Risk Analysis, Vol. 13, No. 6, 1993

Comparing Toxicologic and Epidemiologic Studies: Methylene Chloride—A Case Study

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Received March 18, 1993; revised July 13, 1993

Exposure to methylene chloride induces lung and liver cancers in mice. The mouse bioassay data have been used as the basis for several cancer risk assessments.[1,2] The results from epidemiologic studies of workers exposed to methylene chloride have been mixed with respect to demonstrating an increased cancer risk. The results from a negative epidemiologic study of Kodak workers have been used by two groups of investigators to test the predictions from the EPA risk assessment models.[3,4] These two groups used very different approaches to this problem, which resulted in opposite conclusions regarding the consistency between the animal model predictions and the Kodak study results. The results from the Kodak study are used to test the predictions from OSHA's multistage models of liver and lung cancer risk. Confidence intervals for the standardized mortality ratios (SMRs) from the Kodak study are compared with the predicted confidence intervals derived from OSHA's risk assessment models. Adjustments for the "healthy worker effect," differences in length of follow-up, and dosimetry between animals and humans were incorporated into these comparisons. Based on these comparisons, we conclude that the negative results from the Kodak study are not inconsistent with the predictions from OSHA's risk assessment model.

KEY WORDS: Methylene chloride; cancer; risk assessment; epidemiology.

1. BACKGROUND

Epidemiologic data are often not available for performing quantitative risk assessments. Even when epidemiologic studies have been performed, adequate information for modeling dose–response relationships is frequently unavailable. In this case, the modeling of animal bioassay studies and extrapolation of the results from these models are often used to predict human risk. However, even in this situation, epidemiologic studies may be used to test the reasonableness of predictions from animal-based risk assessment models. Methylene chloride is a useful example of this situation.

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Inhalation of methylene chloride (MC) induces lung and liver cancers in mice and mammary tumors in rats.[5] Data from a NTP mouse study were used as the basis for cancer risk assessments performed by the Environmental Protection Agency (EPA)[1] and the Occupational Safety and Health Administration (OSHA).[2]

The results from epidemiologic studies of workers exposed to MC have not consistently demonstrated an excess cancer risk. A statistically significant excess of liver-biliary cancer was observed in one study,[6] but an excess was not observed in other studies[7,8] of workers exposed to MC.

The results from a study of Kodak workers have been used by two groups of investigators[3,4] to evaluate the predictions of excess risk from the EPA risk assessment.[1] These two groups employed different approaches to this problem, resulting in opposite conclusions regarding the consistency between the predictions from the animal model based predictions and the Kodak study

0272-4332/93/1200-0667$07.00/1

results. Hearne *et al.*[3] compared upper-bound estimates of lung and liver cancer deaths with the number observed, and reported that the linearized multistage model predicted significantly more cancer deaths than were observed. Tollefson *et al.*[4] used the predicted number of cancer cases to estimate the statistical power and concluded that the Kodak study lacked sufficient power to detect the risks predicted by the linearized multistage model. The two approaches are based upon differing assumptions, which has been the subject of some debate in the scientific literature.[9,10]

In this report, we describe methods for exploring the consistency of results from epidemiologic and toxicologic studies. These methods are applied to compare the negative results from the Kodak study, and predictions from an animal-based model is reexamined in relation to a risk assessment developed by OSHA.[2]

2. METHODS

Comparisons of the health effects associated with chemical exposure on animal and human populations are inherently difficult. Animal studies generally involve lifetime exposures where a constant concentration is administered from approximately 6–8 weeks of age until study termination (often 2 years—approximately an average mouse lifetime). This might be viewed as being chronologically equivalent to a human exposure that starts when a human is approximately 4–5 years old continuing until the human is approximately 74 years old (assuming a 74-year average life-span for humans). This clearly differs from the typical pattern of occupational exposure encountered in epidemiologic studies of worker populations, such as the Kodak cohort. Characteristics of the Kodak cohort are presented in Table I, including the average age at end of follow-up, average level of exposure, average duration of exposure, and size of each exposure group.

