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Modeling Epidemiologic Studies of Occupational Cohorts for the Quantitative Assessment of Carcinogenic Hazards

Leslie Stayner, PhD, Randy Smith, MA, A. John Bailer, PhD, E. Georg Luebeck, PhD, and Suresh H. Moolgavkar, MD, PhD

Epidemiologic studies of occupational cohorts have played a major role in the quantitative assessment of risks associated with several carcinogenic hazards and are likely to play an increasingly important role in this area. Relatively little attention has been given in either the epidemiologic or the risk assessment literature to the development of appropriate methods for modeling epidemiologic data for quantitative risk assessment (QRA). The purpose of this paper is to review currently available methods for modeling epidemiologic data for risk assessment. The focus of this paper is on methods for use with retrospective cohort mortality studies of occupational groups for estimating cancer risk, since these are the data most commonly used when epidemiologic information is used for QRA. Both empirical (e.g., Poisson regression and Cox proportionate hazards model) and biologic (e.g., two-stage models) models are considered. Analyses of a study of lung cancer among workers exposed to cadmium are used to illustrate these modeling methods. Based on this example it is demonstrated that the selection of a particular model may have a large influence on the resulting estimates of risk.

Key words: epidemiology, risk assessment, cancer, occupational studies, cadmium hazards

All models are wrong some are useful [Box, 1975].

INTRODUCTION

Epidemiologic studies of occupational groups (cohorts) have played a role in the quantitative assessment of cancer risks associated with several agents (e.g., asbestos, arsenic, benzene, and radon daughters). The usefulness of epidemiologic studies for

Risk Assessment Program, Division of Standards Development and Technology Transfer, National Institute for Occupational Safety and Health, Robert A. Taft Laboratories, Cincinnati, OH (L.S., R.S., A.J.B.).
Department of Mathematics and Statistics, Miami University, Oxford, OH (A.J.B.).
The Fred Hutchinson Cancer Research Center, Seattle, WA (E.G.L., S.H.M.).
Address reprint requests to Leslie Stayner, Risk Assessment Program, NIOSH, Robert A. Taft Laboratories, 4676 Columbia Parkway, MS C15, Cincinnati, OH 45226-1998.
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cancer risk assessment purposes has frequently been limited by the lack of reliable exposure information and other limitations related to the design of these studies [Stayner et al., 1992]. In the future, it is likely that the utility of epidemiologic studies of occupational cohorts will increase along with improvements in exposure characterization and the development of more refined biologic markers of exposure and disease.

Relatively little attention has been given in either the epidemiologic or the risk assessment literature to the development of appropriate methods for modeling epidemiologic data for quantitative risk assessment (QRA). Far more attention has been devoted towards the development of methods for modeling animal bioassay data, which are not readily adapted to epidemiologic data because of differences in data structure. The purpose of this paper is to review currently available methods for modeling epidemiologic data for QRA. The focus of this paper is on methods for use with retrospective cohort mortality studies of occupational groups for estimating cancer risk, since these are the data most commonly used when epidemiologic information is used for QRA. However, these methods can conceptually be adapted to other study designs (e.g., case–control studies) or diseases (e.g., cardiovascular disease).

Analyses of a National Institute for Occupational Safety and Health (NIOSH) study of lung cancer among workers exposed to cadmium will be used to illustrate these modeling methods. This data set was used as the basis for quantitative risk assessments that were previously performed by NIOSH [Stayner, 1992; Occupational Safety and Health Administration (OSHA), 1992; Environmental Protection Agency (EPA), 1984].

THE NIOSH CADMIUM STUDY

The design of the NIOSH cadmium study has been previously described [Lemen et al., 1976; Thun et al., 1985]. Briefly, this retrospective cohort mortality study included 606 male workers who had been employed for at least 6 months between 1940 and 1969 at a cadmium refinery. These workers were followed for vital status ascertainment up to December 31, 1984. The study facility was an arsenic smelter prior to 1926. In order to reduce the potential for confounding by arsenic, the data analyses were restricted to only include workers employed on or after 1926.

DOSE–RESPONSE MODELS

Dose–response models having only an empirical basis (i.e., statistical models) and models that are based on biologic theory (i.e., biologic models) are considered in this paper. It is recognized that this distinction is somewhat superficial, since the biologic models are also probabilistic in nature and some empirical model forms may be justified based on biologic theory.

