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Human cancer risk and exposure to 1,3-butadiene — a tale of mice and men

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Objectives The purpose of this study was to evaluate empirically the relevance of animal-bioassay-based models for predicting human risks from exposure to 1,3-butadiene (BD) using epidemiologic data.

Methods Relative-risk results obtained with a regression model in a recent epidemiologic study were used to estimate leukemia risk for occupational and environmental exposures to BD and to compare these estimates with those previously derived from an analysis of animal bioassay data.

Results The estimates of risk were found to be highly dependent on the model used when low levels of exposure were evaluated that are of environmental concern, but not at the levels of occupational concern. For example, at the level (1 part per million) of the recently revised standard of the Occupational Safety and Health Administration in the United States the estimates of lifetime excess risk ranged from 1 to 8 per 1000 workers. The range of the risk estimates derived from the epidemiologic models was remarkably similar to the range of risk estimates for occupational exposures (1 to 9 per thousand) previously developed by Dankovic et al in 1993 from an analysis of a mouse bioassay study for lymphocytic lymphoma.

Conclusions Results for BD seem to provide another example of a high degree of concordance between the risk predictions from models of toxicologic and epidemiologic data, particularly at occupational levels of exposure.

Key terms epidemiology, leukemia, risk assessment, toxicology.

The use of animal bioassay data for the characterization of human risks and the determination of regulatory policies in the United States (US) is controversial. Ames & Gold (1—3) have argued that the high exposure levels used in experimental studies frequently induce tumors by mechanisms that are not operative at the lower exposures generally experienced by humans. A *Science* editorial (4) has even gone so far as to state that "The standard carcinogen tests that use rodents are an obsolescent relic of the ignorance of past decades". Others have defended the use of animal bioassays with equal vigor (5—7).

A recent debate over the potential carcinogenicity of 1,3-butadiene (BD) exemplifies the current arguments surrounding the relevance of animal bioassay data for predicting human cancer risks (8—11). The mechanistic arguments concerning this issue have been reviewed recently by Melnick & Kohn (12).

Although the theoretical arguments for and against the use of animal bioassay data for human risk assessment may continue, we believe that the science of risk assessment will be well served by the development, to the extent possible, of empirical data comparing the risks observed in humans to those estimated from bioassays. In this paper we have developed estimates of leukemia risk based on a recent analysis of a cohort study of workers exposed to BD and then compared these risk predictions with those previously developed on the basis of animal bioassay data.

Materials and methods

The recently reported findings from a retrospective cohort mortality study conducted by researchers at the University of Alabama (UAB) provided the primary data for this analysis (13—14). This study included 17 964 men employed for at least 1 year between 1943 and 1991 at 8 North American plants that made styrene-butadiene rubber.

The investigators developed a job-exposure matrix for BD, styrene, and benzene on the basis of industrial

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hygiene data, which contained estimates of the average daily exposure (in parts per million based on an 8-hour time-weighted average), and the number of annual peaks (defined as ≥100 ppm for BD and ≥50 ppm for styrene) for each area and job code for each study year. The investigators were then able to estimate cumulative exposure estimates (ppm · years and peak · years) by linking the job-exposure matrix with the subject's work histories.

The results from Poisson regression (15) exposure-response analyses of this study were presented in a report (henceforth referred to as the UAB study) to the International Institute of Synthetic Rubber Workers by the UAB researchers (Delzell E, Sathiakumar N, Macaluso M, Hovinga M, Larson R, Barbone F et al. A follow-up study of synthetic rubber workers. Report submitted to The International Institute of Synthetic Rubber Workers, October 2, 1995). The models controlled for the potentially confounding effects of age (categories of 40—49, 50—59, 60—69, 70—79, ≥80 years), time since hire (categories of 10—19, 20—29, ≥30 years), calendar period (categories of 1950—1959, 1960—1969, 1970—1979, 1980—1989, 1990—1991), and race (black, other). The plant was considered a possible confounder but was dropped from the final models because it did not affect the estimated parameters for BD or styrene. Few subjects were exposed to benzene, and benzene did not appear to confound the relationship between the BD or styrene exposure and leukemia mortality. Hence the model results presented in the report did not control for benzene exposure.