Table I. Summary of Characteristics of the Kodak Epidemiological Study Cohort[a]

Exposure group	Average age at end of follow-up	Average level of exposure	Average duration (years)	Sample size
<150 ppm-years	55.8	19.4 ppm	5.7	430
150–349 ppm-years	57.5	36.8 ppm	16.9	249
350–799 ppm-years	59.4	33.2 ppm	25.8	369
800+ ppm-years	62.6	84.1 ppm	26.5	263

[a] Data kindly provided to us by T. Hearne (Eastman Kodak).

The multistage models that were fitted by Crump[11] for OSHA in its proposed rule for methylene chloride were used to predict the number of excess cancer cases that would be expected among workers in the Kodak cohort. Before applying these dose–response models, adjustments were made for differential length of follow-up (relative to average human life-span) in the occupational cohort, and for an appropriate dose metric for equivalent carcinogenic response. In addition, an adjustment of the results from the epidemiologic study for the "healthy worker effect" was applied and results are presented with and without this adjustment. Following is a detailed description of these adjustments.

2.1. Adjusting for Differential Length of Follow-Up in Human vs. Animal Studies

Comparing results from studies conducted for different lengths of time is a vexing problem. Gold *et al.*[12] employed a polynomial time adjustment when converting tumorigenic potency estimates to a common time value. This was justified from the observation that cancer onset increases "markedly with age." We derive a time adjustment factor that is in fact a polynomial factor of the ratio of study lengths from noting the implications of a time-to-tumor model for a quantal model as described below.

The quantal form of the multistage model was fitted to the NTP mouse carcinogenicity study of methylene chloride by Crump[11] for OSHA. For some fixed time t, this model takes the general form:

$$S(d) = \text{probability of remaining tumor free for animals receiving dose } d = \exp[-(q_0 + q_1 d + q_2 d^2)] \quad (1)$$

where q_0 represents the baseline cumulative hazard, d represents dose, q_1 represents the linear effect of d, and q_2 represents a quadratic effect of d. The parameters of (1) (i.e., q_0, q_1, q_2) are all constrained to be nonnegative.

A Weibull time-to-tumor model can be written that incorporates both multistage model dose effects and a polynomial time (t) term:

$$S(d,t) = \text{probability of tumor onset after time } t \text{ for animals receiving dose } d = \exp[-(a_0 + a_1 d + a_2 d^2)t^s] \quad (2)$$

where a_0 represents the baseline hazard, d represents the dose of the carcinogen, a_1 represents the linear effect of d, and a_2 represents a quadratic effect of d.

A mathematical equivalence exists between the quantal and Weibull multistage models. The parameters

from the quantal (1) and the Weibull (2) forms of the multistage model can be related based on the duration of the study (t). In short, $q_i = a_i t^s$ for $i = 0,1,2$. This suggests one mechanism for adjusting the model parameters from a quantal multistage model based on one study length to another model based on a different study length. Suppose a quantal multistage model is fit to a set of data from a study of length t and parameter estimates (q_0, q_1, q_2) are obtained. Further, suppose a Weibull time-to-tumor structure with shape parameter s is appropriate. Then a prediction of survival (or tumor onset) probabilities for a different study length, say t^* not equal to t, can be obtained using a multistage model with parameters (q_0^*, q_1^*, q_2^*) where $q_i^* = q_i (t^*/t)^s$. This approach was used to adjust the quantal multistage parameter estimates for time in this analysis.

The average age at the end of follow-up for each exposure group (Table I) was used for t^* and the average length of life (t) was assumed to be 74 for humans for this adjustment. A value of 3 was assumed for the shape parameter (s), based on analyses reported by Portier *et al.*[13] Their analyses indicated that both lung and liver tumor onset in the $B6C3F_1$ mouse is reasonably described by a Weibull model with a shape parameter equal to 3.

2.2. Definition of an Appropriate Equivalent Dose Metric

Crump[11] used mg/kg/day as the dose metric that led to equivalent risk for humans and mice. From the Crump report on methylene chloride, human dose (ppm) for a 70 kg human exposed 8 hr/day, 250 day/year for T years of a 74-year life-span was:

$$\text{ppm} = \frac{\text{mg/kg/day} \times (70\text{ kg}) \times (74\text{ years}) \times (365\text{ day/year})}{(1.2 \times 84.9/28.8) \times (10\text{ m}^3\text{/day}) \times (\text{T years}) \times (250\text{ day/year})}$$

where 1.2 = the density of air, 84.9 = the molecular weight of MC, 28.8 = molecular weight of air, and 10 m^3/day = the air breathed per 8-hr workshift.