STATISTICAL MODELS

Modeling Standardized Mortality Ratios

In many cases epidemiologically based QRAs have relied on the modeling of standardized mortality ratios (SMRs). Modeling of SMRs may be the only option available if one does not have access to the raw data, and must instead rely on the summary measures presented in a publication. There are at least two important

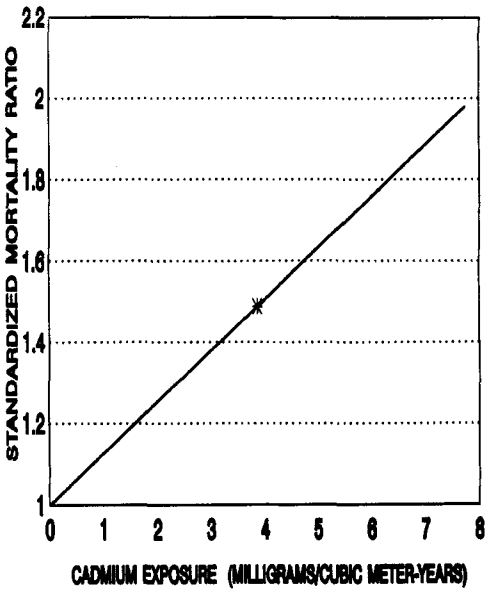

Fig. 1. Model based on average cadmium exposure and overall SMR from the NIOSH cadmium cohort mortality study.

reasons why modeling SMRs may result in biased estimates of risk. First, since SMRs are indirectly standardized measures that use the weights of the study group, they are not mutually standardized and comparable [Rothman, 1986]. Thus, modeling SMRs may introduce confounding biases due to differences in age, race, and sex between the various exposure groups. Second, SMRs may be negatively biased due to the healthy worker effect [HWE; McMichaels, 1976; Fox and Collier, 1976]. This effect can be viewed as a form of selection bias that is introduced by the fact that the general population (which is used as the referent in calculating the SMR) includes individuals who are not healthy enough to work.

The simplest method for modeling using SMRs is to assign a single average exposure level for the entire cohort, and drawing a line from the observed SMR to the origin (SMR = 1). Smith [1988] has suggested this as a simple method for using epidemiologic data for risk assessment when data on individual exposures are missing. This approach is essentially equivalent to fitting the following model:

$$SMR = 1 + x\beta \quad (1)$$

where x represents the exposure and β represents the change in the SMR per unit of exposure (i.e., the slope). This approach is illustrated in Figure 1 for the cadmium cohort where the overall SMR for lung cancer was 1.49 and the average cumulative exposure was 3.87 mg/m^3-years.

A somewhat more sophisticated approach may be applied when several SMRs representing different levels of exposure are available. The QRAs performed by

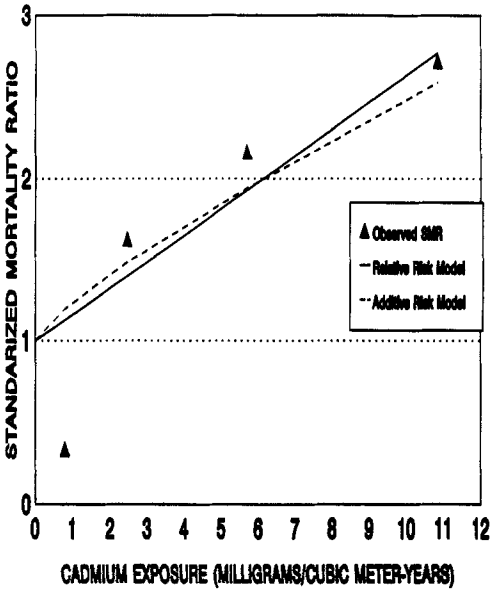

Fig. 2. Models based on several SMRs from the NIOSH cadmium study.

OSHA [1992] and the EPA [1984] were primarily based on fitting the following models to the SMRs reported in the NIOSH cadmium study:

$$\text{Additive rate } \lambda(x) = \lambda_o + x\beta \tag{2}$$

$$\text{Relative rate } \lambda(x) = \lambda_o(1 + x\beta) \tag{3}$$

where $\lambda(x)$ represents the predicted hazard (mortality) rate with cumulative exposure level of x, λ_o represents the background hazard rate, and β represents the regression (slope) parameter. It may be easily shown that the SMR predicted with exposure level x by model (2) is $(\lambda_o + x\beta)/\lambda_o$, and by model (3) is $(1 + x\beta)$. Maximum likelihood methods may be used to estimate the parameters for these models based on the assumption that the observed deaths follow a Poisson distribution with mean $n\lambda(x)$ where n is the number of person-years of follow-up [Crump and Allen, 1985].