Different functional forms of the relationship between the relative rate (RR) and measures of exposure were evaluated in the UAB analysis, including the following: (i) log-linear $RR = e^{\beta X}$; (ii) power: $RR = e^{\beta[\ln(1+X)]} = (1+X)^{\beta}$; (iii) linear: $RR = 1 + \beta X$; (iv) polynomial: $RR = 1 + \beta_1 X + \beta_2 X^2 + ...$; (v) square root: $RR = 1 + \beta_1 X^{1/2}$, where X represents BD or styrene exposures and the β values represent the model parameters. Exposure (X) was either coded as a set of categorical variables or as a continuous variable using the midpoints of the exposure categories. Note that the given models correspond to a case in which X is continuous. Their models also included variables to adjust for the potentially confounding effects of age, calendar period, years since hire, and race.

The Poisson regression analyses revealed a positive exposure-response relationship between cumulative exposure to BD or styrene and leukemia mortality. This relationship was evident in both of the models that represented these exposures as categorical variables and in models in which exposure was represented using continuous variables as already described. The BD and styrene exposures among the exposed subjects were found to be moderately correlated (Spearman's rank correlation, r=0.53). The relationship between cumulative BD exposure and leukemia mortality appeared to be independent of the styrene exposure, and it was not appreciably altered by the inclusion of cumulative styrene exposure in the model. On the other hand, the relationship between cumulative styrene exposure and leukemia mortality was weakened and irregular when cumulative BD exposure was included in the model. These findings suggest that cumulative BD exposure is a more likely explanation for the leukemia excess observed in this cohort than cumulative styrene exposure.

Analyses of peak-years (a peak exposure was defined as any exposure greater than 100 ppm) indicated an association between this variable and leukemia mortality even after control for cumulative exposure, but this relationship was not monotonic in the categorical regression analyses. Excluding exposures that occurred within 5 or 10 years of death (ie, lagging exposures) only slightly increased the exposure-response relationship for cumulative BD exposure, whereas excluding exposures within 20 years of death weakened and almost eliminated the relationship.

The regression parameter for BD exposure was found to be statistically significantly greater than 0 ($P<0.05$) with all of the model forms evaluated.

The power and square root models were found to provide the best fit to the data in a comparison of the model deviances. However, the difference in deviance between the various models was slight. The square root model was identified as the "best model" according to its goodness of fit and its simplicity. This model was refined into a final model (henceforth referred to as the "final square root model") by omitting styrene and race since the effect of these variables on the estimated parameter for BD exposure was considered to have been minimal. In addition, certain age, calendar year, and years since hire categories were collapsed for their final model for similar reasons. The relationship between cumulative BD exposure and leukemia mortality was highly statistically significant in the final model ($P=0.002$).

Prediction of lifetime excess risk of leukemia

The relative rate models presented in the UAB analysis were used as a basis for predicting the lifetime excess risk of leukemia mortality for varying levels of occupational and environmental exposures to BD. Lifetime risk was estimated using the relative rate estimates derived from these models and an actuarial program that takes into account the effects of competing causes of death.[3] US age-specific mortality rates for males (16) were used

3 This program is an adaptation of the approach that was previously used in the BEIR IV study (BEIR IV. Health Risks of Radon and Other Internally Deposited Alpha Emitters. Washington (DC): National Academy Press, 1988:131—4.

to specify the leukemia and all cause background rates in the actuarial program. For estimating occupational risks, it was assumed that workers were exposed for 45 years to a constant BD concentration starting at 20 years of age and ending at 65 years of age, whereas for environmental exposures it was assumed that exposures were for the entire lifetime. Lifetime risks were computed up to 85 years of age. For estimating environmental risks, the occupational BD exposures in the epidemiologic study were converted to equivalent continuous environmental exposures by multiplying the occupational exposure estimates by a factor to account for differences in the number of days exposed per year (365/240 days) and another factor to account for differences in the amount of air inhaled per day (20/10 liters). The reported standard errors for the BD regression coefficients were used to compute the upper 1-sided 95% confidence limit for the relative rates and lifetime risks of leukemia (or the corresponding 95% lower 1-sided limit on exposure) on the basis of a normal approximation.

