Methodologic Issues in Using Epidemiologic Studies for Quantitative Risk Assessment

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Although animal studies have been used most often for quantitative risk assessment, it is generally recognized that well-conducted epidemiologic studies would provide the best basis for estimating human risk. However, there are several features related to the design and analysis of epidemiologic studies that frequently limit their usefulness for quantitating risks. The lack of accurate information on exposure in epidemiologic studies is perhaps the most frequently cited limitation of these studies for risk assessment. However, other features of epidemiologic study design, such as statistical power, length of follow-up, confounding, and effect modification, may also limit the inferences that can be drawn from these studies. Furthermore, even when the aforementioned limitations are overcome, substantial uncertainty exists concerning the choice of an appropriate statistical (or biologic) model for extrapolation beyond the range of exposures observed in a particular study. This paper focuses on presenting a review and discussion of the methodologic issues involved in using epidemiologic studies for risk assessment. This review concentrates on the use of retrospective, cohort, mortality studies of occupational groups for assessing cancer risk because this is the most common application of epidemiologic data for quantitative risk assessment (QRA). Epidemiologic data should not be viewed as a panacea for the problems inherent in using animal bioassay data for QRA. Rather, information that can be derived from epidemiologic and toxicologic studies complement one another, and both data sources need to be used to provide the best characterization of human risk.

Introduction

Risk assessment is an emerging discipline that involves the characterization of risks from human exposures to environmental or occupational hazards. The process has been defined as having the following four steps: 1) identification of hazards, 2) exposure assessment, 3) estimation of dose–response relationships, and 4) the characterization of risk. The numerical quantification of the risk associated with human exposures has been generally referred to as quantitative risk assessment (QRA).[1]

To date, most risk assessments have been based upon analyses of animal bioassay data. Considerable uncertainty generally surrounds risk estimates derived from analyses of animal studies because of the need to extrapolate between species and from the relatively high doses administered to animals to the relatively low levels of human exposures.

These uncertainties have led some authors to question the relevance of data from experiments in which animals are exposed to high doses for predicting human risk[2] and to suggest reliance on epidemiologic data for QRA. Other researchers have demonstrated a reasonably strong correlation between cancer potency estimates derived from assessments based on toxicologic and epidemiologic data[3,4] supporting the validity of using animal bioassay data for predicting human risk.

Despite the uncertainties described above, there will continue to be a need to perform QRAs based on animal bioassay data. The alternative is to wait until greatly improved epidemiologic information is developed, which is socially unacceptable. Furthermore, because of the nonexperimental nature of epidemiologic investigations, data from these studies have their own limitations that may often introduce additional uncertainties into the risk assessment process. The purpose of this paper is to provide a review of the key methodologic issues and attendant uncertainties related to the design and analysis of epidemiologic studies for QRA. This discussion will primarily focus on the use of retrospective, cohort, mortality studies of occupational groups for assessing cancer risk because this is the most common application of epidemiologic data for QRA.

Study Design

In contrast to experimental studies in animals, the observational nature of epidemiologic investigations generally introduces numerous sources of uncertainty into the QRA process. Unlike toxicologists, epidemiologists generally cannot randomly assign exposures to the toxic agent under study, nor can they limit exposures to other potential disease risk factors that may bias and otherwise distort the relationship between exposure and disease. Risk assessors need to be cognizant of the following issues related to the design of epidemiologic studies, which may introduce substantial uncertainties into the QRA process.

Exposure and Dose Estimation

The lack of adequate information on exposure is the most frequently cited reason for rejecting epidemiologic data as the basis for QRA. This is particularly a problem for retrospective, cohort, mortality studies of occupational groups because information on levels of exposure is frequently lacking during the early time periods of these studies. This situation may improve as companies increase their routine collection of data on occupational exposures. Considerable progress has also been made in developing better methods for estimating historical exposures in the workplace.[5]

Even if only crude estimates of exposures are available, epidemiologic data can still be useful for QRA. At the very least, if a range of likely exposures can be estimated for an epidemiologic study, then a range of possible risk estimates can also be derived from the study. This range of risk estimates can then be used to check whether the estimates derived from an animal-based model appear to be reasonable, i.e., are they in the range of the possible epidemiologic estimates.