The results from fitting these models to the cadmium cohort using a SAS [1987] NLIN program are illustrated in Figure 2. It may be seen that both of these models clearly miss the SMR for the lowest exposure category. This poor fit may be due to the HWE, and to the fact that this cohort included a large percentage of Hispanics. Hispanics in the Southwest experience lower death rates from lung cancer and smoke fewer cigarettes per day than non-Hispanics [Samet et al., 1980; Savitz, 1986; Mitchell et al., 1990].

It is possible to make an adjustment for the HWE and other sources of biases in the SMR by fitting an additional parameter to the model to adjust the background hazard rate. For example, the following relative risk model was also fitted to the NIOSH cadmium study in OSHA's [1992] risk assessment:

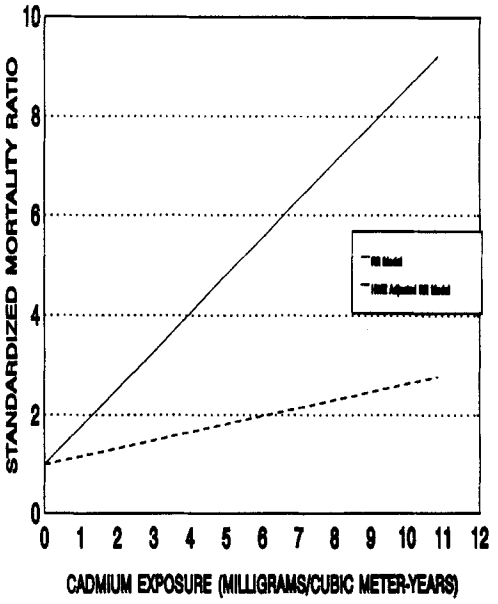

Fig. 3. Relative rate (RR) models of several SMRs from the NIOSH cadmium study with and without adjustment for the HWE.

$$\lambda(x) = \lambda_o \exp(\alpha)\,(1 + x\beta) \tag{4}$$

where $\exp(\alpha)$ represents a positive factor that multiplies the baseline hazard rate and is generally less than 1 when the HWE is present.

The results from fitting model (4) to the cadmium cohort are contrasted with the results from the unadjusted relative risk model (model 2) in Figure 3. The rate ratio (SMR) estimates from the HWE-adjusted relative rate model (4) are substantially greater than those from the unadjusted relative rate model (3).

Models Based on Internal Comparisons

The pitfalls of using indirectly standardized measures (i.e., SMRs) and general population rates as the referent may be avoided by using methods based on internal comparisons within the cohort. These methods also have the advantage of allowing examination of how risks may be modified by other covariates (e.g., age) and lagging or other weighting schemes to adjust exposures for potential latency and induction periods [Checkoway et al., 1990].

Considerable progress has been made in developing statistical methods for modeling hazard rates from occupational cohort mortality studies in recent years. An excellent review of these modeling techniques is presented in Breslow and Day [1987]. These models may be broadly categorized into two classes:

1. Models in which the effect of exposure adds to the background rate (linear or additive models)

2. Models in which the effect of exposure multiplies the background rate (multiplicative models)

Thomas [1981] has also proposed a method for fitting hybrid models that allow for a variety of dose–response relationships that range between additive and multiplicative or even supramultiplicative.

The linear and multiplicative models may be represented mathematically as follows:

$$\text{Linear: } \lambda\{x(t)\} = \lambda_o(t) + r\{x(t)\beta\} \tag{5}$$

$$\text{Multiplicative: } \lambda\{x(t)\} = \lambda_o(t)r\{x(t)\beta\} \tag{6}$$

where $\lambda\{x(t)\}$ represents the predicted hazard rate and $\lambda_o(t)$ represents the background hazard rate at age t, x(t) represents a vector of exposure and other explanatory variables, β represents a vector of regression parameters, and $r\{x(t)\beta\}$ represents a relative (for equation 6) or excess (for equation 5) rate function.

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

$$\text{Exponential: } r\{x(t)\beta\} = \exp(x(t)\beta) \tag{7a}$$

$$\text{Additive relative rate: } r\{x(t)\beta\} = (1 + x(t)\beta) \tag{7b}$$

$$\text{Power: } r\{x(t)\beta\} = (x(t) + k)^{\beta} \tag{7c}$$

where k is positive and is often assumed to be 1. However, it is generally more appropriate to solve for k as an additional parameter.