Consistent with the new cancer guidelines (17) of the US Environmental Protection Agency (EPA) the results from these risk assessment models were also used to estimate the "effective concentration" (EC_p) and lower 95% confidence limits (LEC_p), which is the concentration (or exposure) associated with a specified level of excess risk (p) such as 1% or 0.1%. The advantage of this approach is that it restricts risk estimation to approximately the

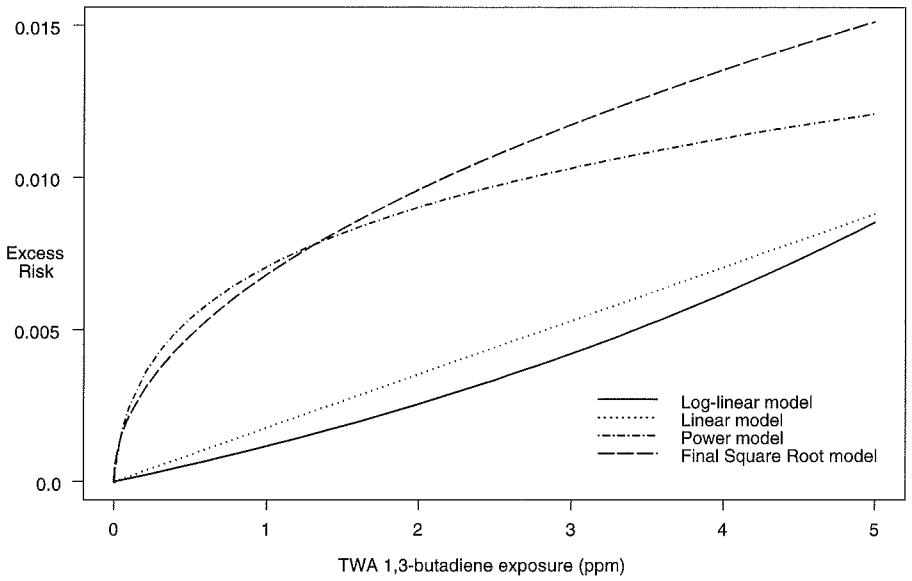

Figure 1. Excess risk for occupational exposures to 1,3-butadiene using alternative models. (TWA = time-weighted average)

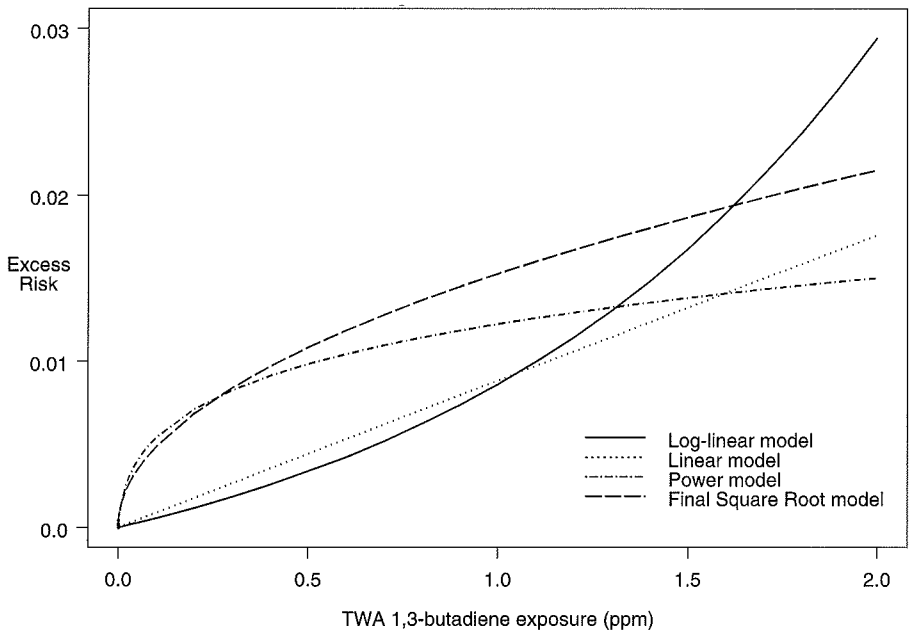

Figure 2. Excess risk for environmental exposure to 1,3-butadiene using alternative models. (TWA=time-weighted average)

range of the data and thus avoids making extrapolations well beyond the data.