Ideally, information on doses to the target tissues should be used for performing QRA using epidemiologic and animal bioassay data. If the target tissue dose is a linear function of the external exposure, then use of the external exposure is appropriate for QRA. However, if one needs to extrapolate beyond the range of the epidemiologic data, then use of the external exposure may produce unrealistic estimates of risk if the relationship between external exposure and target tissue dose is nonlinear. Moreover, extrapolations from models based on epidemiologic data may be undermined by physiologic and other differences within the human population unless estimates of dose rather than exposure are used for the assessment. For example, a model based on a study of the effects of respiratory exposures in a working male population could not be validly used for predicting risk to a nonworking female population unless dosimetric adjustments were made for factors such as differences in ventilation rates.

Direct measurements of target tissue doses will rarely (if ever) be available in occupational, cohort, mortality studies. However, physiologically and pharmacologically based models have recently been applied to the estimation of target tissue doses to improve extrapolations from animal studies to predict human risk.[6] These models may also find applications for improving risk estimation based on epidemiologic studies. In addition, biological markers, such as DNA and protein adducts, may also be useful for estimating at the molecular level the dose to target tissues in epidemiologic risk assessments.[7,8]

The potential influence of exposure misclassification on risk estimates derived from epidemiologic studies is an area requiring additional investigation. It is often assumed that nondifferential misclassification of exposure will result in a weakening of the dose–response relationship and, thus, an underestimation of the risk associated with exposures. However, it has been shown that exposure misclassification may result in biased risk estimates in either direction.[9,10]

Confounding

Perhaps the greatest obstacle toward utilizing epidemiologic studies for risk assessment is the potential for confounding by other risk factors. Confounding is the mixing of effects in which the estimate of the effect of exposure is distorted by the effect of an extraneous factor.[11] In occupational, cohort, mortality studies, potential confounding frequently exists due to the presence of multiple exposures found in the workplace or due to differences between the study population and the referent population in terms of personal risk factors (e.g., smoking).

Confounding in experimental (i.e., animal) studies is effectively limited (although not eliminated) by randomization of exposure. In nonexperimental (i.e., epidemiologic) studies in which randomization of exposure is not performed, confounding variables may not be randomly distributed between the exposed and nonexposed groups. Although the influence of measured confounders may be controlled for in the analysis of epidemiologic studies, the possibility of confounding by unmeasured confounders can never be fully eliminated. Greenland[12] has also emphasized that the failure to randomize and the resulting potential for confounding in epidemiologic studies undermines the interpretability of the inferential statistics that are generally used in these studies (i.e., p values and confidence intervals). Thus, the true uncertainty in the results from epidemiologic studies may not be fully estimable because of unrecognized confounding.

Effect Modification

Effect modification (interaction) in epidemiologic studies is also an important consideration for QRA. Effect modification refers to a change in the magnitude of an effect measure (e.g., rate ratio) according to the value of an additional variable.[11] The risks in occupational cohort studies may be modified by related, time-dependent covariates such as age at first exposure, time since first exposure (empirical induction period), or time since last exposure; risks may also be modified by personal habits such as cigarette smoking or by other exposures found in the workplace. When recognized and properly analyzed, effect modification may be viewed as an advantage of epidemiologic data over animal bioassay data for QRA because it provides information on how exposures interact in the real world. However, unrecognized effect modification may introduce additional uncertainties into the extrapolation of the results from an epidemiologic study to other populations in QRA.

Sample Size and Statistical Power

Epidemiologic studies are relatively insensitive for

TABLE I. Sample Size Estimates for Detecting Varying Levels of Excess Lung Cancer Risk in a Hypothetical, Retrospective, Cohort, Mortality Study

Assumed Excess Risk	Relative Risk (SMR)[A]	Expected Deaths[B]	Person Years[C]	Number of Workers[D]
10^{-2}	1.20	170	217,161	4,343
10^{-3}	1.02	15,605	2.0×10^{7}	399 x 605
10^{-4}	1.002	1.5×10^{6}	2.0×10^{9}	39.6×10^{6}
10^{-5}	1.0002	1.5×10^{8}	2.0×10^{11}	39.6×10^{10}

[A]Relative risks calculated using a background risk (cumulative probability) of 0.06 for developing lung cancer for males over age 15, based upon the proportion of deaths from lung cancer among U.S. males over age 15 in 1982.[13]

[B]Expected number of deaths calculated using formula from Beaumont and Breslow,[14] assuming 80% power ($1-\beta$), α level of 0.05 (1-tail), and the calculated relative risk.