The functional forms described above 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 [Frome and Checkoway, 1985]. The results from fitting Poisson regression models to the cadmium cohort using SAS NLIN and GLIM programs are illustrated in Figure 4. In addition to fitting the functional forms of the model described above, a model was fitted using categorical (indicator) variables representing each of the exposure groups. A lag period of 5 years was used, since this was found to minimize the deviance (i.e., maximize the goodness of fit) of these models. The power function model (model 7c) provided the best fit to the data based on the log–likelihood ratio statistic, but was rejected as an appropriate model because it produced unreasonably low estimates of the baseline hazard [Stayner, 1992]. The additive relative rate (model 7b) fit the data slightly better than the exponential multiplicative models (model 7a). The linear model (model 5) fit the data poorly.

All of the multiplicative models described above (i.e., models 7a, 7b, and 7c) may also be fitted to data from occupational cohort mortality studies by modeling the hazard rate using the Cox proportional hazards model [Cox, 1972]. This method has the advantage that it does not require the categorization of exposure or other covariates as does Poisson regression, which may increase the statistical efficiency of the analysis. The baseline hazard (λ_o) in the Cox model is unspecified and thus linear models (model 5) cannot be fitted with this model.

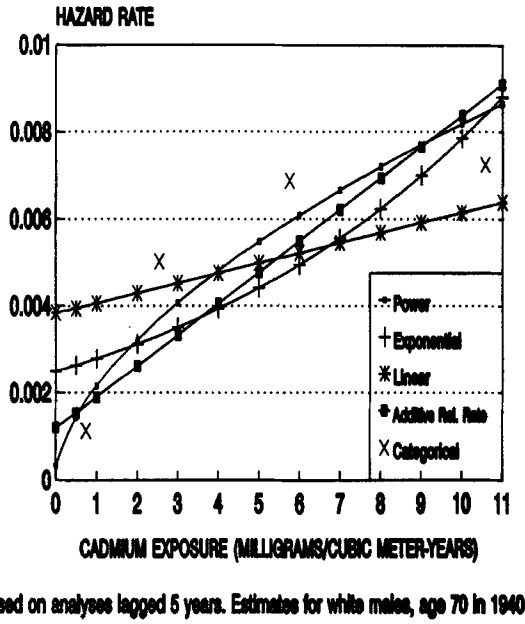

Fig. 4. Hazard rates derived from fitting different forms of Poisson regression models to the NIOSH cadmium study based on analyses lagged 5 years. Estimates for white males, age 70 in 1940–1960.

The results from fitting the additive relative rate (model 7b) form of the Cox proportional hazards model using BMDP [1985] are contrasted with the results from fitting the same model using Poisson regression in Figure 5. These two methods are expected to yield similar results when applied to large samples. In this case the rate ratios estimates differed by a factor of approximately 2 at high exposure levels.

BIOLOGIC MODELS

The Multistage Model

Biologically based models, particularly models based on the Armitage-Doll [Armitage and Doll, 1954] multistage theory of carcinogenesis, have been commonly used for risk assessments based on animal bioassay data. The multistage theory asserts 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 this theory for application to animal bioassay data. The quantal multistage model [Guess and Crump, 1976] has been the most commonly used model, which is fitted to the proportions of tumor bearing animals from an experiment using the following mathematical expression:

$$P(d) = 1 - \exp(-\{q_0 + q_1 d + q_2 d^2 + \ldots + q_k d^k\}) \quad (8)$$

where P(d) represents the cumulative risk, the q's represent the non-negative regression coefficients ($i = 0, \ldots, k$), d represents the dose, and k represents the number of stages affected by the exposure.