The risk estimates for the occupational exposures were compared with those previously derived for occupational exposures (18) based on modeling of the findings from the National Toxicology Program (NTP) studying B6C3F1 mice exposed via inhalation to BD.

Results

The maximum likelihood (point) estimates of the lifetime risk of leukemia in association with varying levels of occupational and environmental exposures to BD are illustrated in figures 1 and 2. Point estimates and lower 95% confidence limits for environmental and occupational exposure levels in association with specific levels of excess lifetime risk are presented in table 1. Environmental regulations are frequently targeted by the EPA to limit risks to below a 1 in a million risk level, whereas occupational standards developed by the Occupational Safety and Health Administration (OSHA) are generally targeted to limit exposures at or below a 1 in a 1000 risk level (19). It can be seen from table 1 that the results are highly model dependent for exposures corresponding to risks of environmental concern (1 in a million) with the estimates of exposure spanning approximately 5 orders of magnitude. In contrast, the results are between 1 and 2 orders of magnitude for exposures at risk levels of occupational concern (1 in a 1000). OSHA recently reduced its permissible exposure limit (PEL) from 1000 to 1 ppm (20). These models predict that, at the revised OSHA standard of 1 ppm, the predicted risks (point estimates) would be approximately 1 to 7 per 1000 workers.

Estimates of the effective concentration

Point estimates and lower 95% confidence limits for the effective concentration (EC_p) for environmental exposures corresponding to levels of excess risk varying from 0.1% to 10% from the alternative models are presented in table 2 and illustrated for the final square root model in figure 3. Although the new EPA guidelines emphasize the derivation of exposure levels associated with a 10% risk level, this procedure does not seem reasonable in this instance. The 10% level of risk is associated with exposure levels that are higher than most of the exposures experienced by the workers in this epidemiologic study. This problem is illustrated by the fact that a 10% risk level would correspond to a relative rate of 19, but the leukemia standardized mortality ratios (SMR) reported in the UAB analysis were considerably lower.[4] Hence, these considerations suggest that using a 10% risk level would be an upward extrapolation in this case. A 1% risk or even a lower (eg, 0.1%) risk level would seem to be a more reasonable choice in this circumstance. The analogous relative rates for increased risks of 1% or 0.1% are 2.7 and 1.17, respectively, which better correspond with the set of standardized mortality ratios reported in the UAB analysis. When a 1% risk level is used, the LEC_1 from these analyses ranges from 0.06 to 0.6 ppm depending on the relative rate model used. Using the "final" model presented in the UAB analysis would yield an LEC_1 of 0.11 ppm.

Ratios that were calculated by dividing the excess risk (p) by the corresponding LEC_p for each model are also presented in table 2. Each ratio is the slope of the line segment connecting the point (LEC_p, p) with the origin. This ratio is essentially a measure of the risk per unit of exposure under the assumption of low-dose linearity (ie, a unit risk). According to the LEC_1, these ratios vary by 1 order of magnitude from 0.016 to 0.16. If these LEC_1-based ratios were used to calculate the concentration

Table 1. Estimates of maximum likelihood and the 95 % lower confidence limit (95% LCL) of environmental and occupational exposures associated with varying levels of lifetime excess risk.