[C]Person-years calculated by dividing the expected number of deaths by the lung cancer rate (7.8×10^{-4}) among males between the ages of 45 and 54 based on U.S. mortality rates from 1982,[13] which is approximately the average of the hypothetical population.

[D]Number of workers calculated by assuming each worker contributed 50 person-years to the study.

detecting the levels of risk that are of general concern to regulatory agencies and that need to be estimated in QRAs. Although rigid criteria for significant (deminimus) risk have not been established, the U.S. Environmental Protection Agency (EPA) and Food and Drug Administration have generally set regulations to limit risks to between 1 per 100,000 and 1 per 1,000,000. The Occupational Safety and Health Administration (OSHA) in its most recent rulings on carcinogens has generally adopted exposure limits that correspond to a lifetime risk of 1 per 1000 workers.

Estimates of the population size required for a retrospective, cohort, mortality study to have 80% statistical power[A] (at $\alpha = 0.05$) for detecting lung cancer risks corresponding to the levels of risk of between 1 per 100 and 1 per million are presented in Table I. These estimates were constructed for a hypothetical cohort of male workers who were followed for 50 years. In practice, the average period of follow-up in most occupational cohort mortality studies is considerably less than 50 years; thus, these estimates are most likely underestimates of the true sample sizes that would be required.

It is readily apparent from Table I that extremely large sample sizes would be needed to detect the levels of risk of concern to U.S. regulatory agencies. Even at the nominal deminimus risk level of 1 per 1000 (used by OSHA), a sample size of nearly 400,000 workers would be required. Few retrospective, cohort, mortality studies have been performed that have included this many workers, and thus, it is extremely unlikely that sufficiently large cohorts can be identified to detect risks below 1 per 1000. It is also noteworthy that few epidemiologists would be willing to accept relative risk estimates as low as those presented in Table I as being causally significant (even if it was statistically significant) because it is difficult to fully dismiss the potential for confounding at such low levels of relative risk.

Therefore, negative epidemiologic studies generally cannot be used to rule out the levels of risk that are of concern to regulatory agencies because of the limitations in statistical power discussed above. Negative epidemiologic studies, however, may still be useful for developing a likely upper bound (i.e., confidence interval) on the risk of exposure.

Meta-analysis, which involves the combination of study results, may be used to improve the sensitivity of epidemiologic studies.[15] However, combining occupational studies to perform a meta exposure–response analysis may be problematic because different methods are often used to estimate exposures in these studies.

Length of Follow-Up, Latency, and Lag Periods

Most regulatory agencies are interested in developing regulations based upon estimates of lifetime risks of exposures. This presents a problem for using occupational, cohort, mortality studies for QRA because, in most studies, only small segments of the population have been followed for an entire lifetime. In contrast, in most animal bioassay studies, the animals are observed for nearly their entire life span. Thus, some epidemiologic investigations may be negatively biased if the study population was simply not followed for a sufficiently long period of time.

The total time from first exposure to the clinical detection of or death from cancer has been termed the "empirical induction time" by Rothman[16] but is more frequently referred to as the time since first exposure (or imprecisely as the latency period). As illustrated in Figure 1, this period of time can be conceptually divided into two phases: 1) the time from first exposure to the development of a malignant cell termed the "induction period" and 2) the time from when a cell becomes cancerous until the clinical detection of the

[A]One minus the probability (β) of making a Type II error (failing to reject the null hypothesis when it is false).