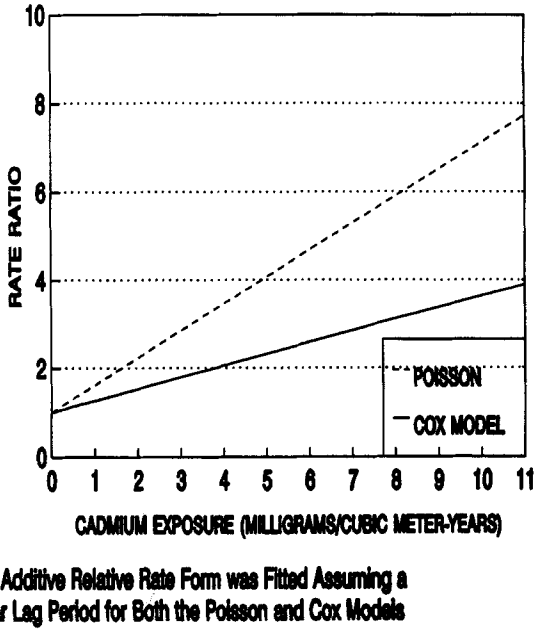

Fig. 5. Comparison of rate ratio estimates derived from Poisson regression and Cox models fitted to the NIOSH cadmium study. The additive relative rate form was fitted assuming a 5-year lag period for both the Poisson and Cox models.

A "linearized" version of equation 8 based on the upper 95% confidence limit on the linear parameter (q_1), often referred to as q_1*, has been used extensively by the EPA for its QRAs [Crump et al., 1977]. 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 [Crump and Howe, 1984].

The methods developed for fitting the quantal multistage model to animal bioassay data assume constant dosing, and for this reason are not easily adapted to epidemiologic studies in which individuals have more complex patterns of exposure. 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 [Brown and Chu, 1983].

An approximate form of the multistage model has been fitted to occupational mortality studies [Mazumdar et al., 1989; Pearce, 1988] using Poisson regression. In these analyses, the exposures were weighted based on the following mathematical relationship that has been shown [Whittemore, 1977] to be consistent with the multistage theory:

$$E(x,t) \approx \int_0^e x(z)(f - z)^{k-1-j} (t_0 + z)^{j-1} dz, \text{ for } j < k \qquad (9)$$

where $\approx$ indicates proportionality, E(x,t) is the excess incidence rate, x is the exposure level, f is the total length of follow-up, e is the length of the exposure period, k

TABLE I. Results From Fitting a Five-Stage Multistage Model to the Results From the NIOSH Cadmium Cohort Mortality Study*

Affected stage[a]	−2 Log likelihood	Beta	Standard error
1	−122.57	0.034	0.034
2	−121.92	0.082	0.075
3	−120.90	0.213	0.208
4	−121.99	0.072	0.062

*Models fitting using the additive relative rate form of the Cox proportionate hazards model and weighting exposures in a manner consistent with the multistage theory.
[a]The stage assumed to be affected by exposure was varied.

is the number of stages in the model, j is the stage affected by the exposure, t_0 is the age at first exposure, and z is the variable of integration.

An attractive feature of using equation 9 as a weighting function is that it provides a means for incorporating information on age at first exposure (t_0) and length of follow-up (f) into the analysis. This approach avoids the potential problems associated with including these as independent covariates, which are related to the fact that they are generally strongly correlated with exposure.

Table I presents the results from fitting an approximate form of the multistage model to the cadmium cohort data using an additive relative rate form of the Cox proportionate hazards model and weighting the exposures in a manner consistent with relationship (9). A five-stage model was fitted and the likelihood of the model was maximized when it was assumed that the exposure affected the third stage. The multistage model yielded a slightly better fit to the data than the additive relative rate (model 6b) form of the Cox proportionate hazards model.

Two-stage Models

Two-stage models of carcinogenesis have also been developed [Moolgavkar and Venzon, 1988; Moolgavkar and Knudson, 1981], which may be applied for QRA. These models, in addition to allowing for two mutational events, also 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-specific incidence curves for many human tumors including hormonally mediated tumors that are not well described by the multistage model. The two-stage model may be represented schematically as shown in Figure 6.

Under this model exposure to a carcinogen may have an effect on the frequency of the first mutational event (μ_0) that results in an intermediate (initiate) cell, the second mutational event (μ_1) that completes the transformation to a malignant cell, the growth (α) or death (β) rate of intermediate cells.

The results from fitting a two-stage model to the cadmium cohort study are presented in Table II. In this model, we assumed that exposure has an effect only on cell proliferation (α-β) and on the first mutation rate (μ_0). Cadmium exposure had a