Excess risk	Environmental exposure (ppm)		Occupational exposure (ppm)	
	Maximum likelihood	95 % LCL	Maximum likelihood	95% LCL
Log-linear ($RR=e^{\beta X}$) model				
1e-6	1.9e-4	1.1e-4	9.4e-4	5.3e-4
1e-5	1.9e-3	1.1e-3	9.4e-3	5.3e-3
1e-4	1.9e-2	1.1e-2	9.3e-2	5.3e-2
1e-3	0.17	9.8e-2	0.87	0.49
Linear ($RR=1+\beta X$) model				
1e-6	1.1e-4	5.1e-5	5.7e-4	2.6e-4
1e-5	1.1e-3	5.1e-4	5.7e-3	2.6e-3
1e-4	1.1e-2	5.1e-3	5.7e-2	2.6e-2
1e-3	0.11	5.1e-2	5.7e-1	0.26
Power ($RR=e^{\beta[\ln(1+X)]}$) model				
1e-6	3.8e-6	2.1e-6	1.9e-5	1.1e-5
1e-5	3.8e-5	2.1e-5	1.9e-4	1.1e-4
1e-4	3.9e-4	2.1e-4	2.0e-3	1.1e-3
1e-3	5.2e-3	2.4e-3	2.6e-2	1.2e-2
Initial square root ($RR=1+\beta_1 X^{1/2}$) model				
1e-6	7.3e-9	1.4e-9	3.7e-8	7.0e-9
1e-5	7.3e-7	1.4e-7	3.7e-6	7.0e-7
1e-4	7.3e-5	1.4e-5	3.7e-4	7.0e-5
1e-3	7.3e-3	1.4e-3	3.7e-2	7.0e-3
Final square root ($RR=1+\beta_1 X^{1/2}$) model				
1e-6	4.2e-9	1.1e-9	2.1e-8	5.5e-9
1e-5	4.2e-7	1.1e-7	2.1e-6	5.5e-7
1e-4	4.2e-5	1.1e-5	2.1e-4	5.5e-5
1e-3	4.2e-3	1.1e-3	2.2e-2	5.5e-3

4 The maximum reported SMR/100% was 13.33. This SMR was based on 2 leukemia deaths among black men from plant 2 with at least 10 years of work (not all of which was salaried) and at least 20 years of elapsed time since hired. (See table 29 of the UAB analysis.)

corresponding to a 1 in a million excess lifetime risk by linear interpolation[5] the values would range from 7 to 64 parts per trillion. The "final" model presented in the UAB analysis would yield a corresponding exposure level of 12 parts per trillion.

Table 2. Estimates of the maximum likelihood effective concentration (EC_p) and the 95 % lower confidence limit (LEC_p) of the continuous environmental exposure concentrations associated with varying levels of excess risk (p) from the alternative models.

Excess risk (p) (%)	1,3-Butadiene exposure levels (ppm)		Ratio[a]
	EC_p	LEC_p	
Log-linear model			
p 10.0%	3.30	1.90	5.3e-02
p 1.0%	1.10	0.63	1.6e-02
p 0.1%	0.17	9.8e-02	1.0e-02
Power			
p 10.0%	7.2e+03	14	7.1e-03
p 1.0%	0.53	6.3e-02	0.16
p 0.1%	5.2e-03	2.4e-03	0.42
Linear model			
p 10.0%	12	5.50	1.8e-02
p 1.0%	1.10	0.51	2.0e-02
p 0.1%	0.11	5.1e-02	2.0e-02
Square root			
p 10.0%	84	16.00	6.3e-03
p 1.0%	0.74	0.14	7.1e-02
p 0.1%	7.3e-03	1.4e-03	0.71
Final square root			
p 10.0%	49.00	13.00	7.7e-03
p 1.0%	0.43	0.11	9.1e-02
p 0.1%	4.2e-03	1.1e-03	0.91

[a] The ratio is the excess risk (p/100%) divided by the one-sided lower 95% confidence limit of the exposure estimate (LEC_p).

Comparison of results with previously derived estimates of risk

It is informative to compare the results from this analysis with those that were previously developed by the National Institute for Occupational Safety and Health (NIOSH) (9) using the NTP mouse bioassay (21). Lifetime estimates of risk for occupational exposures from the analysis based on the NTP bioassay are presented in table 3. For comparative purposes, the risk estimates for leukemia mortality from the models that produced the highest (final square root model) and the lowest risks (log-linear model) from the UAB analysis are also presented in table 3. The analysis of the NTP mouse bioassay presented estimates of risk for both men and women and for several cancer sites that were observed to be significantly elevated. Some of the cancer sites (eg, forestomach and harderian gland) observed in the mouse bioassay are of questionable relevance to humans. Probably, the most relevant comparison was with lymphocytic lymphoma in mice, since these tumors are of lymphopoietic origin, as are the major tumor types observed in human studies (ie, leukemia and lymphosarcoma). The results from our analysis of the NTP bioassay for 1 ppm (current OSHA standard) ranged from 1 (males) to 9 (females) per 1000; in comparison, the estimates of excess risk for leukemia derived from the epidemiologic study range from 1 to 8 per 1000 workers. Thus the excess risk estimates from these epidemiologic and toxicologic analyses are almost identical for tumors of hematopoietic origin at current occupational exposure levels to BD. It should be noted that chemical carcinogens are not always