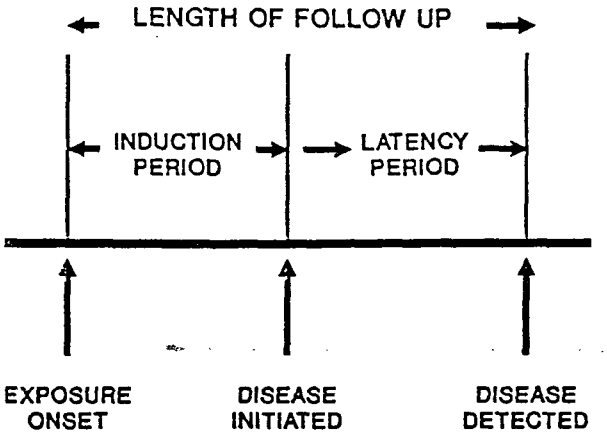

FIGURE 1. Length of follow-up.

tumor (or death from the malignancy) termed the "latency" or "lag" period.[16] Exposures that occur during the lag period may be expected to have no effect on tumor incidence and should be discounted from exposure–response analyses.

Although the actual lag period is generally unknown, it can be estimated empirically by iteratively refitting models with different assumptions about the length of the lag period.[17] The lag period that results in maximizing the goodness of fit of the model may then be chosen for use in the final risk assessment model.

Although the induction period generally cannot be measured in cohort mortality studies, the effect of the empirical induction time (i.e., time since first exposure) can be assessed. If the empirical induction period modifies the effect of exposure, then extrapolations for QRA need to take this into account.

Statistical Analyses

Model Selection

Risk assessors have long recognized the difficulty of selecting an appropriate mathematical model for extrapolation in QRA using animal bioassay data.[18] While it is possible to empirically choose models that describe the data well in the range of the observed data, the true dose–response relationship for the lower dose range is generally unknown and can only be inferred based upon biological and statistical considerations. This problem is generally not circumvented by using data from occupational mortality studies because these studies most often include individuals who were exposed to relatively high exposures in the past and, as demonstrated above, extrapolations beyond the range of the data are generally required for estimating low-dose risk owing to limitations in statistical power.

In the following sections, examples are drawn for heuristic purposes from an assessment recently performed by researchers at the National Institute for Occupational Safety and Health (NIOSH)[19] of the risk of lung cancer associated with cadmium exposure based on a NIOSH retrospective, cohort, mortality study of workers from a cadmium production facility.[20,21]

Statistical Models

Most QRAs based on occupational mortality studies have been based upon purely statistical models as opposed to biologically based models (described below). Considerable progress has been made in developing statistical methods for modeling hazard rates[B] from occupational, cohort, mortality studies in the past decade. An excellent review of these modeling techniques is presented in Breslow and Day.[22] These models may be broadly categorized into two classes: 1) models in which the effect of exposure adds to the background rate (additive models) and 2) models in which the effect of exposure multiplies the background rate (multiplicative models). These two classes of models may be represented mathematically as follows:

$$\text{additive: } \lambda(t) = \lambda_0(t) + r\{x(t)\beta\} \quad (1)$$

$$\text{multiplicative: } \lambda(t) = \lambda_0(t) r\{x(t)\beta\} \quad (2)$$

where: $\lambda(t)$ = predicted hazard rate
$\lambda_0(t)$ = background hazard rate at age t
$x(t)$ = vector of exposure and other explanatory variables
β = vector of regression parameters
$r\{x(t)\}$ = relative rate function (for Equation 2) or an excess (for Equation 1) rate function

Rate functions ($r\{x(t)\}$) that have been commonly used for models of cohort mortality data include:

$$\text{exponential: } r\{x(t)\beta\} = \exp(x(t)\beta) \quad (2a)$$

$$\text{additive relative rate: } r\{x(t)\beta\} = (1 + x(t)\beta) \quad (2b)$$

$$\text{power: } r\{x(t)\beta\} = (x(t) + k)^{\beta} \quad (2c)$$

where: k = small "background" exposure level, which is often assumed to be 1

The functional forms previously described may be fitted to data from occupational, cohort, mortality studies with person-years and observed deaths categorized by the exposure and other explanatory variables using Poisson regression.[23] Alternatively, with the exception of the additive model, all of these functional forms may be fitted to data from occupational, cohort, mortality studies by modeling the

[B]The hazard rate is the instantaneous probability of dying from the disease given survival prior to that time.

hazard rate continuously using the Cox proportionate hazards model.[24]

In theory, these two approaches should yield similar results assymptotically.[25] In practice, as the results presented in Figure 2 from the NIOSH cadmium risk assessment[19] illustrate, these regression methods may yield somewhat different results. The coefficient for cadmium exposure was approximately three times lower from the Cox proportional hazards model than from the Poisson regression model, even though both models had the same functional form (additive relative rate) and parameters.