This equation can be rearranged to determine the mg/kg/day dose for humans that are exposed at a certain level of ppm for T years. This is simply:

$$\text{mg/kg/day} = \frac{\text{ppm} \times (1.2 \times 84.9/28.8) \times (10\text{ m}^3\text{/day}) \times (\text{T years}) \times (250\text{ day/year})}{(70\text{ kg}) \times (74\text{ years}) \times (365\text{ day/year})}$$

2.3. Calculation of Predicted Excess Number of Deaths and SMRs

The expected excess number of deaths in the exposure groups in the Kodak cohort study were derived by multiplying the number of workers in each exposure group by the excess risk as determined from $[P_d(t) - P_0(t)]/[1 - P_0(t)]$ where $P_d(t) = 1 - S_d(t)$. These calculations were performed using the point estimates (MLEs) and the lower and upper bounds on (q_0^*,q_1^*,q_2^*) for estimating the excess numbers of deaths as reported by Crump.[11]

For comparison with the epidemiologic results, the predicted number of excess cases based on the animal bioassay model were added to the expected number (with and without the correction for the HWE as described below) from the Kodak study and the results were divided by the expected number to calculate predicted SMRs and 95% confidence intervals. The predicted SMR (SMR_p) may be represented mathematically as:

$$SMR_p = (E + p)/E$$

where E represents the expected number of deaths from the life-table analysis and p represents the predicted number of excess cases from the animal bioassay model.

2.4. Adjustment of the Epidemiologic Study for the Healthy Worker Effect

The most recent results from the follow-up of the Kodak cohort were used for this analysis. These results were submitted by Hearne[14] to the OSHA Docket for MC, and were kindly shared with us. This investigation included 1311 men who were first employed between 1946 and 1970 in a manufacturing area using MC and were followed for vital status through 1990. Expected deaths for this cohort were estimated by Hearne using New York State mortality rates for males residing outside of New York City.

It is well recognized that comparing the mortality of occupational cohorts with general population rates, such as those used in the Kodak study, are generally negatively biased due to what has been termed the "healthy worker effect" (HWE).[15,16] This bias results from the fact that the mortality rates for the general population include contributions from individuals who are not healthy enough to work. In order to correct for this potential bias, the expected number of liver and lung cancer deaths were reduced by multiplying them by a correction factor. The ratio of observed to expected deaths (252/321 = 0.78) for all causes of death other than liver and lung cancer that was reported for this cohort[14] was used as the ad-

justment factor. Standardized mortality ratios (SMRs) were calculated by dividing the observed number of lung or liver cancer deaths by the HWE corrected expected number. Confidence intervals for the SMRs were estimated using methods described by Rothman and Boice.[17] Separate SMRs and confidence intervals were estimated for each of four career exposure categories (<150, 150–349, 350–799, and >800 ppm-years) and for the combined cohort.

3. RESULTS

Table II presents the observed and expected numbers of liver and lung cancer deaths by level of cumulative exposure to MC. The expected numbers corrected for the HWE are also shown. The HWE adjusted expected number (23.25) for combined cancers in the full cohort is much closer to the observed number (22) than the unadjusted expected number of deaths (29.61).

The predicted numbers of excess liver and lung cancer cases from the multistage models fitted to the male and female mouse NTP methylene chloride studies are presented in Tables III and IV. The upper bound of the predicted number of excess lung and liver cancer cases was less than 2 for males and less than 3 for females. The predicted numbers of cancers were generally slightly greater for the models based on the results for female than for male mice.

Comparisons of the observed results from the Kodak study with the results predicted from the multistage modeling of the NTP mouse bioassay data are illustrated in Fig. 1. Separate comparisons are presented for: (1) lung cancer, liver cancer, and lung and liver cancer combined; (2) predictions based on the male and female mouse bioassay data; and (3) analyses with and without the healthy worker effect correction. In every case, the SMRs and confidence intervals predicted from the animal bioassay data are contained within the observed confidence intervals from the Kodak study. The point estimates from the unadjusted analysis are generally lower than the predicted estimates, but these differences are reduced in the HWE-adjusted analyses. The results from the analyses performed with and without the HWE correction were consistent in so far as the observed 95% confidence limits were greater than the predicted point and upper-bound estimates.

