of benzene-induced toxicity involves a set of complex nonlinear biochemical reactions, the simplicity argument may eventually be shown to be inconsistent with the molecular mechanism.
3. The argument of simplicity is insufficient scientific rationale to justify the strong conclusion that disease incidence is Linear in a heterogeneous human population. Hit theory is based on the premise that rare stochastic events occur as first order processes in a

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homogeneous population. Discussion of the weight of evidence supporting the equisensitivity of all workers toward benzene intoxication is needed if this assumption of the model is to be credible.

4. Metabolic considerations may be critical to understanding the functional relationship between the dose and response. Since the parent benzene molecule is a relatively unreactive molecule at biologic pH and temperature, a spontaneous irreversible reaction with biomolecules at a biochemically significant rate is deemed unlikely. This suggests that the presence of benzene itself in a cell represents only the distribution of a foreign substance in the body and not the critical irreversible event assumed by the model. Benzene is metabolized to phenols and quinones by saturable enzymatic processes. Phenols, quinones, and unstable oxygenated benzene derivatives which lead to the formation of phenols and quinones are substantially more reactive than benzene itself. Kinetically, these reactions are not simple unimolecular reactions but follow higher order, saturable kinetics. Oxygenated metabolic derivatives are sufficiently reactive to covalently bind to tissue constituents, including genetic elements. The importance of these reactions in the molecular mechanisms which determine the dose response relationships for benzene toxicities could (and should) be evaluated in estimating the risk of benzene.

Simplicity in model selection is desirable when the selected model *can* account for the complete set of factual observations. However, our current understanding of human disease processes, including benzene toxicities, suggests that they are multifactorial in nature and more complex than a single, unique, irreversible event. To be credible, prediction of future disease incidence needs to be consistent and coherent with the intertwined biochemical, cellular, physiological, and genetic data. For these reasons, I believe that the best estimate of the true human risk for benzene will require a broader and deeper evaluation of the existing set of relevant facts.