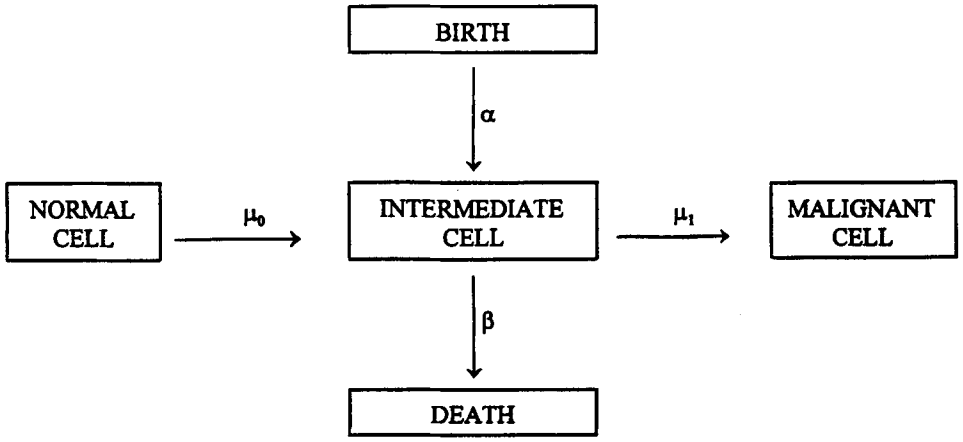

Fig. 6. Schematic representation of a two-stage model.

stronger effect ($X^2 = 4.2$, $p = 0.04$) on the first mutation rate than on the net growth rate of initiated cells ($X^2 = 3.2$, $p = 0.07$).

Estimates of the rate ratio as function of varying concentrations of cadmium exposure derived from the multistage and two-stage models are contrasted in Figure 7. These rate ratio estimates were derived for age 75 and assuming 45 years of exposure starting at age 20 and ending at age 65. The shape of the dose–response relationship is clearly linear for the multistage model and supralinear for the two-stage model.

RISK PREDICTION MODELS

Regulatory agencies generally require predictions of lifetime risk for their decision making processes. The hazard rates (or rate ratios) that are estimable from the statistical and biologic models described in this paper need to be converted to predict estimates of lifetime risk. In order to make this conversion, specification of the duration and timing (i.e., age) of the exposure for the target population needs to be made. For occupational QRAs, the target population have generally been workers who are exposed for approximately 45 years (i.e., a working-lifetime) starting at approximately age 20; whereas, for environmental QRAs, the target population generally have been people who are continuously exposed from birth until the expected age at death (e.g., 70 years).

Gail [1975] has proposed methods for computing lifetime risk based on actuarial methods, which account for the effects of competing causes of death. For example, the risks of occupational exposures to age 75 may be predicted using the following approximate formula derived from Gail's method assuming 45 years of exposure beginning at age 20:

$$\sum_{i=20}^{74} (RR_i - 1)\, c(i) \exp\left[-\sum_{j=20}^{i} \{(RR_j - 1)\, c(j) + a(j)\}\right]. \qquad (10)$$

TABLE II. Summary of Results From Fitting a Two-Mutation Model to the NIOSH Cadmium Cohort Mortality Study*

Parameter	Estimate	Standard error	−2LNLR	p value
β/α	.8650	.2819	—	—
b_0	.2510	.1245	—	—
b_1	.0095	.0089	3.2	0.074
c_0	.0458	.1478	—	—
c_1	.0732	.2167	4.2	0.040

*In fitting this model it was assumed that: 1) the effect of exposure (d) on the net cell proliferation rate $(\alpha - \beta) = b_0 + b_1*\ln(d + 1)$, 2) the asymptotic extinction probability (β/α) is a constant, 3) the effect of exposure is on the probability of the first mutational event $(\mu_0) = c_0 + c_1*\ln(d + 1)$, and 4) the probability of the second mutational event $(\mu_1) = c_0$ is a constant.

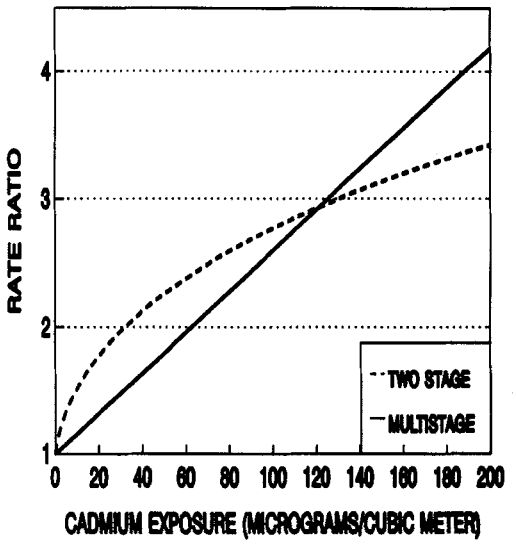

Fig. 7. Comparisons of rate ratio estimates derived from the two-stage and multistage models fitted to the NIOSH cadmium study. Rate ratios for age 70 assuming 45 years of exposure beginning at age 20.