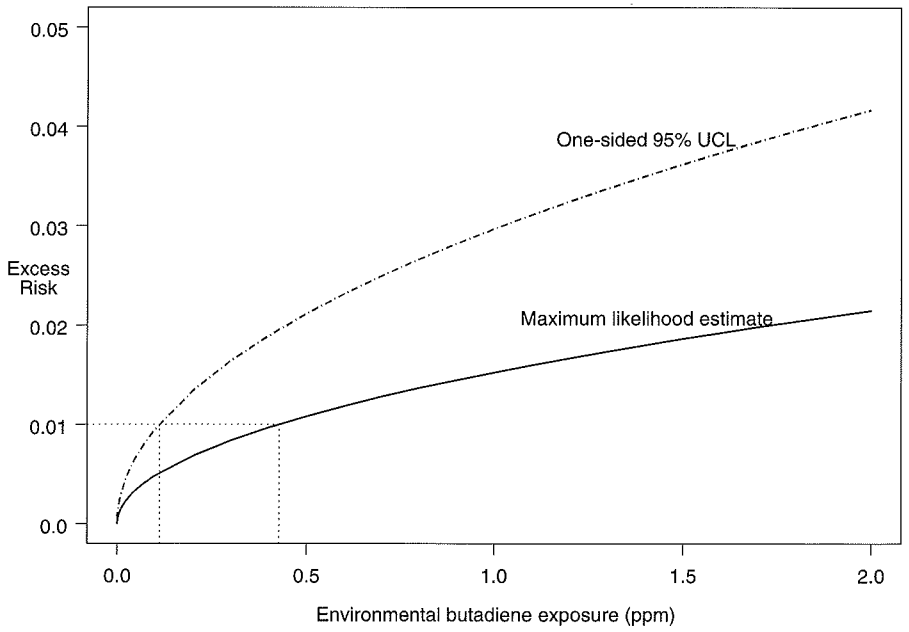

Figure 3. Environmental risk and 95% upper confidence limits based on the final square root model. (UCL = upper confidence limit)

5 Linear interpolation between the origin and the point (LEC_p,p) is also referred to as "linear extrapolation."

expected to produce tumors at identical sites in animals and humans. Using the results from all of the tumor sites in the mouse bioassay would yield a much wider range of risk estimates for a 1-ppm exposure ranging from 3 per million to 3 per hundred for a 1-ppm exposure.

Discussion

The use of animal bioassay studies for predicting cancer risks in humans has been, and will most likely continue to be, a source of scientific controversy. Several investigators have explored the concordance between the risk estimates derived from animal bioassay studies with those developed from epidemiologic studies in which both sources of information exist (22—24). These analyses have generally found a relatively high degree of concordance, with some notable exceptions. It would appear that the case of BD provides another example of good agreement between predictions based on animal bioassays and epidemiologic data.

The results from the epidemiologic risk analysis presented in this paper also suggest that the quantitative estimates of risk that were previously derived from our analysis of the NTP mouse bioassay study were not "exaggerated" as was previously suggested (8). In fact, at the current OSHA standard of 1 ppm the leukemia-risk estimates derived from this epidemiologic analysis are remarkably similar to those that we previously developed for our analysis of the NTP mouse bioassay results for lymphocytic lymphoma.

At the very least, the recent findings by Delzell et al (25—28) provide strong qualitative evidence supporting the concern generated by the NTP bioassay with respect to a significant risk of cancer from occupational exposure to BD. This concern is also supported by the results from the demonstration of an increase in leukemia or other lymphopoietic neoplasms in other epidemiologic studies of BD-exposed workers.