4. DISCUSSION

The results presented above suggest that the negative findings from the Kodak epidemiologic study are not incompatible with the estimates of risk predicted by the OSHA multistage model. The confidence intervals of the SMRs predicted from the animal bioassay are clearly nested within the confidence intervals of from the Kodak study. This is not to suggest that the results from this negative epidemiologic study are equivalent to the positive results from the animal bioassay studies of MC exposure. Rather the results from the Kodak study are not inconsistent with the predictions from the animal bioassays when adjustments for differences in study protocol, the HWE and statistical variability are taken into account.

We used observed and predicted confidence intervals as the basis for testing the consistency of the Kodak study with the animal-based model predictions. This approach incorporates the results and variability from both sources of information. In contrast, Hearne *et al.*[3] com-

Table II. Observed and Expected Numbers of Death Adjusted for the Healthy Worker Effect from the Kodak Study of Workers Exposed to Methylene Chloride[a]

Exposure (ppm-years)	Lung cancer			Liver cancer			Combined		
	Obs.	Exp.	Exp.[b]	Obs.	Exp.	Exp.[b]	Obs.	Exp.	Exp.[b]
< 150	4	7.68	5.99	0	0.33	0.26	4	8.01	6.25
150–349	6	5.64	4.40	0	0.24	0.19	6	5.88	4.59
350–799	6	8.23	6.42	0	0.30	0.23	6	8.53	6.65
> 800	6	7.12	5.55	0	0.27	0.21	6	7.39	5.76
Overall	22	28.67	22.36	0	1.14	0.88	22	29.81	23.25

[a] Observed and expected numbers were provided to us by T. Hearne (Eastman Kodak).

[b] Corrected for the healthy worker effect by multiplying the reported expected numbers by the SMR for all causes of death other than liver and lung cancer (0.78).

Table III. Excess Number of Deaths Based on the Maximum Likelihood (MLE), Lower (LL), and Upper (UL) 95% Confidence Interval Estimates of Excess Risk Predicted by the Multistage Model of the NTP Study of Male Mice[a]

Exposure (ppm-years)	Dose (mg/kg)	Lung			Liver			Lung and liver		
		LL	MLE	UL	LL	MLE	UL	LL	MLE	UL
< 150	0.52	3.0E-3	0.03	0.05	6.1E-7	1.9E-6	0.02	3.6E-6	6.1E-6	0.04
150–349	2.91	0.01	0.11	0.17	1.2E-5	3.9E-5	0.07	7.1E-5	1.2E-4	0.16
350–799	4.01	0.02	0.24	0.37	3.8E-5	1.2E-4	0.16	2.2E-4	3.8E-4	0.35
≥ 800	10.4	0.05	0.53	0.81	2.2E-4	6.8E-4	0.35	1.3E-3	2.2E-3	0.77
Overall	—	0.08	0.91	1.40	2.7E-4	8.4E-4	0.60	1.6E-3	2.7E-3	1.32

[a] Abbreviations used: LL, lower 95% confidence bound; UL, upper 95% confidence bound; MLE, maximum likelihood estimate.

Table IV. Excess Number of Deaths Based on the Maximum Likelihood (MLE), Lower (LL), and Upper (UL) 95% Confidence Interval Estimates of Exess Risk Predicted by the Multistage Model of the NTP Study of Female Mice[a]

Exposure (ppm-years)	Dose (mg/kg)	Lung			Liver			Lung and liver		
		LL	MLE	UL	LL	MLE	UL	LL	MLE	UL
< 150	0.52	0.01	0.04	0.05	3E-6	4E-6	0.01	1.0E-5	0.03	0.08
150–349	2.91	0.04	0.15	0.19	7.2E-5	9.5E-5	0.05	2.1E-4	0.11	0.29
350–799	4.01	0.10	0.34	0.43	2.2E-4	3.0E-4	0.12	6.6E-4	0.26	0.65
≥ 800	10.4	0.22	0.73	0.93	1.3E-3	1.7E-3	0.26	3.7E-3	0.56	1.40
Overall	—	0.37	1.26	1.61	1.6E-3	2.1E-3	0.45	4.6E-3	0.96	2.42