In general, selection of an appropriate functional form for modeling cannot be based solely on statistical criteria of goodness of fit. Several models may provide a reasonable fit to the data, and it is generally necessary to consider additional information (e.g., biologic) for choosing an appropriate model for QRA. On the other hand, a model that does not fit the data in the observed data range is unlikely to be a reliable model for predicting low-dose risks.

An example of this dilemma is presented in Figure 3 from the NIOSH cadmium risk assessment.[19] In this assessment, the goodness of fit of the various functional forms described above was evaluated using Poisson regression. The power function, additive relative rate, and exponential multiplicative models all provided a reasonably good fit to the observed data, whereas the additive model did not appear to fit the data well. The power function model, which fit the data the best (i.e., lowest model deviance), was not chosen for the QRA

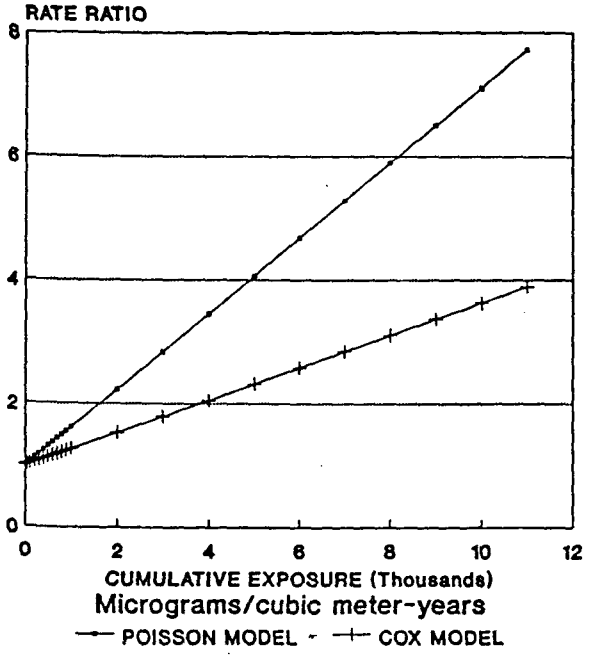

FIGURE 2. Comparison of rate ratio estimates from models of the NIOSH cadmium cohort study. Data lagged 5 years.

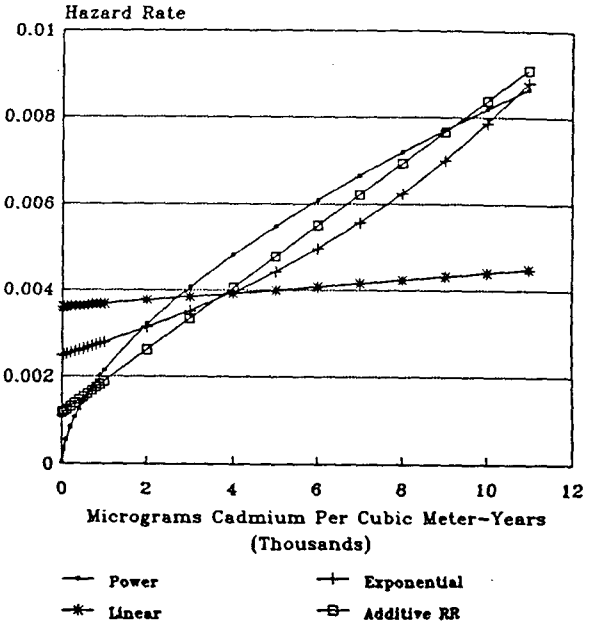

FIGURE 3. Poisson model hazard rates as a function of cumulative cadmium exposure based on lagged 5-year analysis for white males, age 70, 1940–1960.

because the model predicted background hazard rates that were nearly two orders of magnitude lower than the rates in the U.S. general population. The use of the power model for the QRA would have resulted in grossly inflated estimates of relative and excess risk. The additive relative rate model, which was the next best-fitting model, was chosen as the model for the QRA. It is noteworthy that the hazard rate estimates derived from these models diverge by over an order of magnitude at the extremes (i.e., high and low doses) of the exposure–response curves.