Where RR_i is the age-specific rate ratio estimate from the model, c(i) represents the background age-specific rate for the disease of interest, a(i) represents the background age specific mortality for all causes, and i indexes age. The background age-specific rates may be either derived from the general population mortality rates or from the cohort itself. This formula can be modified for an additive model as follows:

$$\sum_{j=20}^{74} [R_i] \exp[-\sum_{j=20}^{i} \{R_j + a(j)\}] \tag{11}$$

TABLE III. Comparison of Risk Estimates for 45 Years of Exposure to Varying Levels of Cadmium Based on Selected Models Fitted to the NIOSH Cadmium Cohort Mortality Study

	Excess risk per 1,000 workers by cadmium exposure level ($\mu g/m^3$)[a]							
Model form	1	5	10	20	40	50	100	200
Single SMR (1)	0.3	1.4	2.8	5.6	11.2	14.0	27.6	54.3
Additive SMR (2)	0.2	1.1	2.3	4.6	9.1	11.4	22.6	44.6
Relative SMR (3)	0.4	1.8	3.6	7.2	14.4	18.0	35.5	69.2
HWE adjusted SMR (4)	1.7	8.4	16.7	33.0	64.4	79.6	150.7	270.7
Poisson additive relative rate (7b)	1.2	6.0	11.9	23.7	46.5	57.7	110.9	205.2
Cox additive relative rate (7b)	0.5	2.6	5.2	10.3	20.4	25.4	49.9	96.4
Multistage (9)	0.8	4.1	8.1	16.2	32.0	39.7	77.4	146.9
Two-stage MVK	8.7	25.4	36.7	50.8	67.9	74.0	95.6	120.7

[a]Excess risk estimates as of age 75 calculated assuming 45 years of cadmium exposure starting at age 20 using the risk projection model (model 10) described in this paper.

where R_i represents the age-specific excess rate estimate derived from the model.

The results from the application of this prediction model to the estimation of lifetime risks from occupational exposure to cadmium based on selected models previously described are presented in Table III. These estimates graphically demonstrate the dependency of risk estimates on the specification of the model. The divergence in risk estimates was the most extreme at low exposure levels. For example, for a time-weighted average (TWA) of 1 $\mu g/m^3$, the risk estimates ranged approximately 40-fold from the additive SMR model (0.2/1,000) to the two-stage model (8.7/1,000). The two-stage model only predicted the highest risks at exposures below 40 $\mu g/m^3$, reflecting the nonlinearity of this model (see Fig. 7). The models that were based on unadjusted SMRs produced estimates of risk that were consistently less than those derived from the survival analyses models; while the SMR model adjusted for the HWE produced estimates of risk that were substantially greater than those derived from the survival analyses models.

The results presented in Table III were derived using U.S. mortality data for the background rates [c(i) and a(i)] in formula (10). An alternative approach would be to use background rates derived from the cohort itself. In order to evaluate the influence of this choice, we calculated excess risk estimates using the age-specific background rates derived from the NIOSH cadmium cohort and results from the additive relative rate form (7b) of the Poisson regression model. The excess risks predicted with this approach were approximately three times lower than the risks predicted using the same model and the U.S. rates (Table III). The choice of which rates to use for the background should be determined by what population one is interested in predicting risks for. If one is interested in predicting risks for a group of workers with similar characteristics as the NIOSH cadmium cohort then the internal rates seem preferable. On the other hand, if one is interested in predicting risks for the general population then the external U.S. rates may be more relevant.

DISCUSSION

The purpose of this paper was to review and illustrate different methods that may be used for modeling epidemiologic data for risk assessment. It is quite apparent

in our cadmium example that the selection of a particular model has a profound influence on the resulting estimates of risk. Maldonado and Greenland [1992] have recently reviewed the extreme potential effects of misspecification of the model form on rate ratio estimates. The fact that estimates of risk are highly model dependent is generally true for assessments based upon both epidemiologic and toxicologic data. What then is the correct model? The answer to this question is that probably none of them is absolutely correct. This is because models are representations of reality and should not be confused with reality itself. It may be possible to rule out certain models as inappropriate for risk assessment, such as the linear model that provided a poor fit to the cadmium cohort study. It seems intuitively obvious that models that do not fit the data in the observed range are highly unlikely to provide reliable estimates of risk in the unobserved range. Probably the most reasonable approach is to fit several models as we have done in this paper, and present a range of risk estimates from the models that fit the data well.