[a] Abbreviations used: LL, lower 95% confidence bound; UL, upper 95% confidence bound; MLE, maximum likelihood estimate.

pared the observed number of deaths from their study with the upper 95% bound estimates predicted from the animal-based models. Their approach only considered the variability from one data source (the animal bioassay). Our approach also differs from that of Tollefson *et al.*[4] who used statistical power as their basis for comparison. Hearne *et al.*[9] criticized Tollefson *et al.*'s approach on the basis that it did not incorporate the results from his study.

Our approach and the approaches used by both Tollefson *et al.* and Hearne *et al.* assume that the cancer sites observed to be in excess in the animal studies (liver and lung) are also the sites that would be expected to be in excess in humans. Concordance of cancer sites between species is not always expected. The State of California[18] performed an assessment of this issue in which they compared the pancreatic cancer mortality which was in excess in the Kodak study with the predictions based on the linearized multistage model, and concluded that the Kodak epidemiologic study findings may be consistent with the animal data.

The comparisons made in this paper were based on several additional assumptions, and their potential impact on our results needs to be considered. First of all, we corrected for the HWE by using a factor based on the mortality for all causes of death other than lung and liver cancer. The use of a correction factor is not accepted by all epidemiologists as an appropriate method for adjusting for the HWE.[19] The validity of this correction rests on the assumption that the HWE is as strong for the causes of interest (i.e., lung and liver cancer) as it is for other causes of death. In fact, the HWE has often been observed to be weaker for cancer than for other causes of death,[16] and there is some disagreement among epidemiologists as to whether there is any HWE for cancers.[19] However, workers in the Kodak cohort were not permitted to smoke cigarettes while working except during breaks and lunch periods (T. Hearne, personal communication). Thus, in addition to the potential bias related to the HWE, the results for lung cancer and other causes of death may have been negatively biased by the company smoking policies. Hearne *et al.*[3] did report information from a survey of workers in their study that indicated that the percentage of current smokers among their study subjects was similar to the percentage among their comparison populations. However, it still seems likely that the consumption of cigarettes among smokers in the study population was reduced by