Internal versus External Analysis

Standardized mortality ratios (SMRs) are generally reported as the effect measure in most occupational cohort mortality studies. The SMR is the ratio of the number of deaths observed to the number expected and is frequently multiplied by 100 to express the ratio as a percentage. The expected number of deaths is calculated by applying the age-, calendar time-, race-, and sex-specific person-years distribution of the study population to the corresponding rates from an external referent group (e.g., the U.S. population).

Risk assessors have modeled SMRs that are reported in occupational, cohort, mortality studies for several exposure groups and, sometimes, even with just one group.[26] The models discussed above may be modified to incorporate external rates yielding the following mathematical forms that are analogous to Equations 1 and 2:

$$\text{additive: } \lambda(t) = \lambda^*(t) + r\{x(t)\beta\} \quad (3)$$

$$\text{multiplicative: } \lambda(t) = \lambda^*(t)r\{x(t)\beta\} \quad (4)$$

where $\lambda^*(t)$ represents the external mortality rates and the other parameters are unchanged from the Equations 1 and 2 described above. Equation 4 may also be expressed in terms of modeling the SMR using the following form:[25]

$$\frac{OBS}{EXP} = r\{x(t)\beta\} \quad (5)$$

where: OBS = observed
EXP = expected number of deaths

Although modeling SMRs may be the only possible approach if the risk assessor only has access to published tables, there are at least two serious potential problems with this approach. First, because SMRs are indirectly standardized, the SMRs from different exposure groups are not standardized to the same standard and, thus, are not directly comparable.[11] Therefore, the modeling of SMRs from several exposure groups may be biased by demographic (e.g., age, race, or sex) or other differences between the categories. Second, and probably of greater significance, is the well-known fact that SMRs may be negatively biased because of the "healthy worker effect";[27,28] i.e., a working cohort may have a lower incidence of disease (or mortality) than the general population (the referent) simply because they are healthy enough to be employed.

An alternative analytic approach, which avoids the pitfalls described above for the analyses of SMRs, is to base the analysis on internal comparisons within the cohort using the modeling techniques described above (i.e., Equations 1 and 2). Although most occupational cohort mortality studies do not include an internal nonexposed group, an internal analysis is still possible as long as there is a range of exposures within the cohort. The inclusion of an internal, nonexposed, referent group, when available, does add some stability to the regression model.

Figure 4 presents a comparison of the results from an analysis of the risk of lung cancer in relation to cumulative exposure to cadmium that was performed by OSHA[29] with the results from the NIOSH cadmium risk assessment[19] to illustrate the potential bias that may be introduced by the modeling of SMRs. Both analyses were performed on the findings of a NIOSH cohort mortality study of cadmium smelter workers,[20] although the NIOSH analysis was based on a more recent follow-up of this cohort.[21] OSHA also produced risk estimates based upon a multistage model of a rat bioassay study,[30] which are also presented in Figure 4 for comparison purposes.

For its analysis of the epidemiologic data, OSHA performed a Poisson regression of the SMRs reported by Thun et al.[20] using an additive relative rate function. The risks predicted from OSHA's epidemiologic risk assessment were approximately seven times lower than the risks predicted by modeling of the rat bioassay data. It was suspected that, at least in part, this discrepancy might be explained by the potential negative bias in the SMR analysis due to the healthy worker effect. In the NIOSH assessment, a similar functional form (i.e., additive relative rate) was fitted using Poisson regression, but the model was fitted to the internal stratum-specific rates generated directly from the study. It can be seen that the NIOSH risk estimates were higher than those from OSHA's epidemiologic assessment, but they were still somewhat lower than the estimates produced by the multistage modeling of the rat bioassay study. Thus, it appears that OSHA's reliance on modeling the SMRs, as opposed to internal analysis of the rates within the cohort, introduced a negative bias in the estimation of risks.