It is often assumed that biologic models provide a stronger theoretical basis for extrapolation beyond the range of the data than statistical models. However this assumption is predicated on the adequacy of the theory underlying the biologic model. The theory underlying the multistage models has been criticized as being incomplete, since it fails to consider what is known about the potential for effects of carcinogens on clonal expansion of initiated cells [Moolgavkar, 1986]. The two-stage clonal expansion model allows a carcinogen to have an effect on cell growth and differentiation as well as on the frequency of mutations. The two-stage models also have the advantage of allowing for the incorporation of additional experimental data such as on the growth rates of initiated cells. This type of information is currently being developed for animal bioassay-based risk assessments. It would be desirable to obtain information on intermediate endpoints in human studies. However, such information is unlikely to be available soon. The primary advantages of statistical models are that they are generally easier to use with existing commercial software and may have better statistical properties (e.g., convergence) than biologically based models.

The results from this analysis clearly illustrate how the modeling of SMRs can produce estimates of risk that are biased towards the null. The risk estimates from the models of the SMRs were substantially lower than the estimates from the internal analyses of the cadmium cohort. This bias may be reduced by adding a parameter to adjust the baseline hazard rate, although in this case the correction seemed to result in inflated estimates of risk. This adjustment does not avoid the potential biases related to the fact that the SMRs are not mutually standardized.

It should be recognized that there are many features of epidemiologic studies that may introduce even greater uncertainties into a QRA than the choice of an appropriate model. Of particular concern is the accuracy of exposure information used in occupational cohort mortality studies. Misclassification of exposures may bias the risk estimates in either direction, even if these errors are assumed to be nondifferentially distributed with respect to disease status [Dosemeci et al., 1990; Prentice, 1982]. In addition, occupational cohort mortality studies frequently lack information on other major disease risk factors. For example, information on cigarette smoking and potential exposure to arsenic was not available for the NIOSH cadmium cohort. Although significant confounding by smoking and arsenic exposure was believed to be unlikely in this study [Stayner, 1992], it has been shown that parameter estimates

and standard errors may be biased if important risk factors are left out of the model, even if these factors are not confounders [Gail, 1986]. The interpretation of the parameters in the biologic models may also be compromised by the lack of information on other disease risk factors.

The statistical variability associated with the parameter estimates derived from the various models was not presented in this paper. It should be noted that, with the exception of the exponential model (7a), the standard errors derived from the models presented in this paper cannot be relied on for either hypothesis testing or for constructing confidence intervals using a normal theory [Moolgavkar and Venzon, 1987]. This is because the assumption that the maximum likelihood estimates are approximately normally distributed is generally unreliable for these models. Hypotheses testing and confidence intervals for these models should be based on likelihood-based methods.

The example used in this paper was based on the analysis of only one study. Although in most situations we are fortunate if there is a single epidemiologic study available for such detailed exposure–response analyses, there are cases in which multiple studies are available and meta-analytic exposure–response analyses may be possible. For example, the EPA [1986] in its risk assessment for asbestos analyzed the results from 14 different studies and based its risk assessment on the geometric mean of the slope for lung cancer. Meta-analytic methods offer the potential of increasing the statistical precision of risk estimates and reducing the degree of extrapolation required from high to low exposures. However, in conducting meta-analysis one needs to consider the influence of heterogeneity of the effects [DerSimonian and Laird, 1986]. One might expect such a large degree of heterogeneity due to systematic differences between epidemiologic studies that it may be difficult to develop sensible summary measures of the exposure–response relationships. In the EPA risk assessment for asbestos referred to above, the slope for lung cancer was found to vary by over 600-fold and it is likely that much of this variability might be explained by differences in fiber dimensions or other differences in the characteristics and patterns of asbestos exposure or exposure to other risk factors (e.g., smoking).

In closing, epidemiology has an obvious role in providing information for quantifying human risks. This role should expand in the future as better methods for exposure characterization and more sensitive markers of disease and exposure (i.e., biologic markers) are developed. Curiously, scant attention has been given towards developing methods for risk assessment using epidemiologic data. The reasons for this are unclear, but it may in part reflect a reluctance on the part of many epidemiologists to engage in QRA. We hope that this paper will stimulate further interest among epidemiologists, and will serve as a starting point for identifying appropriate methods for using epidemiologic data for QRA.

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