It should be noted that our 1993 risk assessment for BD made use of the inhaled dose of BD as a dose metric. Since that time 2 physiologically-based pharmacokinetic models have been published which incorporate in vitro data on the metabolism of BD in humans (29, 30). These models represent an effort to improve the risk assessment process for BD by utilizing scientific data rather than generic assumptions regarding interspecies scaling. At this point we have not examined the degree to which the use of these models would alter our risk estimates for BD.

Sources of uncertainty

As with any risk assessment, there are several assumptions and sources of uncertainty that need to be clearly recognized. One critical source of uncertainty is the validity of the statistical models used. The UAB analysis included analyses of residuals and of influential data points, which did not indicate any problems with their models. The Pearson chi-square test (P=0.93) and the deviance in their final model did not suggest a lack of fit to the data. Thus their models appeared to be appropriate according to classical statistical criteria. Since the difference in deviance between the alternative models was small, it is difficult to choose 1 model over another for the analysis as the "best" model. The findings from our analysis suggest that estimates of risk are not highly model dependent for occupational exposures of current concern. However, estimates of risk for environmental exposures (eg, at 1 in a million risk level) were found to be highly dependent on the model chosen. On the other hand, the results were not found to be highly model dependent when an approach based on the effective dose (EC_p) was used, as proposed in the new EPA cancer guidelines (17), particularly when a 1% risk (p) criterion was used.

The other major source of uncertainty in this analysis is the potential for misclassification of exposures in the UAB analysis. This is a frequent limitation of nearly all epidemiologic studies of this type for quantitative risk assessment purposes. The exposures of this study were based on the modeling of a relatively extensive set of data. However, questions have been raised concerning the accuracy of exposure estimates particularly for some

Table 3. Comparison of the maximum likelihood estimates of lifetime excess risk due to 45 years of occupational exposure to 1,3-butadiene, using the toxicologic and epidemiologic data. (TWA = time-weighted average)

	Lifetime excess risk (8-hour TWA concentration)			
	0.5 ppm	1 ppm	2 ppm	5 ppm
Epidemiologic data for leukemia				
Final square root	4.8e-3	6.8e-3	9.6e-3	1.5e-2
Multiplicative	5.6e-4	1.2e-3	2.6e-3	8.5e-3
Data from male mice				
Forestomach	8e-6	3e-5	1e-4	8e-4
Harderian gland	7e-3	1e-2	3e-2	7e-2
Heart hemangiosarcoma	1e-4	5e-4	2e-3	1e-2
Histiocytic sarcoma	4e-3	8e-3	2e-2	4e-2
Liver	2e-3	4e-3	7e-3	2e-2
Lymphocytic lymphoma	4e-4	9e-4	2e-3	4e-3
Lung	6e-3	1e-2	2e-2	6e-2
Data from female mice				
Forestomach	3e-3	5e-3	1e-2	2e-2
Harderian gland	4e-3	7e-3	1e-2	3e-2
Heart hemangiosarcoma	4e-7	3e-6	2e-5	4e-4
Histiocytic sarcoma	6e-3	1e-2	2e-2	6e-2
Liver	3e-3	7e-3	1e-2	3e-2
Lymphocytic lymphoma	4e-3	9e-3	2e-2	4e-2
Lung	2e-2	3e-2	6e-2	0.1
Mammary gland	2e-3	4e-3	7e-3	2e-2
Ovary	4e-3	9e-3	2e-2	4e-2

ill-defined tasks. For example, the work histories of the maintenance laborers did not indicate whether they were vessel cleaners (a high-exposure category) or building cleaners (a low-exposure category). Researchers at the UAB are currently working on a reevaluation of the exposure estimates used in their study.

Another concern that has been expressed is regarding the assignment of peak exposures, defined as average exposures equal to or greater than 100 ppm over 15 minutes, in the analysis. Additional analyses concerning peak exposures have been conducted by the UAB researchers (Delzell E, Macaluso M, Lally C, Cole P. Mortality study of synthetic rubber workers: additional analyses of data on monomer peaks and employment in certain work areas. Report submitted to the International Institute of Synthetic Rubber Producers, October 16, 1996). Peak exposures were defined for these analyses as any exposure that occurred that was >100 (BD100) or 500 (BD500) ppm. A weak but positive association was observed between leukemia and the BD100 peak exposures. However, there was no evidence of a dose-response relationship for the peak exposures when cumulative exposure was controlled for in the analysis. The investigators concluded that their analysis did not provide a firm basis for distinguishing between the importance of BD ppm-years and BD peaks as a cause of leukemia.