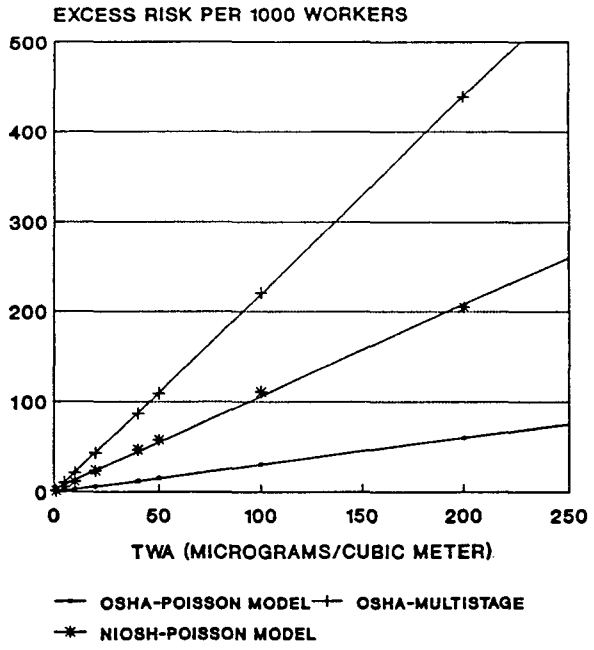

FIGURE 4. Comparison of NIOSH and OSHA excess risk estimates for cadmium exposure, assuming 45 years of exposure.

Biologic Models

Biologically based models, particularly models based on the multistage theory of carcinogenesis,[31] have often been used for producing risk estimates from animal bioassay data. These models have the advantage over statistical models of being based on biologic theory, thus providing a theoretical basis for extrapolation to low doses. On the other hand, these models may be oversimplified representations of the complex processes involved in carcinogenicity, and the validity of these models warrants further investigation.

The multistage theory suggests that, in order for a cell to become cancerous, it must progress through a series of ordered, independent, and irreversible stages. Stochastic models have been derived based on the multistage theory for

application to animal bioassay data. The quantal multistage model[32] has been the most commonly used model, which is fitted to the proportions of tumors at the end of the experiment using the following mathematical functional form:

$$P = 1 - \exp(-\{q_0 + q_1 d + \ldots + q_k d^k\}) \quad (6)$$

where: P = cumulative risk
q = regression coefficients
d = dose
k = number of stages affected by the exposure

A "linearized" version of Equation 6, based on the upper 95% confidence limit on the linear parameter (q_1) has been used extensively by EPA for its QRAs.[33] A time-to-tumor version of the multistage model has also been developed for modeling the time to the event (tumor) in animal bioassay studies.[34]

The multistage model has been shown to provide a reasonable description of the relationship between cancer incidence and age[31] for most nonhormonally mediated cancers in humans. Doll[35] has reported that the effect of cigarette smoking on lung cancer risk appears to be consistent with smoking altering the first parameters stage of a five-stage model, whereas other analyses indicate that smoking may act on both the first and fourth stages.[22] The multistage model has only been applied in a few cases to the analysis of occupational, cohort, mortality data.[36,37]

The implications of the multistage model may be explored indirectly by examining how the patterns of relative (or excess) risk in an epidemiologic study are modified by age at initial exposure and time since last exposure.[38] If a carcinogen acts on the first stage of the process, then 1) relative and excess risk are increasing functions of time since last exposure and 2) excess risk is independent of age at initial exposure, whereas the relative risk decreases with increasing age at initial exposure. If a carcinogen acts on the penultimate (next to last) stage of the process, then 1) relative and excess risk increase with age at initial exposure and 2) the excess risk is independent of time since last exposure, whereas the relative risk decreases with increasing time since last exposure. For example, in a NIOSH[39] assessment of radon daughters and lung cancer risk, the relative risk was observed to increase with age at initial exposure and decrease with time since last exposure, suggesting that radon acts on a late stage in the carcinogenic process.