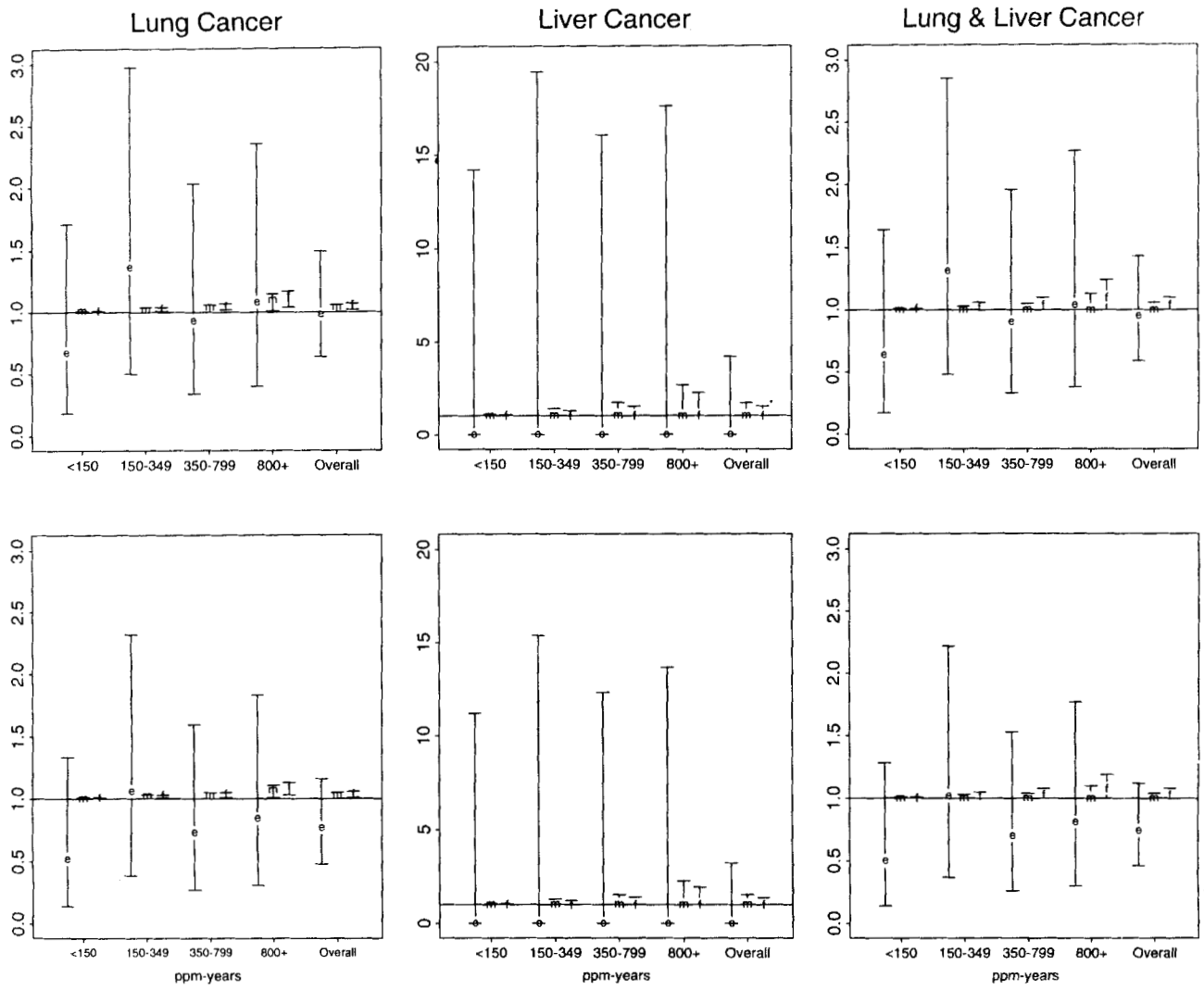

Fig. 1. SMRs (e = epidemiologically based,; f = predicted based on the female mouse model; and m = predicted based on the male mouse model) and 95% confidence intervals with and without correction for the healthy worker effect for cancers of the lung, liver, and lung and liver combined.

the company's nonsmoking policies. The fact that essentially the same results were obtained when an analysis was performed without the HWE adjustment indicates that the use of this factor was not a critical assumption in our analysis.

The second important assumption is related to our treatment of dose. In order to make this comparison, we averaged the workers cumulative exposure over the observation period for each exposure group. In doing so, we were assuming that total methylene chloride exposures received over a long or short period of time are equivalent (i.e., dose-rate has no effect). In fact, there is no information available to test the appropriateness of this dose-rate assumption. Secondly, we assumed that the exposures of animals and humans are comparable on a mg/kg/day basis, which was the same assumption made by OSHA in their risk assessment. Reitz *et al.*[20] have proposed an alternative method for comparing animal and human exposures to methylene chloride using a PBPK model. The use of this model may improve the basis for extrapolation from the results from animal studies to predict the risk for humans. However, the conclusions from our analysis would not change if we had used the Reitz *et al.* model, since this approach would result in even lower estimates of human risk.

Finally, we assumed that the cancer incidence rates

from the animal bioassay models could be adjusted for the shorter than lifetime follow-up of the epidemiologic study, by using a factor based on age raised to the 3rd power. Empirically, it has been reported that the incidence rate of liver and lung cancer increases with age raised to approximately the 3rd power in the NTP historical control data set.[13] This time adjustment is simple in that it does not incorporate any information on competing risks. If such information is available, recent work by Bailer and Smith[21] may be applicable.

Results from epidemiologic studies are a crucial source of information for evaluating the predictions from animal-based risk assessment models. As Tollefson[4] observed, there is a need "for the development of methodology to relate animal and human data for use in a weight-of-the-evidence assessment of risk—hopefully, techniques which can command the consensus of the scientific community." The methods presented herein are an attempt to account for the protocol differences and other sources of variability to a greater extent than those previously used.

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