Finally, there is the possibility that the excess leukemia observed in the UAB study was related to confounding from another chemical that was also used at the plant. Initially, the analyses conducted by the UAB researchers considered potential confounding by benzene and styrene. Benzene was only weakly associated with leukemia in the analysis, and the effect of benzene was eliminated when the analysis was controlled for BD and styrene (14). Leukemia mortality did appear to increase as the styrene exposure levels increased, although not as strongly and as consistently as for the BD exposure. Studies of workers exposed to styrene alone have not demonstrated an increased risk of leukemia (31—35). Thus it appears highly unlikely that either benzene or styrene exposure was a significant confounder in this study. It has recently been suggested that exposure to dithiocarbamates may have potentially confounded the observed association between BD exposure and leukemia in the study by Delzell et al (36). Dithiocarbamates have been shown to be hematoxic and immunotoxic, but they have not been associated with leukemia risk in animals or humans.

There are also several areas of uncertainty in the comparisons of the carcinogenicity of BD in animals and humans, for example, the choice of which tumors sites to use for the comparison, the choice of statistical models, the manner in which dose is measured in the model, and the method of animal-to-human extrapolation. Our mouse-to-human comparison has focused primarily on tumors of hematopoietic origin, although numerous other tumor types have been observed in the mouse. Although we believe that this a reasonable choice, it must be recognized that the results from modeling the other tumor sites observed to be in excess in mice produced a wide range of risk estimates. For example, at occupational exposures of 1 ppm the estimates of excess risk ranged from 3 per million to 1 per 100, which is over 4 orders of magnitude. The more extreme estimates of risk were for tumor sites that do not occur in humans (ie, forestomach and heart hemangiosarcoma).

Our analyses of the mouse bioassay data for BD was limited to a single class of statistical models (ie, multistage Weibull time-to-tumor models). The BD dose was measured in terms of the inhaled concentration of BD, as opposed to, say, the concentration of BD or a BD metabolite at the site of tumor origin. Mouse-to-human extrapolation was based of the assumed equivalency of doses expressed as $mg/kg^{3/4}$-day. It should be recognized that analyses based on different statistical models, dose metrics, methods of species extrapolation, and assumptions regarding tumor site concordance would probably yield somewhat different results.

Concluding remarks

The finding of a highly significant exposure-response relationship between BD exposure and leukemia in the UAB analysis certainly provides substantial support for the concerns over human cancer risk that were previously raised by the NTP mouse bioassay studies. The similarity of the risk estimates derived from models of the mouse bioassay study for lymphocytic lymphoma and the epidemiologic data for leukemia for the occupational exposures of concern provides some support for the continued modeling of animal bioassay data for predicting risks. On the other hand, the estimation of risks for exposure levels of environmental concern were found to be highly model dependent when either the epidemiologic or toxicologic data were used. This is not a surprising result, since one would expect the predictions from these models to be highly model dependent when extrapolation is made well beyond the range of the observed data. The results from using a procedure based on the estimation of an effective dose (EC), as proposed by the new EPA cancer guidelines, is far less model dependent, and this lack of dependency is an attractive feature of this alternative approach.

Clearly there have been, and will be, situations in which the results from toxicologic studies may not produce reliable estimates of human cancer risks. On the other hand, it is possible that several calamitous human exposures to toxic agents could have been prevented had the proper toxicologic tests been conducted and the proper regulatory policies been set (7). We believe that BD represents an example that supports the prudence of past

US policies that have relied on animal bioassay studies for developing regulatory standards rather than waiting for epidemiologic studies to detect the tragic effects of carcinogenic exposures on workers or other exposed human populations. Additional comparative analyses of this kind are needed to permit a systematic evaluation of the concordance between the predictions from toxicologic and epidemiologic risk assessment models.

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