Recently, two-stage models of carcinogenesis have been proposed for use in risk assessment.[40] In addition to allowing for two mutational events, these models allow for the influence of exposures on cell growth and differentiation. Two-stage models have been shown to provide a reasonable description of the age incidence curves for most human tumors, including hormonally mediated tumors that are not well described by the multistage model.[41] These models have not as of yet been applied to QRA for occupational or environmental exposures.

Translating Rates to Risks — Extrapolation Models

As mentioned earlier, regulatory agencies generally require estimates of lifetime risk for their decision-making process. Thus, the hazard rates (or rate ratios) that are estimable from the statistical models described in this paper need to be converted to estimates of lifetime risk. In order to make this conversion, assumptions need to be made about the duration and timing of the exposure. For occupational QRAs, it has generally been assumed that the workers are exposed for approximately 45 years (i.e., a working lifetime) starting at age 20, whereas for environmental QRAs, the exposure has generally been assumed to be initiated at birth and to last until death at approximately 70 years of age.

Gail[41] has proposed methods for computing lifetime risk based on actuarial methods, which account for the effects of competing causes of death. For multiplicative models, the lifetime risks of occupational exposures may be estimated using Gail's method to estimate the risks of 45 years of exposure at age 75 based on the following formula:

$$\sum_{i=20}^{74} (RR_i - 1)\, q_d(i) \exp\left[-\sum_{j=20}^{i} \{(RR_j - 1)\, q_d(j) + q_a(j)\}\right] \quad (7)$$

where: RR_i = rate ratio estimate from the model for exposure achieved at age i
$q_d(i)$ = background age-specific rate for the disease of interest
$q_a(i)$ = background age-specific mortality for all causes
i = age indices

The results from the application of this approach to the estimation of lifetime risks from occupational exposure to cadmium based on the additive relative rate models from the NIOSH[19] QRA are presented in Table II. Based on this assessment, the lifetime risk of dying from lung cancer after 45 years of exposure at the current OSHA standard for cadmium fumes of 100 $\mu g/m^3$ was estimated to range from 5 to 10 per 100 workers. Note that in this model (Equation 7), the rate ratio is assumed to be constant with age at risk and length of follow-up and is solely dependent on the exposure achieved (at age i). Adjustments to the extrapolation model need to be made if there is evidence that the effect of exposure is modified by these or other covariates.

Conclusion

The purpose of this paper was to review and discuss the major methodologic issues related to the use of epidemiologic data for risk assessment. Although animal studies have been most often used for QRA, it is generally recognized that well-conducted epidemiologic studies would provide the best basis for estimating human risk. However, the observational

TABLE II. Estimates of Excess Risk per 1000 Workers Based on the Poisson Regression and Cox Proportional Hazards Additive Relative Rate Models in the NIOSH Cadmium Risk Assessment*

TWA ($\mu g/m^3$)	Excess Risk Estimates (per thousand workers)	
	Poisson Model	Cox Model
1	1.2	0.5
5	6.0	2.6
10	11.9	5.2
20	23.7	10.3
50	57.7	25.4
100	110.9	49.9
200	205.2	96.4

*Risk estimates are based on the results from the 5-year lagged analysis.

nature of epidemiologic studies often introduces several sources of uncertainty that are generally not present in QRAs based on animal experiments.

The lack of adequate exposure (or dose) information is the most frequently cited reason for not using epidemiologic data for QRA. There is reason to hope that, in the future, improvements will be made in the estimation of exposure in epidemiologic studies and that biologic markers and pharmacokinetic models will be used to estimate target tissue doses. Other aspects of epidemiologic study design, e.g., confounding, effect modification, length of follow-up, and statistical power, may also limit the usefulness of epidemiologic data for QRA. Even if these limitations can be overcome, as with animal studies, substantial uncertainties exist as to the choice of a proper statistical (or biologic) model for extrapolation from epidemiologic results.

Because of the limitations discussed in this paper, epidemiologic data should not be viewed as a panacea for the problems inherent in using animal bioassay data for QRA. This is not to belittle the importance of epidemiologic data. On the contrary, epidemiologic data is of vital importance to QRA and hopefully will play an even greater role in the future. The information that can be derived from epidemiologic and toxicologic studies complement one another, and both data sources need to be used to provide the best characterization of human risk.

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